Recurrent Pregnancy Loss and Thrombophilia

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Abstract: In the last few decades we found a number of data concerning the association between a hypercoagulable state and its causes and adverse pregnancy outcome, in particular, recurrent pregnancy loss (RPL). In this review several factors involved in pathophysiology of RPL related to thrombophilia were evaluated. Inherited thrombophilia due to clotting inhibitors deficiency or to clotting factors gene variants as prothrombin A20210G and factor V Leiden were firstly evaluated. Thereafter, acquired thrombophilic conditions, such as antiphospholipid syndrome or acquired activated protein C resistance or increased levels of factors VIII, were described. At last, the role of combined thrombophilic defects in pathophysiology of RPL or LPL was described.

INTRODUCTION

Recurrent pregnancy loss (RPL) represents a major health problem with two-three or more losses in up to 5% of women of reproductive age and is actually one of the most common causes of female sterility [1]. Several reports identify inherited predisposition to thrombophilia as one of the main causes of RPL, in particular if several diseases potentially responsible of RPL have been already excluded such as endocrine diseases (e.g. ovarian dysfunction, anovulation, hypopituitarism, diabetes), uterine malformation, genetic alterations (e.g. chromosomal aberrations), inflammatory diseases, (in particular systemic lupus erythematosus) and infectious diseases [2-5]. From a pathological point of view, women affected by thrombophilia during their pregnancy show a hypercoagulable state that is already increased during pregnancy, which may impair placental flow and then its function and fetal growth and may predispose to develop venous thrombosis [6].

During pregnancy, in fact, many changes have been observed in the haemostatic balance with a trend towards thrombophilia in order to be prompt for the haemostatic challenge of delivery [2, 6, 7]. Thus, pregnancy is a condition associated to thrombophilia per se, and for this reason it is associated with the increase of several clotting factors (i.e. factor VIII, vWF, fibrinogen, factor VII) [7]. Moreover, other markers of a hypercoagulable state are also increased during pregnancy, such as D-dimer and/or prothrombin fragment 1+2 [7, 8]. For this reason, episodes of venous thromboembolism (VTE) have been observed during pregnancy [9]. Moreover, women carrying further thrombotic risk factors (e.g. inherited thrombophilia) show an additionally increased risk of thrombotic events during pregnancy, such as venous thromboembolism and/or abortion [10].

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INHERITED THROMBOPHILIA AND PREGNANCY LOSS

Thrombophilia has been identified as one of the main causes of RPL until 40%, in particular early RPL [11]. Although several studies on this topic are available in the literature to confirm this trend, rates of thrombophilia seem to differ from study to study because of different inclusion criteria and different ethnic backgrounds of the selected patients [12].

In this clinical setting, may differ inherited thrombophilia, acquired thrombophilia and combined thrombophilia [13, 14].

Inherited thrombophilia may be due to deficiency of clotting inhibitors or to gene variants leading to a hypercoagulable tendency.

Gene variants frequently associated with RPL are prothrombin A20210G and/or factor V Leiden. Prothrombin A20210G has been identified as a risk factor for pregnancy loss in several studies and has been associated mainly to early RPL [15-19]. On the other hand, factor V Leiden, which is responsible for more than 75% of inherited activated protein C resistance, is the more commonly inherited thrombotic risk factor associated to RPL [20-22]. In particular, a case control study by Ridker *et al*. has reported an increased prevalence of FVL in women with RPL, while other studies revealed a strong relationship between FVL and early RPL [23]. FVL has been identified as a risk factor also for late RPL [24]. Also, deficiency of clotting inhibitors, such as protein S, protein C and/or antithrombin, has been clearly associated to RPL since 1996 [25].

HYPERHOMOCYSTEINEMIA

A pathogenetic role of hyperhomocysteinemia (HHCY) in RPL has been underlined by several reports on this topic, but no univocal data are actually available in the Literature. Several Authors reported increasing evidences for the relationship between HHCY, methylenetetrahydrofolate

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reductase gene polymorphism C677T (MTHFR C677T) and RPL, in particular, early RPL [26-29]. On the other hand, further authors found a negative association between HHCY and early RPL [30, 31].

ACQUIRED THROMBOPHILIA

Several authors underlined the role of the antiphospholipid syndrome (APS) in the pathophysiology of RPL [32-44]. To confirm this point, adverse pregnancy outcome is considered one of the diagnostic criteria of APS (Table **1**) according to the guidelines of the International Society of Thrombosis and Hemostasis and the American Rheumatology Association [45, 46]. During APS, a large variety of autoantibodies also towards clotting factors, as factor XII, have been found [47, 48]. However, a clear explanation of all involved processes on the roles of antiphospholipid antibodies and of autoantibodies toward clotting factors is still a matter of discussion.

Table 1. Diagnostic Criteria to Detect Antiphospholipid Syndrome

Clinical Criteria

Vascular thrombosis of arterial and/or venous vessels in any tissue or organ

Pregnancy Morbidity

- One or more unexplained deaths of a morphologically normal fetus at or beyond the 10^{th} week of gestation
- One or more unexplained deaths of a morphologically normal neonate before the 34^{th} week of gestation because of eclampsia or severe eclampsia or placental insufficiency
- Three or more unexplained consecutive spontaneous abortions before the 10^{th} week of gestation

Laboratory Criteria

- Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart, detected according to the International Society of Thrombosis and Haemostasis (ISTH)
- Anticardiolipin antibody (aCL) of IgG and/or IgM isotype in serum or in plasma present in medium or high titer on two or more occasions at least 12 weeks apart
- Anti-β_2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or in plasma present on two or more occasion at least 12 weeks apart

For more details we suggest to consult Miyakis S, *et al*. J Thromb Haemost 2006; 4: 295-306.

On the other hand, a new evidence seems to be available for the role of increased maternal plasma levels of clotting factor VIII and the risk of RPL [49].

Furthermore, acquired activated protein C resistance (i.e. not associated with the presence of FVL) has been described in several women with RPL, but also in this case not all involved mechanisms are known [50].

COMBINED THROMBOPHILIA

Combined thrombophilia (i.e. inherited thrombophilia associated with acquired thrombophilia or more than one inherited thrombophilic defect) has also been identified as a cause of RPL, but its real frequency is not clear. Several studies in the last years identified combined thrombophilic defects in women with RPL, both early RPL and late RPL [51-53].

CONCLUSION

Active surveillance of women referred to gynecological centers for RPL should be supported by thrombophilia screening. This approach may be helpful to fight this major health problem that involves up to 5% of women of reproductive age by an appropriate antithrombotic treatment.

Thromboprophylaxis in fact may have a protective role for the pregnancy related outcomes in particular, early RPL. Furthermore, thrombophilic evaluation should be performed also for patients who appear to be at high risk of VTE because of a previous VTE event or a first degree relative with early onset of VTE, as pregnant subjects carriers of such thrombophilic conditions.

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Received: February 2, 2009 Revised: February 5, 2009 Accepted: February 25, 2009