

# THROMBOPHILIA IN PREGNANCY

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- ✖ One of the first treatments in RIF or RSA is using heparin. WHY?

- ✖ Heparan sulphate proteoglycans (HSPGs) are expressed throughout the reproductive tract and are involved in the regulation of endometrial cycling.



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- ✖ The primary biological activity of heparin is anticoagulation or the antithrombin effect, where heparin catalyzes the inhibition of factor Xa and thrombin.

# HEPARIN

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- ✖ modulates:
  - endometrial receptivity
  - decidualization of endometrial stromal cells and improves implantation.
  
- ✖ Increases:
  - production of prolactin
  - insulin-like growth factor (IGF-1)
  
- ✖ Inhibits:
  - production of insulin-like growth-factor-binding protein (IGFBP-1).
  
- ✖ These proteins plays an important role in endometrial development and receptivity during the 'implantation window'.

# ADDITIONALLY,

- ✗ heparin regulates heparin-binding epidermal growth factor (EGF), which is expressed maximally at the time of implantation, thus enhancing implantation, trophoblast invasion and promoting the early stages of embryo development.



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- ✖ It has been shown that LMWH can enhance invasiveness of extravillous trophoblast cells by inducing activity of specific metalloproteases (MMP).

# IN ANIMAL MODELS,

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- ✗ heparin has been demonstrated to act on adhesion molecules like the E-cadherin system to regulate implantation.



# IN *IN VITRO* MODELS,

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- ✖ Interestingly, heparin has been shown to reduce aberrant apoptosis in the trophoblasts and enhance cell survival.

# MOREOVER,

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- ✖ in the presence of APLS, apart from its antithrombin effect, LMWH prevents APA binding to the trophoblast cells
- ✖ Heparin has also been shown to block complement activation
- ✖ and modulates inflammatory responses in women with APA.

# IN IMPLANTATION

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- ✘ Thrombophilia may cause microthrombosis at the implantation site and thereby impairing the initial invasion of maternal vessels by the syncytiotrophoblast, leading to implantation failure.
- ✘ In these women, heparin treatment can potentially enhance the implantation process.



- ✘ However, observational and randomized controlled trials (RCTs) using heparin as an adjuvant to IVF treatment have shown conflicting evidence for improved fertility outcomes in women with thrombophilia with or without RIF.

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- ✖ Heparin has been shown to be effective in improving implantation rates (IRs) without the presence of thrombophilia.

# THROMBOPHILIA

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- ✖ Major
- ✖ Minor



# MAJOR THROMBOPHILIA

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- ✗ FVL mutation or decreased level of APCR
- ✗ Prothrombin (Factor II) mutation
- ✗ Antithrombin III deficiency
- ✗ Protein C deficiency
- ✗ Protein S deficiency
- ✗ Antiphospholipid Syndrom

# ANTIPHOSPHOLIPID SYNDROM

- × LAC
  - × ACA – IgG
  - × ACA – IgM
  - × Anti $\beta$ 2GP – IgG
  - × Anti $\beta$ 2GP – IgM
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- × In two tests in 8-12 weeks
  - × WHY TWO TESTS?

# MINOR THROMBOPHILIA

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- ✗ MTHFR C677T mutation
- ✗ MTHFR A1298C mutation
- ✗ PAI-1 mutation
- ✗  $\beta$  fibrinogen mutation
- ✗ FxIII mutation



# MTHFR C677T MUTATION

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✕ MTHFR C677T

✕ Wild type homozygote means CC

# MTHFR A1298C MUTATION

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✕ MTHFR A1298C

✕ Wild type homozygote means AA

# PAI-1 MUTATION

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✗ 4G/5G

✗ Wild type homozygote 5G/5G



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- ✖ Major thrombophilia in RIF and blighted ovum
  - ✖ Minor thrombophilia and RIF and blighted ovum

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## ✖ Thrombophilia and ovarian hyperstimulation syndrome

# 23 VENOUS THROMBOEMBOLISM AND ASSISTED REPRODUCTION

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- ✗ In some studies:
- ✗ The greatest risk of *in vitro fertilization-related VTE* was seen in the first trimester.
- ✗ There was no statistically significant increase in venous thromboembolic risk associated with *in vitro fertilization in the second or third trimester* or in the postpartum period.



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- ✖ Women conceiving with frozen embryos were not at increased risk of VTE, presumably due to less frequent or absent ovulation induction.
  - ✖ Although the majority of events were deep vein thrombosis, the risk of pulmonary embolism was similarly increased.

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- ✖ In other studies
  - ✖ venous thromboembolic risk was increased similarly during all 3 trimesters and, in multiple pregnancies only, during the postpartum period as well.

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- ✖ Is it necessary to evaluate thrombophilia in all women with one abortion or implantation failure?



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- ✗ Preeclampsia
  - ✗ PROM
  - ✗ Autoimmune diseases

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## ✖ Hydrops fetalis and major thrombophilia



