



(REVIEW ARTICLE)



## Acquired thrombophilia and fetal factors associated with recurrent pregnancy loss

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GSC Advanced Research and Reviews, 2022, 10(01), 177-181

Publication history: Received on 25 December 2021; revised on 31 January 2022; accepted on 02 February 2022

Article DOI: <https://doi.org/10.30574/gscarr.2022.10.1.0041>

### Abstract

Recurrent pregnancy loss is the most common complication of pregnancy, is the spontaneous loss of a pregnancy before the fetus has reached viability. Improvement of pregnancy outcome is considered as an important area of action for those concerned with the improvement of women's health and pregnancy outcome. Several studies identified thrombophilia as the principal cause of recurrent pregnancy loss. However, reported studies often do not evaluate other causes of miscarriages in their inclusion and exclusion criteria. So, the aim of this review is to investigate the role of acquired thrombophilia and fetal factors and their role in recurrent pregnancy loss.

**Keywords:** Recurrent Pregnancy Loss; Acquired Thrombophilia; Fetal Factors

### 1. Acquired thrombophilia

Recurrent Spontaneous abortion is defined as consecutive pregnancy loss before 20 weeks gestation or fetal weight of 500 g or less [1]. Acquired thrombophilia are hypercoagulable states secondary to various etiologies. During pregnancy the risks are exaggerated due to the underlying physiological changes. The most common acquired thrombophilia associated with RM is the antiphospholipid syndrome (APS) [2].

#### 1.1. Acquired hyperhomocysteinemia

Hyperhomocysteinemia has been underlined as an emerging risk factor for several diseases such as arterial and/or venous thrombosis. Hyperhomocysteinemia may be acquired secondary to dietary and lifestyle factors such as a reduced intake of folate, vitamin B6 or vitamin B12, excessive caffeine consumption and excessive coffee intake. The acquired form of hyperhomocysteinemia may also result from certain medical conditions such as hypothyroidism or renal impairment. Inherited and acquired conditions have been involved to explain pathophysiology as gene polymorphism. The Homocysteine Lowering Trial Collaboration [3]. Has suggested that endothelial dysfunction, alteration of platelet reactivity and disruption of prostacyclin pathways, may be some of the mechanisms responsible for the reported venous thrombosis risk as well as the theoretical risk of pregnancy loss. A meta-analysis of ten studies concluded that acquired Hyperhomocysteinemia is a risk factor for recurrent pregnancy loss [4].

#### 1.2. Acquired activated protein C resistance

APCR is the most prevalent risk factor for thrombosis. The presence of the factor V Leiden mutation produces a protein that is intrinsically resistant to activated protein C, causing the pathological phenotype. The pathophysiology underlying APCR not caused by the FVL mutation is still not completely understood. In different studies, it has been suggested that acquired factors might be the cause of APCR in the absence of FV Leiden.

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A number of coagulation factors can affect the activated partial thromboplastin time (aPTT). Previous literature suggested a possible positive correlation between levels of factors V, VIII and IX and acquired APCR. Protein S and protein C, levels can (or may) affect acquired APCR. [5].

### 1.3. Antiphospholipid syndromes

Antiphospholipid syndrome is the most important treatable cause of recurrent miscarriage. Anti-phospholipid antibodies are a family of about 20 antibodies that are directed against phospholipid binding plasma proteins. Evidence for pregnancy loss having a thrombotic basis is based mostly in the association between anti-phospholipid (aPL) antibodies and RPL [6].

They include lupus anticoagulant and anti-cardiolipin antibodies. Antiphospholipid syndrome was originally defined as the association between antiphospholipid antibodies and recurrent miscarriage, thrombosis, or thrombocytopenia, anti-phospholipid antibody syndrome is characterized by the presence of aPL, anti-lupus coagulant, anti-cardiolipin, and/or anti-beta-2-glycoprotein I antibodies that bind to negatively charged phospholipids on the membranes of endothelial cells, monocytes, and platelets [7].

### 1.4. Disseminated intravascular coagulation (DIC)

Disseminated intravascular coagulation is a pathological disruption of hemostasis characterized by a systemic activation of coagulation leading to widespread fibrin deposition (stage I), subsequent depletion of platelets and coagulation factors that culminates in severe bleeding (stage III) [8]. The most commonly described obstetric causes of DIC include amniotic fluid embolism, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, pre-eclampsia/eclampsia, placental abruption, and septic abortion. The pathophysiological mechanisms that lead to DIC are unknown, but in many cases placental insufficiency and utero-placental hypo-perfusion are thought to play a causal role. The classical findings associated with DIC include prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), low platelet counts, elevated products of fibrin breakdown (e.g. D-dimer), and low plasma levels of coagulation inhibitors (ATIII) [9,10].

Although these features together with clinical evidence of simultaneous bleeding and micro thrombi can aid diagnosis, they are not without limitations. The current tools used to diagnose DIC pose problems since a correct diagnosis can be masked by hemostatic changes that occur during pregnancy. For instance, the levels of D-dimers are inherently high in normal pregnancy and cannot simply be attributed to DIC.

## 2. Fetal Factors

Chromosomal anomaly is the commonest fetal cause of RM. Aneuploidy is the most prevalent chromosomal abnormalities of abort uses in RM [11]. Evidence from preimplantation genetic diagnosis (PGD) has shown that women with RM had a higher incidence of chromosomally abnormal embryos after Aneuploidy screening than those without RM [12, 13].

### 2.1. Fetal-blocking antibodies

Fetal blocking antibodies work to protect the baby from the mother's immune system, which will recognize the father's genetic material as foreign to her body and attack it. When the sperm penetrate the egg, it provides foreign material, but it also contains histocompatibility locus antigens (HLA). The sperm's HLA will "talk" to the mother's HLA, which would normally attack the baby, and stimulate the mother's body to protect the baby. In some cases, however, the father's genetic material is too similar to the mother's in that case; the mother's response is weak and insufficient to prevent her white blood cells from attacking the new cells. This type of problem usually causes an early miscarriage, well before 12 weeks, and is often suspected when several miscarriages have occurred at the exact same time in the pregnancy [14].

### 2.2. Umbilical cord abnormalities

The umbilical cord is a narrow, tube-like structure that connects the developing fetus to the placenta. The umbilical cord begins to form about five weeks after conception. There are three blood vessels inside the umbilical cord—two arteries and one vein. The vein carries oxygen-rich blood and nutrients from the placenta to the baby, while the two arteries transport waste from the baby back to the placenta where waste is transferred to the mother's blood and disposed of by her kidneys. A number of abnormalities can affect the umbilical cord. Sometimes the cord is too long, too short, connects improperly to the placenta or becomes knotted or compressed. Cord abnormalities can lead to problems

during pregnancy or during labor and delivery. In some cases, cord problems can affect mother and baby. The followings are some of the most frequent umbilical cord problems and how they can affect mother and baby [15].

### 2.3. Environmental Factors

Environmental factors; Heavy metals, organic solvents, and ionizing radiation are confirmed teratogens, and exposure to these can contribute to pregnancy loss. Alcohol and cocaine are also confirmed teratogens, while caffeine and smoking are suspected teratogens, but their teratogenic impact is still controversial. Caffeine consumption and smoking has been implicated in increasing the risk of miscarriage [16]. Recent studies have shown that women who are homozygous for CYP1A2 -1F alleles (an enzyme responsible for caffeine metabolism) had a high risk of RM with a dose dependent effect of daily caffeine intake [17]. Other studies have shown that women exposed to environmental tobacco smoke had a high risk of spontaneous miscarriage in combination with caffeine and alcohol consumption [18].

### 2.4. Stress factor

During pregnancy, the pregnant mother undergoes significant anatomical and physiological changes in order to nurture and accommodate the developing fetus [19]. These changes begin after conception and affect every organ system in the body. Pregnancy is a special time for a woman and her family. It is a time of many changes in a pregnant woman's body, in her emotions and in the life of her family. Stress stimulation can trigger a series of physiological adaptive responses. These changes often add new stresses to the lives of busy pregnant women who already face many demands at home and at work. However, when physical or emotional stress builds up to uncomfortable levels, it can be harmful for pregnant women. The systems that respond to stress are the hypothalamo-pituitary-adrenal (HPA) axis and the sympathoadrenal system. Stress can affect the secretion of the parvocellular neurons (PVN) in the hypothalamus and the release of neuropeptides, corticotrophin releasing hormone (CRH) and arginine vasopression (AVP). Recently, the impact of psychological stress on RM has received more attention. Studies have suggested that stress may play a role in RM through maternal neuro-endocrine-immune network response [20]. Stress, namely pressure or tension, has been defined as a form of psychological, physiological and behavioral transaction between people and environment, i.e. Person- environment fit. In this definition the external environmental stimulus is regarded as a stressor and the psychological response to the external stimulus is termed as stress [21]. The effect of stress may be beneficial to enable fight or flight adaptive response to escape from the harmful situation and the homeostasis may still be resumed. However, effect of stress may be detrimental by mediating a series of physiological responses resulting in adverse somatic consequences, including impaired cognition, abnormal metabolism, immune function and impaired reproduction. Two types of stress are differentiated including acute stress and chronic stress. Acute stress is a response to an immediate threat, such as an exam or a public presentation.

### 2.5. Alcohol and smoking:

Drinking alcohol during pregnancy can cause physical and mental birth defects. According to the Centers for Disease Control and Prevention each year between 1,300 and 8,000 babies in the United States are born with fetal alcohol syndrome (FAS), a combination of physical and mental birth defects. Consuming alcohol during pregnancy increases the risk of miscarriage, low birth weight and stillbirth. Heavy drinkers are two to four times more likely to have a miscarriage between the fourth and sixth months of pregnancy than are nondrinkers [22]. This is a major public health problem because not only can smoking harm a woman's health, but smoking during pregnancy can lead to serious health problems in newborns [23]. Smoking has been associated with a number of pregnancy complications. Early in pregnancy smoking appears to increase a woman's risk of having an ectopic pregnancy, placental complications, thus increasing the risk of miscarriage [24].

Thrombophilia either inheritance or acquired has been shown to be a major cause of recurrent pregnancy loss, patients with recurrent fetal loss should be evaluated for clotting disorders, even in the absence of clinical signs because there were some studies concluded that many positive hemophilic causatives finding without any clinical signs. This evaluation may be useful in the Improvement of gynecological care of women with recurrent pregnancy loss and accurate knowledge of all significant complications in these women regarding thrombophilia and formulate a plan to diagnosis and treatment of these conditions [25-28]. So, an appropriate clinical evaluation focused on diagnosis and therapy of RPL should also consider thrombophilia [29]. Defects, hypertension especially during pregnancy [30]. And other causes which could be related to RPL.

### 3. Conclusion

Acquired Thrombophilia and fetal factors has been shown to be a major cause of recurrent pregnancy loss. We recommended that more prospective studies are required to explain the relationship between acquired and inherited thrombophilia.

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