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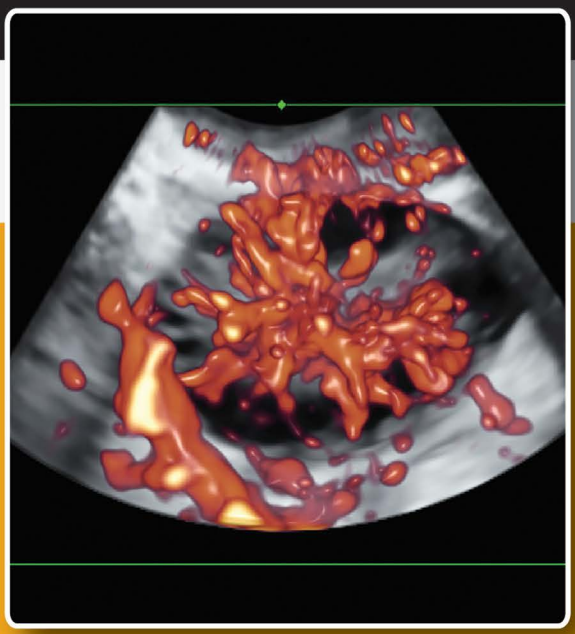
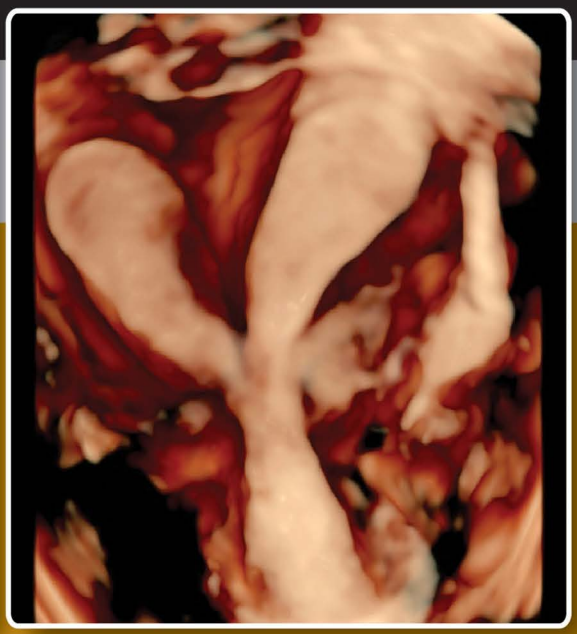
Practical Guide to Recurrent Pregnancy Loss





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Chapter 4

Thrombophilia

INTRODUCTION

In the nonpregnant state in hemostatic pathway, there is equilibrium between:

- *Procoagulant factors:* Factors V, VII, VIII, and fibrinogen
- *Anticoagulant factors:* Protein C, protein S, and antithrombin III
- *Fibrinolytic factors:* High plasminogen activator inhibitor (PAI) 1 and 2 genes.

These all are shifted in favor of a procoagulant state during pregnancy.

HEREDITARY/CONGENITAL

Thrombophilia can be classified as:

- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency.

These are less common but more thrombogenic types of thrombophilias.

- Others are more common but weak thrombogenic factors. These are endogenous inhibitors of coagulation.
- *Factor V Leiden (FVL) mutations/activated protein C resistance (APCR) (Northern Europe) (G1691A):* Common but is rare in Asians and Africans.
- Prothrombin G (20210A) mutations (Southern Europe).
- *Methylenetetrahydrofolate reductase (MTHFR) (C677T):* There is an increased level of procoagulant factor. The risk is higher when it causes two mutations, A1298C and C6777T loci in MTHFR.[1] However, screening is not recommended.
- *Antithrombin III deficiency:* It is an inhibitor of thrombin and prevents conversion of fibrinogen to fibrin. Antithrombin III has a thrombin-binding site and a heparin-binding site. The latter of the two has 100-fold higher antithrombin activity. As a large number of mutations are seen in antithrombin III gene, its deficiency can be assessed by functional clot-based assays such as thromboelastography. However, it is not recommended as a screening test.

What is thromboelastography?

Hemostasis is a dynamic process of interaction between prothrombotic and antithrombotic cellular and plasma components. Measurement of any single factor is therefore not useful, but the net result of the process must be studied. Elastography assesses the whole process and decides if it is in a hypo- or hypercoagulation state and thus provides dynamic information.

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- *Protein C deficiency:* Protein C is activated by thrombin to exert anticoagulant effects. It inactivates factors Va and VIII. Protein C deficiency can also be diagnosed by clot-based assay.
- *Protein S deficiency:* Protein S is a cofactor for protein C and is vitamin K dependent. It inactivates factors V and VII and requires a clot-based assay for diagnosis.
- *FVL mutations:* Substitution of glutamine from arginine at amino acid 506 in factor V protein abolishes the cleavage site for activated protein C and thus factor V is resistant to activated protein C. It is seen in 10–15% of people of Northern Europe origin. It is a single-point mutation. It has a weak thrombogenic potential but if it is a heterogeneous mutation, it is 3–8 more thrombogenic, and if homogeneous mutation, it is 80-fold more thrombogenic.
- *Hereditary factor XIII deficiency:* Autosomal recessive trait. Its concentration decreases to 50% in normal pregnancy and only 0.5–2% is required for normal hemostasis. This is important for implantation and attachment of placenta to uterus. Its deficiency adversely affects fibrin–fibronectin cross-linking. Recombinant factor XIII is available with a half-life of 10–12 days and is to be given in a dose of 20 IU/kg, once every 4 weeks.
- *Fibrinogen deficiency:* This may present as afibrinogenemia, hypofibrinogenemia, or dysfibrinogenemia. Normal fibrinogen level to maintain pregnancy is 60 mg/100 mL. Its half-life is 4 days, and its infusion in case of deficiency is given twice a week. It may lead to catastrophic thrombosis, and therefore heparin is advocated.

ACQUIRED THROMBOPHILIA

Hyperhomocysteinemia

Homocysteine is an intermediate by-product formed during metabolism of methionine. It generates H_2O_2 through its effect on endothelium and impairs endothelial cell thrombomodulation. Its modest elevation is described in association with the inherited polymorphism of MTHFR with vitamin B12 and folic acid deficiency. C to T mutations at nucleotide 677 in gene coding of MTHFR enzyme leaves only 30% of functionally active enzyme. This results in increased homocysteine levels and increases thrombogenicity by two- to three-fold.

Currently identified thrombophilias are less common in African and Asian populations. Meta-analysis from 31 studies found that thrombophilias are commonly associated with second- and third-trimester losses. Evidence says that thrombophilia predisposes patients to a high risk of both early and late pregnancy loss. However, reproductive performance is normal with thrombophilia in some patients. It is not possible to establish which patient with recurrent pregnancy loss (RPL) has increased risk of thrombophilia?

PATHOPHYSIOLOGY OF PREGNANCY LOSS IN THROMBOPHILIA

- Thrombosis in placental vessels in second and third trimesters causes fetal loss.
- Placental contact of spiral artery and placental intervillous space starts developing only after 8 weeks and therefore pregnancy loss before 10 weeks may not be related to hemostasis. Early pregnancy loss in patients with thrombophilia therefore cannot be explained.

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- Fetal thrombophilia can cause thrombosis in fetal vessels. Paternal thrombophilia can also cause fetal vessel thrombosis when the fetus is homozygous or there is a combined maternal and paternal defect. Genetic mutation, therefore, increases the risk of pregnancy loss in subsequent pregnancies.
- Only a minority of patients with thrombophilia experience RPL. It is usually a combination of genetic and acquired risk factors.
- However, several studies have found no correlation between thrombophilia and pregnancy loss. It causes venous thrombosis and not arterial.
- FVL deficiency is usually responsible for third-trimester loss. However, it is not recommended for screening.
- Prothrombin 20210A mutation may lead to late trimester but nonrecurrent fetal loss. It is not recommended for screening.
- Protein S deficiency also causes late-trimester fetal loss.
- MTHFR, protein C, and antithrombin III deficiency are not associated with fetal loss.

It has been shown in a meta-analysis by Rey et al.[2] that:

- Thrombophilia increases fetal loss.
- But not all thrombophilias are associated with fetal loss.
- First trimester losses are associated with FVL, protein C deficiency, and prothrombin mutation. These are not recommended in patients with RPL.
- Late-trimester losses are associated with FVL deficiency and prothrombin mutation.

TREATMENT

- *Prophylactic low-molecular-weight heparin (LMWH):* LMWH is safe and has minimal risk of allergic reaction. It has a high bioavailability and a long half-life with predictable therapeutic response. It is given at a dose of 40 mg daily. Rarely, it may cause thrombocytopenia or osteoporosis. But it is not useful in unexplained RPL.

  Low molecular weight heparin therapy should be monitored by:
  - The baseline assessment of platelets was repeated after 1 week and repeated every month during therapy.
  - Antifactor Xa levels are assessed for assessment of the drug response. But the results are not very consistent and thus are less suitable to follow.
  - Tissue factor pathway inhibitor (TFPI) can also be used for monitoring LMWH therapy.
  - If a patient requires regional anesthesia, the dose of LMWH is omitted for a day to prevent spinal hematoma.
- Aspirin is still an optional treatment. It is given at a dose of 100 g/day. However, majority of trials did not show a significant effect in unexplained RPL.
- Progesterone produces interleukin (IL)-4 cytotoxins and therefore Th2 responses.
- Human chorionic gonadotropin (hCG) helps in cytokine production of endometrium [tumor necrosis factor-alpha (TNF-α) and IL-4].

However, heparin is preferred in patients with pregnancy loss after 10 weeks. Most times, both heparin and aspirin are combined. Heparin also has an anti-inflammatory effect. Its

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anti-inflammatory effect is mediated by increase in serum TNF-α-binding protein. Heparin inhibits TNF-α production. It has a direct effect on trophoblasts and increases hCG production.

More research is required to find out why only a few women get pregnancy loss. There are some other factors that play role in coagulation, such as protein Z and vitamin K. These factors need further study. There are some more mutations that have been found to be responsible such as thrombomodulation gene, plasminogen activation gene, and factor V Cambridge mutation. These mutations also need further research to know their exact role.

CONCLUSION

- Thrombophilia increases the risk of pregnancy loss by three- to eight-fold.
- Screening for thrombophilia is done in patients with three or more first-trimester losses after 8 weeks or with two or more second-trimester losses or with past history or family history of RPL.
- Patients with unexplained stillbirth must also be screened.
- However, the patient should be counseled for the clinical uncertainty of the results and should be referred to a hematologist.

TAKE HOME MESSAGE

- Routine screening for FVL mutations and prothrombin mutations is not recommended by the American Society for Reproductive Medicine (ASRM) for patients with RPL.
- Hereditary thrombophilia is rare in Indian and African populations.
- No treatment has been found to be useful for hereditary thrombophilia.
- Investigation may be required for history of thrombosis.
- Heparin + aspirin has a doubtful role in thrombophilia.

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Practical Guide to Recurrent Pregnancy Loss

Recurrent pregnancy loss is a very frustrating condition for the patient and equally frustrating for the treating specialist. Though numerous causes have been discussed in literature for recurrent pregnancy loss and so many investigations have been suggested, there are very few cases in which specific treatment protocols can be applied though lots of empirical therapies are suggested. Failures are not uncommon even in treated cases and the counseling therefore is the difficult most task. This book *Practical Guide to Recurrent Pregnancy Loss* is a "to the point practice guide" to investigate, counsel and manage the patients with recurrent pregnancy loss.

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