



## **Thrombophilias**

Thrombophilias are inherited blood clotting disorders that predispose women to developing blood clots (thrombosis) in their veins. These genetic abnormalities are caused by gene mutations. They can also cause complications during a pregnancy. In pregnancy or when taking birth control pills, there is a tendency for increased blood clotting (hypercoagulable state). As a result, women with inherited thrombophilia are at increased risk of blood clots forming in the legs (deep venous thrombosis or DVT) which may travel to the lungs (pulmonary embolism) during pregnancy.

With thrombophilias, obstetrical complications such as miscarriages and stillbirths may be increased. Other conditions such as placental abruptions, toxemia and fetal growth restriction are also increased. Thrombophilias combined with other risk factors such as age over 35, smoking, surgery, obesity and immobilization greatly increase the possibility of thrombosis. All inherited thrombophilias do not have the same degree of risk for blood clots.

Thrombophilias may be acquired or inherited. The most common acquired thrombophilia is called antiphospholipid syndrome.

### **Antiphospholipid Syndrome (Acquired Thrombophilia)**

This syndrome may be responsible for recurrent pregnancy loss and thrombosis risk. It is an autoimmune condition where the body produces antibodies against proteins that bind to phospholipids. Patients who have these antibodies are at increased risk of blood clots in arteries and veins and also recurrent miscarriage. The two most common antibodies are called lupus anticoagulant and anticardiolipin antibodies. The reason the body develops these antibodies is unknown but can be seen in other autoimmune diseases such as systemic lupus.

In patients with recurrent miscarriage approximately 10-15% will have either cardiolipin antibody or lupus anticoagulant. Patients who have phospholipid antibodies have a low risk of developing a thrombosis, approximately 1% per year. However, with a pregnancy loss and a prior thrombosis, the risk of a new blood clot is approximately 30%. Lupus anticoagulant has also been associated with other obstetrical problems. Fetal growth restrictions with small placentas and early onset toxemia of pregnancy have been observed.

The treatment in pregnancy consists of anticoagulation using heparin or low molecular weight heparin and baby aspirin daily. The aspirin is used to prevent arterial thrombosis. These medications should be continued until 36 weeks.

## **Inherited Thrombophilias**

- I. Factor V Leiden mutation
- II. Prothrombin gene mutation
- III. MTHFR mutations
- IV. Protein C deficiency, Protein S deficiency, Antithrombin III deficiency

### **I. Factor V Leiden Mutation**

This is the most common inherited factor. It occurs in about 5% of the general population. If one of the two genes has a mutation (heterozygous) there is a 7-fold increase in developing a blood clot. If both genes have a mutation (homozygous), there is an 80 fold increase in thrombosis. However, most women who have the mutation will never develop a thrombosis. There is an increased incidence of intrauterine growth retardation and pregnancy induced hypertension in patients with Factor V Leiden Mutation.

### **II. Prothrombin (Factor II) Mutation**

The Prothrombin mutation is the second most common inherited thrombophilia factor. The mutation occurs in about 1-2% of the population. A heterozygous condition can increase the risk of thrombosis 3-5 fold. The homozygous condition is very rare, but will greatly increase the risk of deep vein thrombosis. This mutation can also increase the risk of premature heart attacks 4 fold. Patients with this mutation and diabetes, hypertension and increased cholesterol can have 40-fold increase in heart attacks.

### **III. MTHFR Mutations**

MTHFR is an enzyme that is important in homocysteine metabolism. If a mutation occurs, homocysteine levels in the blood may increase. Increased homocysteine levels may increase the risks of coronary heart disease, arteriosclerosis, blood clots, neural tube defects and recurrent pregnancy loss. Patients with normal homocysteine levels have little risk.

Any mutation in MTHFR can cause a doubling of the risk for neural tube defects (open spine) in a fetus. To prevent this from occurring folic acid supplementation is suggested. Elevated homocysteine levels should also be suppressed with folic acid. If there is a history of a deep vein thrombosis (DVT), anticoagulation is recommended during pregnancy.

There are two mutations that occur in MTHFR. The major mutation is at the C677T site. Heterozygous mutation occurs in 40-45% of the population. Homozygous mutations are much less common. It results in increased blood homocysteine levels in 5-10% of patients. A minor mutation can also occur at the A 1298C site of the gene. About 30% of the population has this mutation. This mutation does not result in increased homocysteine levels. However, a mutation at this site if combined with a heterozygous mutation at the C677T site may result in elevated levels of homocysteine.

#### **IV. Protein S, Protein C and Antithrombin III**

These three proteins are natural anticoagulants circulating in blood. Deficiencies can lead to increased blood clotting. Mutations of the genes responsible for these factors are rare but can result in a significant risk of thrombosis during pregnancy. Some studies have demonstrated that 50-70% of patients with Antithrombin III deficiency develop DVT's during pregnancy or the post partum period.

#### **Who should be screened for thrombophilia?**

- Personal history of a DVT or pulmonary embolism
- Family history of DVT or pulmonary embolism
- Recurrent pregnancy loss
- Recurrent stillbirth
- Prior placental abruption
- Prior pre-eclampsia (toxemia of pregnancy) before 36 weeks gestation
- Prior intrauterine growth restriction

#### **Treatment of Inherited Thrombophilia**

Treatment depends on the type of thrombophilia and prior thrombosis history. Prior pregnancy outcome is also very important in the decision to treat or not treat. The most common treatment if needed is low molecular weight heparin (Lovanox, Arixtra) given subcutaneously everyday. Although more expensive than Heparin, Lovanox is longer acting and causes less osteoporosis and less thrombocytopenia (low platelet counts).