Coagulation factor deficiency associated with the recurrent abortion

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Abstract

Recurrent abortion is defined as three or more consecutive spontaneous abortions before 20 weeks of gestation. The incidence is 0.5-1% of all pregnancies, but the risk of recurrence increases with the number of previous pregnancy failure. Only in 50% of the cases it is possible to identify a causing factor. Most of the cases are due to genetic factors, anatomic abnormalities of the uterus, endocrine factors, infections and immunological factors. Increasingly, however, are discussed the hematological factors, acting either via specific antibodies, or directly, with implications for coagulation and thrombosis process. The fibrinogen deficiencies, the disorders of the Factor XIII and the thrombophilia are still studied and their treatment requires randomized clinical trials for clarification.

Keywords: *recurrent abortion, thrombophilia, Factor XIII, fibrinogen*

Introduction

World Health Organization defines abortion as the termination of pregnancy by the removal or expulsion from the uterus of a fetus or embryo before fetal viability, which corresponds to a fetus or embryo less than 400 grams. Habitual abortion is defined as spontaneous loss of three or more sequential pregnancies, before obtaining fetal viability, by fetal demise or expulsion of the concepts. Many of the authors review the definition, accepting as valid the loss of two consecutive pregnancies before starting to investigate this condition.

Recurrent pregnancy loss is defined before 26 weeks of gestation, but as the number of abortions between 20-26 weeks is quite low, the two populations are practically overlapping.

The etiology of recurrent abortion remains unclear even after exclusion of uterine abnormalities or immunological, genetic, infectious and endocrine factors. Acquired or hereditary trombophilia was demonstrated as cause of recurrent miscarriage in patients without other apparent causes of the disease. The evidence for pregnancy loss having a thrombotic basis is due to the widely reported association between antiphospholipid antibodies and recurrent abortion.

Antiphospholipid antibodies cause thrombosis of the decidual vessels, affecting blood supply to the fetus and leading ultimately to fetal death. Moreover, any prothrombotic status may cause recurrent pregnancy loss by this thrombotic mechanisms that can be repeated three or more times.

There are pro- and anti-coagulant factors acting on trophoblast like procoagulants: Factor XIII, homocysteine, fibrinogen, increased production of thrombin, Factor V Leiden (FVL), mutation G20210A of prothrombin gene, cytokines interleukin (IL)-6, tumor necrosis factor (TNF)α, membrane phospholipid microparticles; anticoagulants like protein S, C, antithrombin, tissue factor pathway inhibitor, fibrinolytic system and cytokine IL-4, IL-10. Hereditary thrombophilia associated with recurrent abortion include deficiencies of antithrombin, protein C and S, FVL, G20210A mutation of Factor II, and homozygosity for the thermolabile variant of methylenetetrahydrofolate reductase, hyperhomocysteinemia, characterized by the presence of small amounts of folate.

Factor XIII and fibrinogen deficiencies are associated with recurrent abortion. Both are bleeding diathesis that become symptomatic in childhood and associated with prolonged wound healing, recurrent abortion and prolonged bleeding.

Bleeding conditions associated with recurrent abortion

Fibrinogen deficiency

Fibrinogen, a major blood glycoprotein, is a dimmer composed of three polypeptide chains A, B and C. It is synthesized by the liver parenchymal cells and its half-life is 3 to 4.5 days. Thrombin causes the formation of fibrin monomers from fibrinogen, polymerization and fibrin stabilization occurs under the action of Factor XIII. Fibrin is also the target of fibrinolytic factors which dissolve the clot and maintain the patency and permeability of blood vessel. Fibrinogen is also a primary binding molecule, connecting platelets together via activated glycoprotein GPIIb/ IIIa.

There are three inherited deficiencies of fibrinogen, partially overlapped: afibrinogenemia, hypofibrinogenemia and disfibrinogenemia, all associated with recurrent abortion. Afibrinogenemia is an autosomal recessive inherited bleeding diathesis, a defect in hepatic secretion or release of fibrinogen. It is associated with poor wound healing and recurrent miscarriage. A similar condition is for hypofibrinogenemia. Disfibrinogenemia is characterized by the biosynthesis of structurally or functionally abnormal fibrinogen. Brenner[1] has reported that women with disfibrinogenemia are candidates for recurrent abortion. The mechanism of spontaneous

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abortion is related to the tendency to thrombosis. Using the experimental mouse model, he demonstrates that the absence or significant decrease of fibrinogen in maternal serum is sufficient to cause rupture of the maternal vessels and impaired trophoblastic infiltration, causing bleeding and recurrent abortion.

The available treatment uses cryoprecipitate, fresh frozen plasma and fibrinogen concentrate. The treatment during pregnancy is suitable only for patients correctly diagnosed with recurrent abortion. The minimum level of fibrinogen in pregnancy is 60mg/100ml. Cryoprecipitate infusion of 50mg/kg body weight provides a level of fibrinogen of 100mg/dl. As fibrinogen half-life is four days, two weekly infusions are sufficient to maintain a minimum level of fibrinogen of 60mg/dl and prevent pregnancy loss. The risk of such therapy remains thrombosis, occurring especially in women with severe afibrinogenemia or disfibrinogenemia. It also carries the risk of transmission of viral infections and formation of specific antibodies[2]. In these patients it is recommended the administration of unfractioned heparin during the peripartum.

Hereditary Factor XIII deficiency

Coagulation Factor XIII (FXIII) is a transglutamise participating in the final stage of coagulation cascade. Once activated by thrombin to FXIIIa, it determines the linkage of fibrin chains into stable fibrin, resistant to fibrinolysis. In plasma, FXIII is found as a heterotetramer (A2B2) composed of two catalytic units (FXIII-A) and 2 units of transport B (FXIII-B). FXIII-A is synthesized by megakaryocytes and monocytes, while FXIII-B is synthesized by hepatocytes. Platelets, monocytes and macrophages contain only subunit A of FXIII.

Unlike other factors, FVIIa, FVIII, FIX, FX and fibrinogen, which concentrations increase in plasma during pregnancy, FXIII decreases to half of normal value. FXIII-A is low in the serum of patients with recurrent abortion. FXIII deficiency is a hereditary disorder characterized by severe bleeding, delayed wound healing and recurrent miscarriage in homozygous patients. Its first manifestation is bleeding from the umbilical cord immediately after birth[3].

Women who are homozygous carriers for FXIII deficiency will not carry the pregnancy to term if not treated with FXIII concentrate throughout pregnancy. FXIII-A minimum level necessary for a normal pregnancy is unknown, but to ensure normal hemostasis the sufficient level is 0.5-2%. FXIII is essential for implantation and placental attachment; also to the further development of the placenta and acts as ligand not only between chains of fibrin, but also between those of fibronectin and collagen, major components of connective tissue matrix. In addition, FXIII appears to play an essential role in the interaction between blastocyst and endometrium during implantation. FXIII-A chain link fibrinogen and fibronectin, both important in maintaining the placenta attached to the uterus. FXIII deficiency can lead to bleeding and therefore to spontaneous pregnancy loss. This hypothesis is supported by evidence from the mouse model: decreased maternal FXIII-A cause heavy uterine bleeding and lead to embryo death[4].

Kobayashi et al.[5] reported the presence of FXIII-A in the extracellular space of extravilous cytotrophoblast near Nitabuch's layer. FXIII-A was also localized in Nitabuch's layer together with fibrinogen and fibronectin. The absence of the placental bed leads to the formation of deficient cytotrophoblastic shell. Thus, FXIII-A deficiency prevents implantation and the normal attachment of the placenta, resulting in detachment of the placenta from the uterus and subsequent loss of the pregnancy[6]. Recent studies show that FXIII-A has proangiogenic activity both in vitro and *in vivo*[7]. Angiogenesis requires proper embryo implantation, so the role of FXIII-A in implantation becomes evident. Whatever the cause of FXIII deficiency, the administration of this factor throughout pregnancy leads to remarkable results. Plasma-derived FXIII concentrate is available since 1980. It has a half-life of 10-12 days. Recently, has become available the FXIII-A recombinant concentrate, with similar half-life of plasma-derived product. There are no studies that can recommend the dose and timing of FXIII during pregnancy, but there is a phase III clinical trial in development that is expected to establish the posology[8]. FXIII plasma level necessary to maintain a pregnancy is 10% in women with factor XIII deficiency. Prophylactic treatment is done every 4 weeks with 20UI/kg to maintain a level of FXIII higher that 3%. Before amniocentesis or delivery a single dose of 1000 IU IS is recommended.

Other deficiencies of factor XIII

While plasmatic FXIII-B increases during pregnancy, the level of FXIII-A tends to decrease steadily, reaching a level of 50% at term. Subunit A begins to increase during labor and decreases postpartum. This change is in contrast to increased levels of fibrinogen, FVIII, FVIII, FIX and FX during labor. It is not clear whether this decrease of factor FXIII-A in pregnancy is the result of decreased synthesis, increased destruction or use or simply a dilution by increased plasma volume. In a cohort study with patients without FXIII deficiency but with a history of two or more first-trimester abortions, plasma level of FXIII was not statistically significant modified[9].

Thrombophilia

Procoagulant status conferred by thrombophilia is demonstrated to be involved in the etiology of recurrent abortion: increased prevalence of thrombophilia in patients with recurrent abortion, increased incidence of spontaneous pregnancy loss in patients with thrombophilia and thrombosis in the decidual vessels.

Hereditary thrombophilia causes an increased tendency to thrombosis and include deficiencies of antithrombin, protein C and S, FVLeiden, mutation G20210A of prothrombin gene, C677T homozygous mutation of MTHFR gene, and increased Factor VIII.

The most common acquired procoagulant status is the antiphospholipid syndrome (APS). Protein S and C and antithrombin are physiological anticoagulants. Their deficiencies are quite rare. FVL is the most common inherited thrombophilia. It results by replacing adenine with guanine at nucleotide 1691 of factor V gene resulting a new protein called factor V Leiden. This mutation

slows the inactivation of FVa by activated protein C, leading to increased production of thrombin. G20210A prothrombin gene mutation involves replacement of adenine with guanine at position 32 of the prothrombin gene. The result is a more efficient processing of prothrombin gene, increased levels of prothrombin and thrombin accordingly. FVL and G20210A mutation are common in healthy white population (prevalence of 5% and 1.5% respectively), but are rare in the population of Asia and Africa. The homozygoticity for MTHFR can lead to hyperhomocysteinemia, especially when folate stores are reduced, which also predispose to thrombosis, the mechanism being multifactorial.

Thrombosis in decidual vessels

Thrombophilia has been suggested to be a cause of microembolism in the placenta, resulting in abortion or stop the evolution of pregnancy. Genetic polymorphism of the thrombophilia genes result in the transmission to 50% of the fetuses, affecting the trophoblastic function. In a study of 1486 cases of miscarriage, placental thrombosis was identified in 12.1% of cases[10]. Many et al.[11] studied the placentas of women without/with severe complications of pregnancy. Placental villous and infarction was much higher in patients with thrombophilia. The number of placentas with fibrinoid necrosis of deciduous vessels was significantly higher in the group with thrombophilia. A recent study[12] did not confirm these results, but indicates an increased incidence of placental infarctions (50%) and thrombosis in women with and without thrombophilia who had miscarriages. Arias et al[13] assessed 13 placentas from pregnancies complicated by last trimester preeclampsia, premature birth, IUGR or intrauterine fetal death. 10 of 13 women had thrombophilia, including antiphospholipid syndrome, protein S or C deficiency, FVL. What prevailed was not the decidual thrombosis but the fetal thrombotic vasculopathy with fibrous obliteration. It is important to note that these changes belong to the fetal compartment, not to the maternal's. There has also been identified fetal vessel thrombosis, stroke in the fetal compartment, spiral artery hypoplasia or thrombosis, perivilous fibrin deposits. There are probably still unidentified thrombophilia explaining the high incidence of placental pathology and placental lesions resulting from inflammatory changes. Even in the antiphospholipid syndrome, thrombosis has not been convincingly demonstrated in the decidual vessels. After treatment with monoclonal antiphospholipid antibodies, the most important reactivity of the placenta was identified in the cytotrophoblast, suggesting that the trophoblast is most likely affected by mechanisms unrelated to thrombosis. Membrane surface receptors are involved in changes in the fetal compartment.

Conclusion

The maternal spiral arteries are remodeled by the action of hormones and trophoblast invasion, becoming uteroplacental arteries towards the end of the first trimester. Their lumen is larger and the median layer is replaced by trophoblast cells. Pathological vessel thrombosis most likely takes place after first trimester of pregnancy. First-trimester abortion is due to the failure of implantation or fetal genetic abnormalities, while the second trimester abortion is a consequence of placental thrombotic events. The prevalence of thrombophilia is between 3 and 42% in patients with spontaneous pregnancy loss. This wide range is explained by the fact that studies conducted so far take into account all forms of miscarriage, the first and second trimester. When the study does not divide patients into subgroups, the prevalence of thrombophilia is higher. A recent study[14] evaluated women with three or more first trimester abortions, with two or more second trimester abortions and with one or more third trimester abortions. FVL was more frequent in the study group than in the control group, MTHFR C677T and prothrombin mutations were similar in both groups. Thrombophilia has been frequently identified in patients with abortion in the second and third trimester, but not in the first trimester. The conclusion of the 31 studies in the literature was that there was a statistically significant association between hereditary thrombophilia and spontaneous abortion. Krabbendam[15] assessed this link in a meta-analysis of 11 studies in the literature. Serum homocysteine was significantly higher in women with a history of recurrent abortion, but there was also an increased prevalence of MTHFR C677T mutation. The meta-analysis could not establish any relationship between recurrent abortion and the level of antithrombin, protein C and S.

In conclusion, the hematological disorders causing recurrent abortion must be known by the obstetrician and requires multidisciplinary collaboration for diagnosis and treatment. ■

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