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Inherited thrombophilia and obstetric complications

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A B S T R A C T

Inherited thrombophilia can be detected in at least 40% of patients with venous thromboembolism. More recently, inherited thrombophilia has been reported to be associated with an increased risk for obstetric complications, including fetal loss, preeclampsia, intrauterine growth restriction (IUGR) , abruptio placentae, those latter likely due to inadequate placental perfusion. The estimate of risk largely depends on the type of thrombophilic trait analyzed and on the criteria applied for the selection of the patients, producing in some cases contradictory results. Convincing evidence is available that deficiency of antithrombin (AT), protein C (PC), or protein S (PS), is a risk factor for late fetal loss. Factor V Leiden and prothrombin G20210A are associated with a doubled risk for unexplained recurrent early fetal loss and for non-recurrent late fetal loss.

The association of inherited thrombophilia with preeclampsia is much more uncertain, being perhaps restricted to factor V Leiden and to more severe cases.

Less data are available for IUGR and abruptio placentae. Treatment with s.c. low-molecular weight heparin for preventing recurrence of fetal loss among women with thombophilia is under investigation.

The term *thrombophilia* describes a tendency to develop thrombosis on the basis of inherited or acquired disorders of blood coagulation or fibrinolyisis towards a prothrombotic state. Since 1965, a number of inherited hypercoagulable disorders have been firmly associated with an increased risk of venous thromboembolism: they include deficiency of natural anticoagulants antithrombin (AT), protein C (PC) or protein S (PS) and two common gain-of-function polymorphisms mutations in genes encoding coagulation factor V (factor V Leiden) and prothrombin (PT G20210A). At least one abnormality was found in 40% of patients with venous thromboembolism and in near 10% of the general population with Caucasian ancestry.[1]

Thrombotic risk during pregnancy and puerperium among women with inherited thrombophilia

The incidence of venous thromboembolism (VTE) among women of fertile age is high as 0.18 per 1000 per year.[2] During pregnancy and puerperium the risk for VTE increases, probably due to hemostatic imbalance towards a prothrombotic state and compression of the venous system by the gravid uterus. The incidence of VTE is 0.85 per 1000 deliveries, with a higher incidence during puerperium[3,4,] so that the risk during pregnancy and puerperium is 4.2-fold and 14.1-fold increased, respectively, in comparison with non-pregnant women of fertile age.[5] The risk is further increased by carriership of inherited thrombophilia by 3 to 41-fold, depending on the type of thrombophilic genotype, being the likelihood of VTE higher among women with deficiency of natural anticoagulants or homozygosity for factor V Leiden. [6-8]

Complications of pregnancy other than thrombosis among women with inherited thrombophilia

Obstetrical complications such as fetal loss, severe preeclampsia, fetal growth retardation, and abruptio placentae are associated with inadequate placental perfusion. Overall, 38% of women investigated for obstetrical complications has been reported to have inherited thrombophilia.[9]

Fetal loss

In Western countries up to 18% of pregnancies ends in fetal loss,[10,11] in the large majority of cases as miscarriage (early fetal loss) and in 0.5% - 0.8% of pregnancies as stillbirth (late fetal loss).[12] Recurrent fetal

loss is a common health problem as well, with two or more losses affecting approximately 5% of women in the fertile age and three or more fetal losses affecting 1% to 2% of women.[13] In 1996 the EPCOT (European Prospective Cohort on Thrombophilia) group reported convincing evidence that women with inherited thrombophilia (AT, PC, and PS deficiency or factor V Leiden) have a 3.6-fold increased risk of stillbirth (late fetal loss after the 28th week of gestation) and a 1.3-fold increased risk of miscarriage (fetal loss before the 28th week of gestation).[14] A 2-fold increase in the risk of fetal loss among carriers of AT, PC, and PS deficiency and factor V Leiden has also been reported in several family studies.[15-17]

A number of case-control studies confirmed that factor V Leiden is a weak but well-established risk factor for unexplained recurrent fetal loss (two or more events) and for one or more late fetal loss, with a 2- to 7- fold increase in risk. 8 In two recently published meta-analyses factor V Leiden was found associated with a double risk of experiencing two or more miscarriages fetal losses in respect to non-carriers.[18,19] The risk was 3.3-fold increased for non-recurrent fetal loss after the 19th week of gestation and 7.8-fold increased for recurrent late fetal loss.[18] The risk for miscarriage was similar (odds ratio 2.1 or 2.5) independently of including studies recruiting women having suffered from two or more miscarriages or recruiting women having suffered from three or more miscarriages.[19] In contrast, many reports denied a significant association between prothrombin G20210A and fetal loss.[8] However, meta-analyses reached a statistical power able to detect a significant 2.5 fold increased risk for early recurrent fetal loss and a 2.3-fold increased risk for non-recurrent late fetal loss;[18] the association of prothrombin G20210A with recurrent miscarriage was found significantly increased (4.5-fold) among women with two or more miscarriages but not among women with at least three miscarriages.[19]

Recently in a large population study on 32,683 women during their first pregnancy factor V Leiden and prothrombin G20210A were found associated with a significant increase in risk of miscarriage (3.2-fold and 2.4-fold respectively); the association was significant only in the group of women having had miscarriage from the 10th week of gestation (3.5-fold and 2.6-fold, respectively).[11]

Preeclampsia

Preeclampsia is estimated to complicate 2.6% of births.[20] Scarce data are available about the risk of preeclampsia associated with deficiency of natural anticoagulants; a study reported a 10.7-fold increase in risk in PS-deficient women.[21] In 12 published series of women with a history of pre-eclampsia or HELLP syndrome (with a total of 1,458 patients) factor V Leiden was diagnosed from 4% up to 26% of the cases.[8] Accordingly, the association of factor V Leiden with a higher risk of pre-eclampsia is uncertain, since not all the studies reported positive results.[8] A meta-analysis on 2,742 patients found a 3.1-fold increased risk associated with factor V Leiden in studies published up to 2000, while no association was seen in studies published in 2001-2002 and in the largest studies.[22] A systematic review of the literature evidenced that factor V Leiden does not seem to be associated with the development of pre-eclampsia *per se* but that it favors progression to the severe forms of disease.[23] This view is supported by a recent meta-analysis showing a 2.2-fold increased risk for severe pre-eclampsia associated with factor V Leiden. 24 Prothrombin G20210A was not found to be associated with either mild or severe pre-eclampsia.[8,23,24]

Intrauterine growth restriction

In a large cohort study on 1,100 live neonates born from 755 women factor V Leiden or prothrombin G20210A were associated with a 1.7-fold increase in the risk of having a baby under the 10th growth centile; statistical association for single polymorphisms was confirmed only for prothrombin G20210A.[25] On the opposite, a case-control study denied any association of factor V Leiden and prothrombin G20210A with IUGR among 493 neonates and their mothers.[26] The association between inherited thrombophilia and IURG has been recently systematically reviewed.[27] There was clinical heterogeneity among studies, with respect to IUGR criteria and definitions. The overall magnitude of the risk for IUGR was 2.7 for factor V Leiden and 2.5 for prothrombin G20210A, in both cases statistically significant. Yet , combining the only two prospective cohort study published in extenso and investigating only factor V Leiden, the relative risk associated was 1.0.[27]

The results of the meta-analysis suggest that the overall association between factor V Leiden – prothrombin G20210A and IUGR may be driven by small and poor quality studies. In conclusion more research is required to determine whether an association between factor V Leiden – prothrombin G20210A and IUGR exists.

Abruptio placentae

In small series of patients with abruptio placentae (< 30) the prevalence of factor V Leiden was reported to be present in 30 to 50% of cases[9,28] ; similar results have been reported for prothrombin G20210A.[9] In a multicenter study recruiting 50 consecutive women with severe abruptio placentae heterozygosity for fac-

tor V Leiden or prothrombin G20210A was found in 42% of cases.[29] On the opposite, in a prospective study on 2.480 pregnant women the prevalence of abruptio placentae was 0.7% among carriers of factor V Leiden and 0.5% among non-carriers.[30] In conclusion, so far no conclusion on the impact of inherited thrombophilia on abruption placentae can be drawn, given the scarcity of available data.

Prophylaxis of obstetric complications other than venous thromboembolism

Whether or not antithrombotic prophylaxis for women with inherited thrombophilia and a history of obstetric complications is warranted during subsequent pregnancies is a matter for controversy.[31,32] Enoxaparin administed during pregnancy has been reported effective in improving the rate of live births in women with inherited thrombophilia and history of a single fetal loss[33] or a history of recurrent fetal losses or non-recurrent late fetal loss.[34] However, the evidence derived from such studies is considered weak from many experts.[35] Nevertheless, the Seventh Conference of the American College of Chest Physicians has recently recommended (grade 2C) treatment with aspirin plus low molecular weight heparin for pregnant women with inherited thrombophilia and previous obstetric complication (recurrent miscarriages, non-recurrent late fetal loss, severe or recurrent preeclampsia, or abruptio placentae).[36] Further controlled trials are urgently needed, making a special effort in planning their design: it would be very difficult, in fact, recruiting women with previous fetal loss accepting the possibility of receiving only a placebo in respect to an investigational drug possibly favoring the pregnancy outcome.

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