Kofinas Perinatal

Providing Care to the Unborn ®

Alexander D. Kofinas, MD
Director, Kofinas Perinatal
Associate Professor, Clinical Obstetrics and Gynecology
Cornell University, College of Medicine

Thrombophilia: patient information

What you need to know about the condition and how it may affect your pregnancy and your future health (after your pregnancy is over).

Thrombophilia is a condition that makes the patients who suffer from it to have an increased tendency to clot within their own vessels. Normally the blood flows throughout the vascular system without clotting. When a vessel has broken down (injury) and bleeding commences, the clotting mechanism of a normal person is forming a plug in order to stop the bleeding. This plug is the result of a very complex coagulation mechanism, which requires a significant coordination of many different proteins, antibodies and other chemicals produced within the human tissues.

In patients with Thrombophilia, the clotting may take place without any break down of the normal barriers (vessel wall). In such a case the clot will form within the vessel and thus block the vessel. Thrombophilia is exactly the opposite of **hemophilia**, in which case the patient has a tendency to bleed excessively. **Thrombophilia (thrombos=clot and philia=friendship)** should not be confused also with **thrombocytopenia** where people may bruise very easily because their platelets are either too few or the platelets are not functioning properly. There are two types of thrombophilia:

1) **Inherited Thrombophilia:** in which case the person inherits some gene from one or both parents and this gene produces defective coagulation proteins that affect the ability of the person to coagulate properly.

2) **Acquired Thrombophilia:**

   a) a disturbance of the immune system, which produces antibodies against molecules (chemicals) that are important in the coagulation mechanism and thus the antibodies interfere with proper coagulation that leads to Thrombophilia.
   b) disturbances of various coagulation factors that happen in response to pregnancy or other conditions (infection, decreased mobility, dehydration etc.)

During pregnancy the development of the fetus depends on the placenta. The human placenta is of the hemochorial type, which means that the baby's blood is protected within his own vessels and the vessels are literally bathed in maternal blood, which comes out of the maternal vessels at the base of the placenta (intervillous space). Oxygen and nutrients are extracted

from the maternal circulation and are transferred to the fetal circulation. Fetal metabolic waste is transferred to the maternal circulation for disposal. The process of developing the placenta is a very delicate and extremely complex one. The placental cells (trophoblastic cells) invade the uterine endothelium (lining) in order to get access to maternal blood vessels. In the process, they perforate the maternal vessel wall. Subsequently, these trophoblastic cells destroy muscle cells from the vascular wall of the maternal vessels. This is done in an effort to completely paralyze the vessels and make them unable to constrict therefore to secure abundant and continuous blood flow towards the baby's placental circulation. This process is very delicate and it is achieved while maternal blood continuously flows through these vessels. The process of opening the hole into the maternal circulation and at the same time keeping the vessel from bleeding is very complex and it depends on a perfectly balanced coagulation mechanism. This is where difficulties start with patients who have Thrombophilia. The process of the placental development is affected negatively by the inability of these patients to maintain the blood flowing properly and when the blood clots, the development of the placenta does not proceed normally with various consequences.

The placenta is the single most important organ in the human existence. Without the placenta there is no pregnancy and without a good placenta there is no healthy baby. Because of the importance of this organ, nature has provided the means to develop 100% excess capacity during placental development. In other words, in the normal pregnancy there is twice as much placental functionality and capacity. This extra capacity helps the fetus grow and realize its full genetic potential. In addition, such excess placental functionality helps the fetus withstand the stress of labor. In cases where this additional capacity is not developed, because of placental damage (degeneration) from thrombosis (clotting) or any other reason, then the baby might be affected depending on the level of damage and the degree of placental dysfunction.

The placenta develops completely by the end of the first half of the pregnancy (about 24-26 weeks) as far as maternal vascular supply is concerned. There are two stages in the development of the placenta; the first one is complete by twelve to fourteen weeks and the second one by twenty-six weeks. In that time period there is a lot more placenta available to the baby since the baby only grows by 1/3 of its final size in the first twenty-eight weeks. Therefore, the placenta must be built to capacity at twenty-six weeks and then continue to supply a growing baby with ever increasing demands up to forty weeks. Any damage that happens early in pregnancy could be magnified if that damage is not repaired; such damage eventually leads to a significant impairment in the function and the quality of the placenta towards the last ten weeks of the pregnancy. This can be dangerous to the baby since the baby's needs increase significantly during this period.

In patients with Thrombophilia, damage of the placenta happens mostly because of blood clot formation into the maternal as well as the fetal vessels. In addition, because the maternal blood comes out of the maternal vessels and flows very slowly between the branches of the fetal vessels (intervillous space), maternal blood is vulnerable to clot formation. If maternal blood clots in this space, then the fetal vessels will be destroyed because there will not be

enough nutrients and oxygen for them. That leads to placental degeneration and fetal vessel damage. Impaired placental development has been associated with the following conditions:

1) Failure of the embryo to attach to the uterine lining (implantation).
2) Miscarriages
3) Growth failure of the fetus because of insufficient placental growth.
4) Hypertensive disorders of the pregnancy (Preeclampsia/Toxemia).
5) Decreased amniotic fluid volume (Oligohydramnios).
6) Partial or complete separation of the placenta (Abruptio placentae).
7) Silent premature cervical changes that may lead to premature delivery.
8) Pre-term labor and delivery.
9) "Unexplained" intrauterine fetal demise (death).
10) Severe fetal deprivation of oxygen, which may lead to variable degrees of mental problems including cerebral palsy.
11) Finally, clots may form within the maternal veins and that can lead to thrombophlebitis or deep vein thrombosis, which can be dangerous for the mother. However, this last one is less frequent and it is more likely to happen in patients with specific coagulation problems. Most of the time, we are concerned with the effects to the placenta and the baby.

Although the precise risk of abnormal pregnancy outcomes (obstetrical complications) in patients with thrombophilia is not known, it is significantly higher to warrant close pregnancy monitoring and treatment. We know from several studies that examination of patients with abnormal pregnancy outcomes and complications involving both the mother and the baby reveals a very high incidence of various types of thrombophilias as shown below.

Incidence of Inherited Thrombophilia in Women with Obstetrical Complications

Pre-Eclampsia	**53%**
Abruptio Placenta	**60%**
Growth Retardation	**50%**
Stillborn Babies	**42%**

Incidence of all types of Thrombophilia (Inherited and Acquired) in Women with Obstetrical Complications

Pre-Eclampsia	**68%**
Abruptio Placentae	**70%**
Growth Retardation	**61%**
Stillborn Babies	**58%**

The above figures are very significant and one should not forget the associated morbidity on babies that survive in a hostile placental environment with diminished nutrient and oxygen supply.

The good news however is that most of the above complications if not all, can be eliminated if patients are treated and the pregnancy is monitored properly.

Diagnosis of Thrombophilias

Thrombophilia is diagnosed by measuring the following parameters. However, although all of the following conditions may not pertain to thrombophilia directly, when it comes to pregnancy and placental development, they are all important because either directly or indirectly affect placental growth and quality.

Genetic thrombophilias

- Factor V Leiden Gene Polymorphism (Heterozygous or Homozygous)
- Homocystinemia
- MTHFR Gene Polymorphism (Heterozygous, Homozygous or compound heterozygous)
- Prothrombin (Factor II) Gene Polymorphism 20210 (Heterozygous or Homozygous)
- 4G/5G Gene Polymorphism (Heterozygous or Homozygous)
- ACE (angiotensin converting enzyme) gene mutation (Heterozygous or homozygous)
- Protein C deficiency
- Protein S Deficiency
- Protein Z deficiency
- Activated Protein C (APC) resistance (Related or unrelated to Factor V)
- Anti-Thrombin III deficiency
- Elevated Plasminogen Activator Inhibitor type 1 (PAI-1) {causes hypo-fibrinolysis and inhibits placental growth}
- Elevated Lipoprotein (a) (highly thrombogenic, associated with poor pregnancy outcomes)
- Hyper-fibrinogenemia (excessive fibrinogen-the glue that forms the clot)
- Elevated Factor XII
- Elevated Factor VIII
- Elevated Factor IX
- Elevated Factor XI
- Elevated D-dimer –Elevated thrombin-anti-thrombin complex (TAT) and PTF (1,2)

Acquired Thrombophilias (autoimmune disorders)

- Beta2- Glycoprotein antibodies
- Extractable nuclear antibodies (Anti-RNP / anti-SM)
- Anti-cardiolipin Antibodies
- Anti-phosphatidylserine antibodies
- Anti-phosphatidylinositol antibodies
- Alpha-2-antiplasmin (strong thrombogenic molecule due to hypofibrinolysis)
- Anti-Annexin-V antibodies (Annexin is a natural anticoagulant at the maternal fetal interphase in the placenta; antibodies against it cause poor placental development and fibrin deposition on the chorionic villi surface.
- Anti-prothrombin antibodies (have increasing clotting effect)
- Anti-platelet antibodies (Glycoprotein / indirect)
- DS-Antinuclear antibodies
- Anti-nuclear antibodies (ANA): elevated titers increase the risk for recurrent pregnancy loss.
- Lupus Anticoagulant (a serious thrombogenic factor)
- Anti-thyroid antibodies
- Elevated natural killer cells (NK cells) or increased activity

The above are some of laboratory measurements provided by commercial laboratories contracted by the various insurance plans. The test results take one to three weeks.

Many physicians may not be familiar with these problems. It is very common for patients to be told that these problems do not happen frequently and that subsequent pregnancies will be fine. ***There can be nothing further from the truth.*** These are recurrent problems and many patients we have seen have lost, more than three or sometimes more than ten babies, while they were told that the next pregnancy would be fine. No matter how devastating a pregnancy can become from such a condition, proper early diagnosis accompanied by proper treatment and continuous close follow-up during the pregnancy can assure, to the extent possible not only a viable pregnancy but a healthy pregnancy too.

Therefore, at Kofinas Perinatal we exert a very intense scrutiny of all patients prior to conception as well as during the early stages of pregnancy. It is not unusual to have a patient who tests negative before the conception and once the baby starts developing, the immune system starts producing antibodies against the placenta that could destroy the placenta in a way that would not be suspected by clinical means. We monitor our patients very closely from the time before the baby is even visible. We evaluate the very early stages of placental development by monitoring the quality of the placental tissue with high-resolution ultrasonography as well as by evaluating the development of new vessels under the placental area. These are crucial and very important measures for the quality assessment of the developing placenta. Any lesions that are noted in early pregnancy, even in the absence of

positive tests, are treated aggressively to assure proper placental development and thus assure proper fetal development in the weeks to come until the end of the pregnancy.

It is worthwhile mentioning here that the tests that we can measure represent only a small fraction of the things that can go wrong with the placental development. A few years ago, we could only measure one or two of these tests. Now we can measure more than 25. However, we also know that there are numerous proteins involved in the normal formation of the placenta and we do not know yet how to measure them. Therefore, placental damage in the absence of positive testing is treated at Kofinas Perinatal, as if there is some unknown antibody damaging the placenta, which is usually the case. A few years ago, we were treating patients with placental damage likewise without having any positive tests because there were very few tests available then. Today, we know that most of these patients have had specific problems that are measurable with today's capabilities. For this reason, we are going forward by treating patients with documented placental damage even in the absence of abnormal blood testing.

Treatment of thrombophilia

The treatment consists of one or more of the following individually or in various combinations:

1. 81 mg Aspirin (one baby aspirin) per day and if needed,
2. Heparin or Lovenox (Lovenox is more expensive but is preferable due to fewer complications and safer usage overall). Some insurance plans do not cover the use of Lovenox. In such cases we may use Heparin instead.
    a. If Heparin is used, the dosage is usually 5,000 IU to 10,000 IU subcutaneously twice a day
    b. If Lovenox is used, the dosage is usually 40 mg subcutaneously once a day. In patients with decreased bioavailability twice a day dosing is used.
    c. The dosage of the above two injectable medications may be adjusted according to the results of the monitoring of the various blood tests, and the response of the placenta.
3. In rare occasions in patients with acquired thrombophilia, we may use Prednisone orally in addition to Heparin/Lovenox.

The treatment of inherited thrombophilia requires inhibition of the clotting mechanism (anticoagulation therapy). The treatment of acquired thrombophilia may require Prednisone in addition to the anticoagulation therapy in order to inhibit antibody production by immune system suppression. The intent of the treatment is to normalize the patient's clotting mechanism. Rarely, some patients may be more sensitive to the treatment and present with bleeding complications.

We try to avoid such complications by careful monitoring of the patient's response to the prescribed treatment.

We perform this monitoring with measurements of the anti-Xa factor activity in the patient's blood. In addition, we monitor the patient's platelets since platelets may drop

during treatment with Heparin or Lovenox. Our treatment aims at getting the anti-Xa value between 0.2 and 0.5 assuming that the placenta grows normally. In rare occasions and when the placenta does not respond well to the treatment we may increase the dosage to achieve a level higher than 0.5. We adjust medication administration in order to maximize the benefit with minimal risk to the mother.

All patients have a baseline assessment with a complete blood count (CBC) with platelets and a baseline PT/PTT to rule out the possibility of any pre-existing bleeding disorder that might have been masked by the pregnancy.

Treatment Related Complications

The complications that can result from treatment with Heparin or Lovenox are the following:

1. Excessive bleeding. Heparin has anticoagulant activities due to its effect on the platelets **but Lovenox does not**. Lovenox exhibits mostly anti-thrombotic and minimal anti-coagulant activity. Therefore, Lovenox is less likely to cause excessive bleeding.) In contrast, aspirin is more likely to do so due to its effect on the platelets. Therefore, if you plan any kind of surgery or dental work that may cause bleeding, you need to stop the aspirin 4-5 days prior to scheduled surgery. Lovenox needs only 12-24 hours to be eliminated prior to any surgery.
2. Osteopenia (loss of calcium from maternal bones), and in rare occasions osteoporosis. However, this happens only to patients who take Heparin. *Lovenox does not have the same effect on maternal bones.*
3. Thrombocytopenia (significant decline in the number of maternal platelets). Again, this is mostly the function of Heparin and not Lovenox. In fact, in more than 9,000 patients under our care, we have never experienced Lovenox induced thrombocytopenia. A small number of pregnant patients experience pregnancy induced mild thrombocytopenia. However, the platelet count never drops below 90,000 in such cases; this does not cause any problem and does not require treatment of any kind.

The incidence of bleeding with prophylactic use of Heparin and Lovenox (this is the usual treatment we employ on patients at risk for pregnancy complications because of Thrombophilia) is very small. ***However, the risk of bleeding with Lovenox is less than with Heparin.*** Low-molecular-weight heparins (Lovenox) cause less bleeding than unfractionated heparin (Heparin) in laboratory animals, for several reasons. First, Lovenox inhibits platelet function less than unfractionated heparin because it binds less to platelets. Second, unlike unfractionated heparin, fractionated low-molecular-weight heparins (Lovenox, Fragmin, etc.) do not increase microvascular permeability. Third, Lovenox has **lower affinity** for endothelial cells (the inner lining of the vessels), high molecular forms of von Willebrand factor, and platelets, and as such it is less likely to interfere with the interaction between platelets and endothelial cells in the vessel walls. This lesser interaction with platelets and the vessel walls reduces the bleeding complications unlike Heparin.

To date, we have treated more than 10,000 patients and no patient treated according to the above protocol has experienced excessive bleeding as a result of this treatment. When patients follow our protocol instructions, the chance of bleeding is very-very small. Most patients who bleed, do so because of placental problems secondary to thrombophilia and without treatment, such patients usually loose their babies. Aspirin increases the patient's bleeding time. What this means is that if a patient experiences a cut, she will need to apply pressure for a minute or two instead of ½ a minute. Such kind of bleeding would never compromise the patient's health. Because we schedule the delivery of our babies at about 39 weeks, we always stop the Lovenox and Aspirin in time so when patients have their babies, they are free of any bleeding complications.

In respect to Thrombocytopenia, we monitor platelet counts periodically every 4 weeks and more frequently if indicated.

For the Osteopenia, there is no need for monitoring. However, we recommend to our patients to receive 1 to 1 ½ gram of calcium per day in order to replace the calcium taken by the baby for the formation of his/her bones. During the course of the normal pregnancy and if the mother does not take supplemental calcium, she is likely to loose 5% of her bone mass that may never be replaced. Osteopenia may be exaggerated in patients who are on prolonged usage of Heparin in addition to bed rest.

There is no evidence that Lovenox causes any defects to fetuses in addition to the natural (spontaneous) defects, and this certainly makes sense since Lovenox like Heparin does not cross the placenta. At Kofinas Perinatal over the last 15 years of use of these medications, the incidence of congenital defects has been the same or less than the incidence of the general population

Lovenox is known to be safer than Heparin regarding the Osteopenia and the Thrombocytopenia side effects. Never the less, recent studies have shown that even Lovenox may affect the function of bone osteoblasts (cells that are responsible for new bone formation) and thus we recommend calcium supplementation even in patients who take Lovenox.

Both Heparin and Lovenox have been extensively studied and it is known that they do not cross the placenta. Therefore, there is no effect on the baby's coagulation system or any other effect. All normal patients have a risk as high as 6%-8% to have a baby with some kind of congenital defect and a risk of 4% to have some major defects. One poorly documented study has mistakenly reported that patients treated with Lovenox have babies with congenital defects. In this report, patients receiving Lovenox were found to have the same number of congenital defects as patients who did not receive Lovenox. Subsequent studies and our own experience with more than nine thousand patients have revealed that Lovenox is as safe as Heparin since it does not cross the placenta. The incidence of congenital abnormalities in our patients happens to be less than the average American population because all of our patients are taking supplemental Folic Acid and prenatal vitamins prior to conception.

Breast-feeding in patients receiving Aspirin, Heparin and/or Lovenox.
Aspirin and other salicylates are transferred into breast milk. A milk: plasma ratio of less than 1.0 was found from the available studies involving salicylates, suggesting that only a small fraction (4 to 8%) of a single maternal dose would be ingested by a suckling infant. This translates to a total daily exposure of 3-6 mg of aspirin getting into the milk. This amount can be further reduced if the mother takes the aspirin immediately after the breast-feeding.
Heparin is known **NOT** to cross the breast barrier and it is not excreted in the milk. Lovenox however, is excreted in breast milk in small quantities ($1/20^{th}$ of the maternal level) but according to a French study breast-feeding in patients receiving Lovenox is safe ***(Arch Pediatr. 1996 May; 3(5): 513-4).*** This makes sense since Lovenox is a protein and if the baby ingests it by mouth, it will digest it and there will be no effect on the baby. This is the reason you have to take Lovenox by injection and not in a pill form.

After Delivery
After the pregnancy is over we prefer to test patients 3-6 months post-delivery for certain of the tests that may be affected by the pregnancy and normalize afterwards. These tests include:

1. Protein S, Protein C and anti-thrombin III deficiencies.
2. PAI-1
3. Acquired components of thrombophilia
4. Some of the heritable mild coagulation defects.

Genetic thrombophilias caused by gene polymorphisms are present for life and there is no need for further repeat testing after pregnancy. If the abnormal non-genetic factors remain abnormal three to six months after the time of delivery, then the patient's future health will be at risk for certain complications related to vascular problems. In fact, a recent population study involving more than a hundred thousand female subjects revealed that women with pregnancy related complications such as pregnancy loss, fetal death, preeclampsia, abruptio placentae, preterm delivery and fetal growth failure (IUGR) have a 2-15-fold risk for death from ischaemic heart disease after menopause. ***{Lancet 2001;357:2002-06}***

Below is a list of thrombophilia related conditions that may affect patients especially after menopause. In addition, some of the thrombophilic factors have been found to be associated with certain cancers as listed below but the precise nature of the association is not yet clear.

1. Coronary artery disease (heart attack and related heart problems)
2. Increased risk for cerebral vascular accidents (strokes)
3. Increased risk for Deep Vein thrombosis (DVT). This is a condition where a clot forms in one of your major veins of the either leg. This clot may be dislodged and then go into your lungs with serious complications, including death.
4. Some of the genetic thrombophilias may be markers for other diseases (associated with other condition but not necessarily causing them). MTHFR gene mutation is associated with deficient conversion of Folic acid to its active metabolic equivalent. This causes the creation of defective (mutated) DNA in many new cells. Such mutated DNA may lead to cancerous transformation and thus cause cancer over the individual's lifespan. Due to

the above problems, MTHFR gene mutation has been associated with the following conditions:

a. Increased risk for Down syndrome
b. Increased risk for Cancer
    i. Lung
    ii. Ovarian
    iii. Colon
    iv. Breast
    v. Other cancers
c. For the above reasons, we recommend to patients who have MTHFR gene polymorphisms to take a formulation of active vitamin metabolites in the form of a daily pill (Metanx) for life. Folic acid supplementation has been found to reduce the incidence of stroke by 40% and it may even reduce it more in individuals with MTHFR gene mutations.

5. Some of the acquired thrombophilias may be associated with certain autoimmune conditions such as thyroid problems, kidney problems, and hypertensive disorders.
6. Finally, the 4G/5G gene mutation causes insulin insensitivity and this predisposes to the development of diabetes later in life. Such patients should be cautious about their weight and diet and have annual blood sugar checks. A test that is very helpful in such patients is the glycosylated hemoglobin. (HbA1c). Done once annually can be an excellent indicator of your average blood sugar level. This should be less than 6% and the lower the longer your life will extend.

The family history of patients with placental thrombosis is usually strongly positive for thromboembolic episodes (stroke, heart attack, deep vein thrombosis, etc.). This applies to both parents of the unborn since many times the fetus suffers from thrombophilia that was inherited from the father. **At Kofinas Perinatal we recommend that siblings and parents of our patients be tested for the specific genetic types of thrombophilia according to the type of gene mutations present.** *Due to the fact that many insurance plans may not pay the laboratory expenses for the fathers and siblings, it is your responsibility to request from us if you wish to have such testing done so we can provide you with appropriate requisition forms for the appropriate laboratory. Kofinas Perinatal will not be responsible for any laboratory expenses you or your family may incur from paternal and sibling testing.*

The goodness of knowing about the above potential risks is that one may be able to prevent most of their complications with proper medical preventive care and mostly by eliminating conditions that are known to aggravate the above problems. A healthy life style is very important in minimizing the risks from thrombophilia complications. Healthy diet, smoke avoidance, proper body weight and moderate consistent exercise are essential. Avoiding stress of all kinds is very important also since stress is known to cause chronic inflammation which in turn is one of the leading mechanisms of thrombosis.

Patients with the genetic types of thrombophilia that pose increased risk for vascular complications (stroke, heart attack, and deep vein thrombosis) are referred to a hematologist or cardiologist for appropriate life-long follow up.
We hope you found this document helpful for your understanding of the risks of thrombophilia. If you have any questions in addition to the above or need to discuss the content of this document further feel free to ask Dr. Kofinas during one of your visits.

For more information on the causes of thrombophilia please visit the link below:
http://www.kofinasperinatal.org/files//dmfile/ThrombophiliaLabsInterpretationVer1.03.pdf