The physiologic and therapeutic role of heparin in pregnancy

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Interaction between heparin and AT-III
-conformational change in AT-III
that accelerates up to 1,000 fold its ability
to inactivate
thrombin, factor Xa, and factor IXa

Size of heparin has decisive importance
in the inhibition of thrombin by AT-III
but **no importance in the inhibition of factor Xa by AT-III**

LMWH, fondaparinux etc.....

Heparins / Nader et al 1999 Romero et al., 2002, Quaranta et al.2015/

- True physiologic role in the body remains uncertain
- Mast cells granules – released at sites of tissue injury
- Anticoagulation
- Anti-inflammatory effects
- Physiologic role in establishment of normal pregnancy – direct effect on trophoblast (cytotrophoblast mitosis and syncytiotrophoblast formation, proangiogenic activity) /Kingdom JCP and Dewio S, 2011/

Aposition
Adhaesion
Invasion

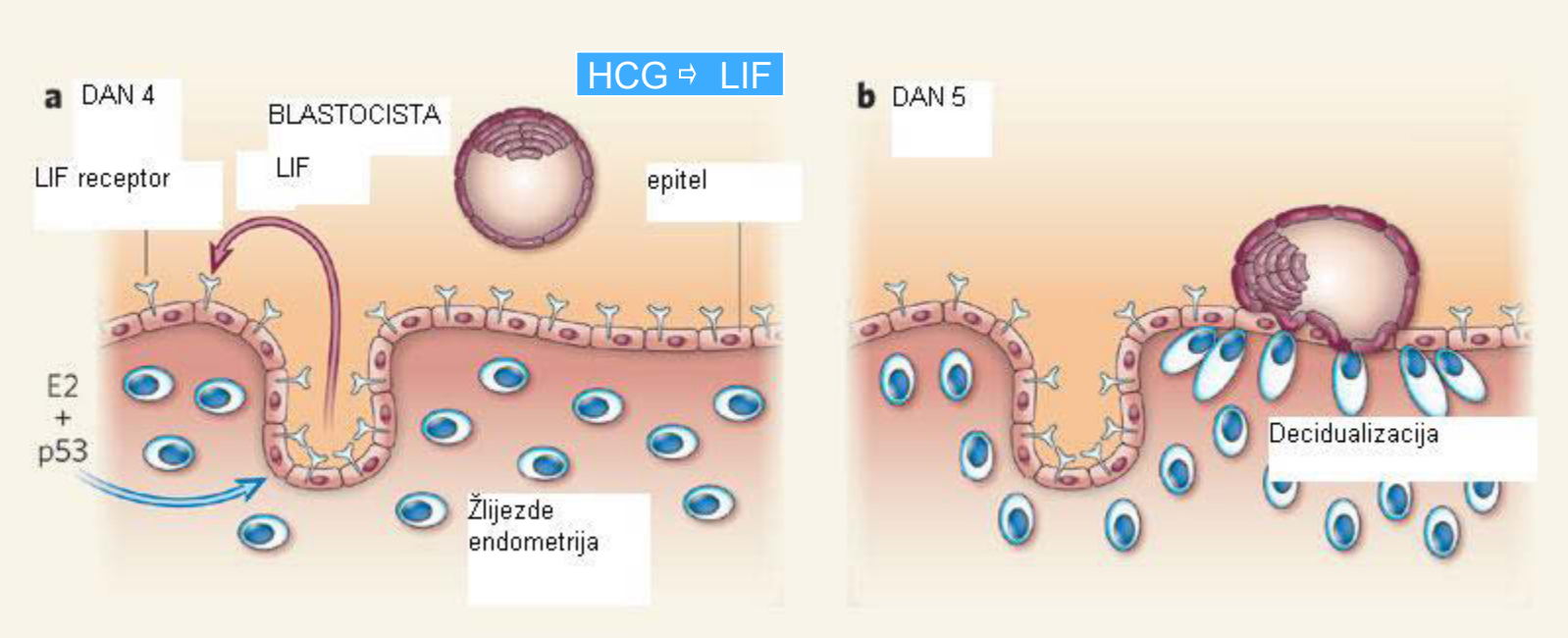
Successful implantation

Materno-fetal dialogue

- Competent blastocyst
- receptive endometrium

Loss of inhibitory molecules
Acquisition of adhaesion ligands

LIF and p53 (Stewart LC, Nature 2007; 450:619, Hu W et al. Nature 2007; 450:721)



LIF – receptor interraction
➡ endometrial receptivity

Process of implantation is orchestrated by:

Sex steroids, HCG

Growth factors: TGF-B, **HB-EGF**,IGF-1,LIF, cytokines, IL-6, IL-11

Adhesion molecules: L- **selectin**, **E- cadherin**

ECM proteins

PG

/Dey et al., 2004/

Effect of heparin on selectins:

Heparin binds selectins

The binding is dependent upon percentage of fragments larger than 8kDa

Warious heparins bind selectins differently

Heparins with high proportion of fragments larger than 8kDa may affect blastocyst adhaesion by blocking selectin binding sites

/Stevenson, Choi, Varki 2005/

Effect of heparin on cadherins:

E-cadherin - important role in maintaining cell adhesion

In cancer cells,
reduction of E-cadherin expression promotes acquisition of invasive phenotype
Choriocarcinoma, hydatiform mole →
→lower E-cadherin trophoblastic expression than in normal first-trimester placenta
In placentas of patients with preeclampsia
-higher trophoblast E-cadherin expression /Xue et al., 2003, Li et al, 2003/

Different heparins have different effect on
trophoblast and decidual cadherin expression /Erden et al., 2006/

Various heparins could promote trophoblast cell differentiation and motility

Effect of heparin on **heparin-binding EGF-like growth factor**

-mitogen and chemoattractant for a number of different cell types
- high levels expression in the first trimester trophoblast
/Yoo, Barlow, Mardon 1997/
- promotes adhesion of the blastocyst to the uterine wall
/Raab and Klagsbrun, 1997/
-conversion of human cytotrophoblasts into invasive phenotype and the motility
/Leach et al.2005/
- prevent hypoxic induced apoptosis **/Armant et al.2006/**

LMWH
induce decidual expression and secretion of HB-EGF
in a dose-dependent manner
Heparin
- capable of activating the EGF receptor in primary villous trophoblast
/D Ippolitto et al., 2012/

Beneficial effect of heparin
in preventing placental mediated pregnancy complications

Effect of heparin on **matrix metalloproteinases (MMPs)**

-a group of matrix degrading enzymes

-MMP-2 and MMP-9 type IV collagenases involved in trophoblast invasion into endometrial tissue

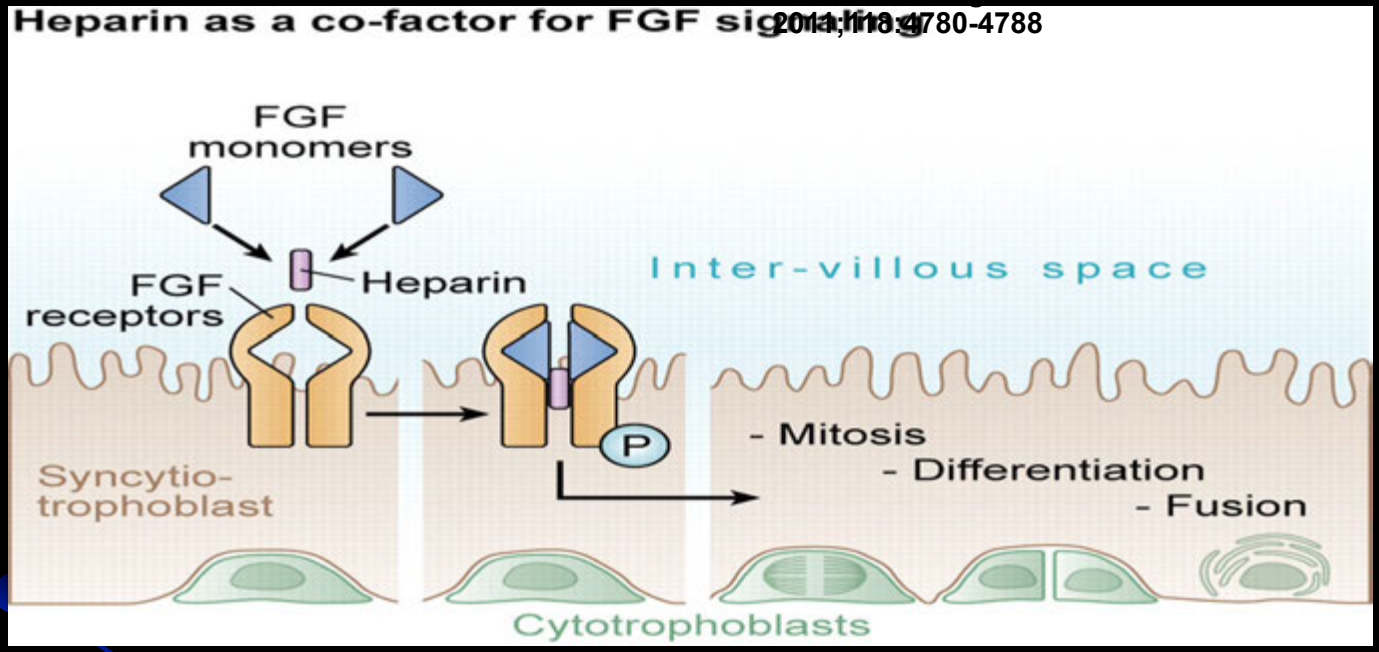
/Librach et.al., 1991/

Heparin

- effect MMP 2 and MMP 9 and their tissue inhibitors (TIMPs)

/Di Simone et al., 2007/

Successful placentation



Heparin facilitates dimerization of FGFs to enhance mitotic signaling. This action of heparin may reduce the risk of severe PE by promoting the production of cytotrophoblasts for syncytial fusion and maintenance of a healthy outer syncytiotrophoblast in contact with maternal blood.

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heparin - an impact on the immune system

- effect on the migration and adhesion of leukocytes during an inflammatory response /Stevenson, Choi and Varki 2005/
- Supression od complement activation pathway /Salmon JE et al. 2011/
- Supression of T cell adhaesion and migration /Christopherson TWII et al.2002/

Anti-inflammatory effects of heparin

- Negatively charged molecules, such as heparin, repulse the negatively charged leukocytes and prevent their adhesion to the endothelium
- Heparin-Mac1 *(MAC1-coordinates adhesive functions of leucocytes)* bond interferes with myeloid cell adhesion and transmigration
- Heparin - capable of binding PECAM1 (platelet/endothelial cell adhesion molecule 1)
- LMWH

- decrease expression of IL-1β and of IL-10 mRNA
  ⟹ down regulation of inflammatory cytokines production.
- imitates the function of Syndecan-1 *(wound repair, cell morphogenesis, mediating inflammatory responses aiding the clearance of pro-inflammatory chemokines* /Gotte, 2003/

Clinical usage of heparin in humans

- Clinical trials in patients suffering from rheumatoid arthritis and bronchial asthma /Gaffney and Gaffney, 1996/
- In nine out of ten patients with refractory ulcerative colitis treated with combined heparin and sulphasalazine - remission of disease /Gaffney and Gaffney, 1996/
- Subjective improvement of asthma /Fine, Shim and williams, 1968, Boyle, Smart and Shirley 1964/
- Reduced bronchoconstrictive responses in patients with exercise-induced asthma /Garigol Danta, Ahmed 1996, Ahmed et al 1993/

Clinical usage of heparin in obstetrics and reproductive medicine

- RIF
- RPL
- EI, IUGR, abruption, stillbirth

3000 $
per pregnancy!!!!!

SIDE effects
HIT I, HIT II

Anticoagulation or other effects?

The use of heparins in the prevention of RIF in IVF patients

RIF /Halbmayer et al., 2005/

- Antibodies against annexin V
- Resistance against protein C
- LAC
- ACA
- Anti beta 2-glycoprotein –I

Improved outcome with LMWH

The presence of aPL alone does not appear to adversely affect pregnancy rates or outcome in patients who are undergoing IVF
/Steinvil A et al., 2012/

The use of heparins in the prevention of RIF in IVF patients

- =>3 RIF, one trombophilia

Qublan H et al, 2008

	enoxaparin 40mg/day on ET N=42	placebo N=41
PR	20,9%	6,1%
LBR	23,8%	2,8%

p<0,00

- =>2 RIF, unexplained

Urman B et al, 2009

	LMWH	Nothing
PR	45,3	38,7
LBR	34,7	26,7

p =n.s.

Noci et al., 2011

First IVF-ET (N=172)
no trombophilia

→ dalteparin
PR 26%, LBR 21%

→ control
PR 20% LBR 16%

p= n.s.

The use of heparins in the prevention of RIF in IVF patients

Trombophilic patients
Sigg increased PR
only in women over 36 years, not in younger
/Lodigiani C et al., 2011/

- **No difference**

/Berker B et al., 2011/

2RCT and 1 quasi-RCT:
Although the use of LMW as an adjunct to IVF treatment significantly improved the life birth rate (79%) , extreme caution is needed……
Meta analysis by Potdar N et al., 2013/

Akhtar MA et al.Cochrane Database Syst.Rev. 2013, 2015

- **3 RCT – 386 women**
- Sigg improved LBR (odds 1,77)
- **But:** the results were dependant upon the choice of statistical method – no longer sigg. with more sophisticated tests….
- **And:** **high proportion of side effects that were increased with the duration of usage**
- **Conclusion:** "The results do not justify the use of heparin outside the well-conducted research trilas. Further evidence could focus on local and not systemic application

Effect of heparins on pregnancy success in women with RSA

Trombophilic women

- 90 - aspirin alone versus aspirin and UH – LBR: 42% and 71% /Rai H et al. 1997/

Cohort sudies

– sigg. improved outcome in retrospective studies / Brenner B et al., 2000/

- improved outcome, but without statistical sigg in prospective studies. / Carp H, Dolitzky M, Imbal A, 2003/.

Effect of heparins on pregnancy success in women with RSA /RCT- trombophilic RPF patients/

- 180 – randomized to 40 or 80 mg enoxaparine – no difference in outcome /Brenner B et al., 2005/
- 104 women randomized to enoxaparine or aspirin – similar LBR, similar BW, similar preterm delivery rate, similar Apgars

/Dolitzky M et al., 2006/

Same results: Larskin Ca et al 2009 (859 patients) and Farquarson RG et al. 2002 (119 patients)

ALIFE study – RSA irrespective of trombophilia /Kaandorp SP et al., 2010/

- 364 women randomized to aspirin and nadroparin, aspirin alone or placebo starting as soon as live pregnancy was diagnosed
- LBR 54,5% - 50,8% - 57,0%
- No sigg. difference in trombophilic patients

RSA- RCT irrespective of trombophilia /Visser et al., 2011/

- 207 women randomized to enoxaparine 40 mg + placebo, enoxaparine 40 mg + aspirin 100 mg or aspirin 100 mg alone

  - LBR : 71% - 65% - 61%

  - No difference in pregnancy complications, neonatal outcome or adverse effects

Effect of heparins on pregnancy success in women with RSA

- **Trombophilic women**
  - **Inherited** /Tan WK et al.2012/
    - Medline –PubMed and Cochrane databases 2000-2010
    - 3RCT studies

    → **No improvement in LBR**
  - **APS** /Wong LF, Porter TF, deJesus GR 2014/
    - 47 studies: 27 positive association, 7 no association,12 could not report association- no controls
    - 10 RCT – heterogenous inclusion criteria

    → **More convincing data are needed**

→ **At present no evidence of beneficial effect**

- **Nontrombophilic women**
  - 9 studies- only 1 placebo controlled – no effect /deJong PG et al., 2014/
  - Rdouble blind, placeboCT – 258 women – no increase in LBR /Pasquier E et al., 2015/
  - LMWH 85%:no LMWH 66% LBR /Yuksei H et al., 2014/
  - Multicenter RCT – 449 women LMFH does not increase PR or LBR / Schleussner E et al., 2015/

→ **LMWH Is not indicated**

Effect of LMWH in prevention of pregnancy complications — without trombophilia /Kupferminc M, et al 2011/

LMWH N=32	Without LMWH N=40
3,1% EI, abruption 6,25% IUGR 9,4% adverse outcome	20% EI, abruption 22,5% IUGR 60% adverse outcome

No difference in prior EI, IUGR,abruptio stillbirth

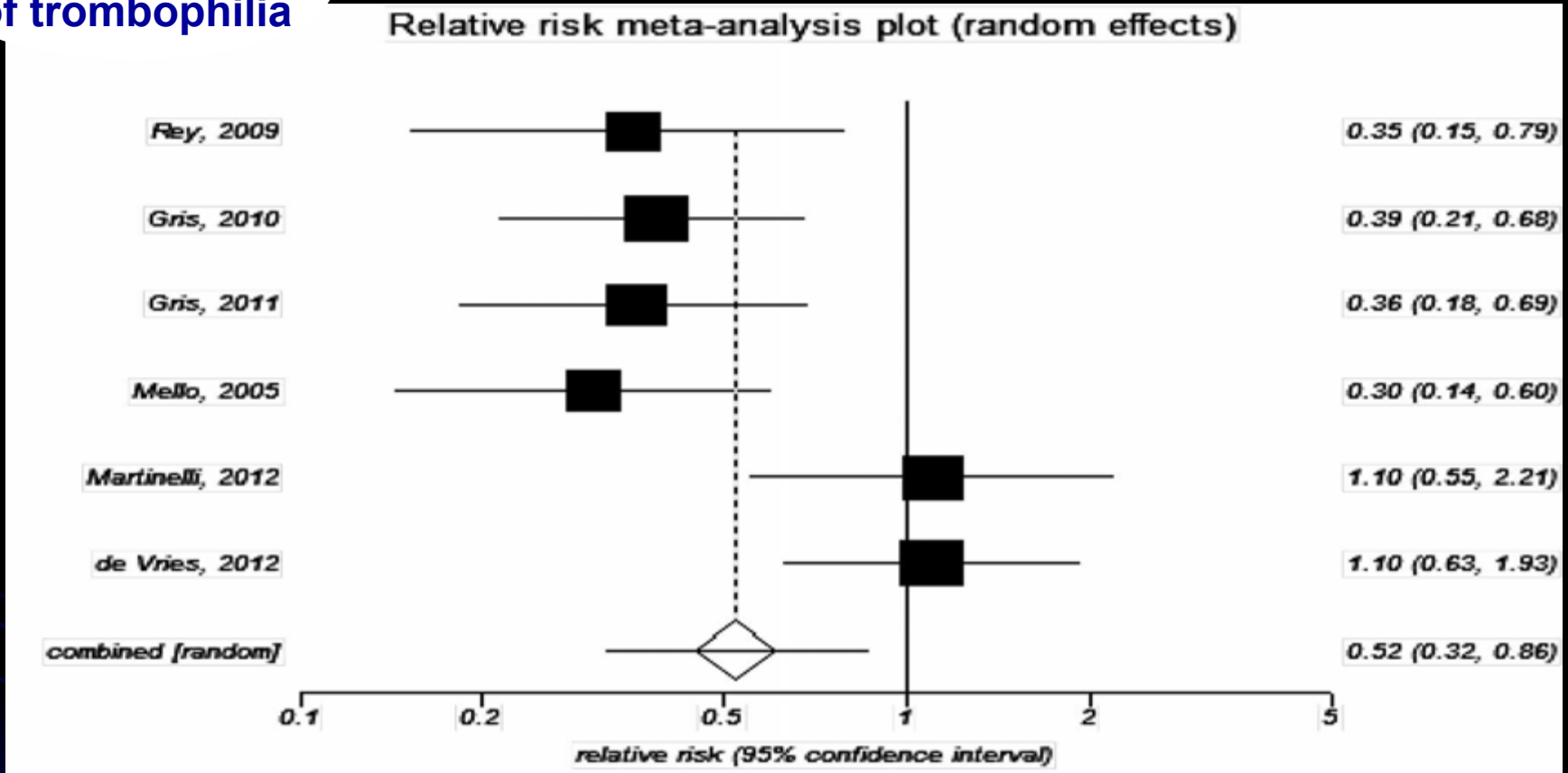
Sigg.dicreased EI,IUGR, abruption,stillbirth

P= 0,03-0,001

Same positive effect in trombophilic women
/Kupferminc M, et al 2011a/

Rodger MA er al., 2014

irrespective of trombophilia



(p=0.01).Heterogeneity I2= 69%

no effect in reducing early pregnancy loss!!!

Primary outcome analysis.
RR reduction of recurrent placenta-mediated pregnancy complications in women with prior placenta-mediated pregnancy complicationsoss

blood

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