

THROMBOPHILIA IN PREGNANCY

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

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- ✘ 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

- ✘ 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,

- ✘ 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

- ✘ 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.

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- ✘ 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

- × Major
- × Minor

MAJOR THROMBOPHILIA

- ✘ 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 β 2GP – IgG
 - × Anti β 2GP – IgM
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- × In two tests in 8-12 weeks
 - × WHY TWO TESTS?

MINOR THROMBOPHILIA

- ✘ MTHFR C677T mutation
- ✘ MTHFR A1298C mutation
- ✘ PAI-1 mutation
- ✘ β fibrinogen mutation
- ✘ Factor XIII mutation

MTHFR C677T MUTATION

× MTHFR C677T

× Wild type homozygote means CC

MTHFR A1298C MUTATION

- × MTHFR A1298C
- × Wild type homozygote means AA

PAI-1 MUTATION

× 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

VENOUS THROMBOEMBOLISM AND ASSISTED REPRODUCTION²³

- ✘ 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

✘ Hydrops fetalis and major thrombophilia

