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Multiple Autoantibodies Associated with Autoimmune Reproductive Failure

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***Purpose*:** Autoimmune factors are involved in some of the cases of reproductive failure. The aim of this paper is to discuss the association between autoantibodies and reproductive failure.
***Methods*:** Literature review of autoantibodies associated with reproductive failure.
***Results*:** Several autoantibodies were found in association with such clinical manifestations, mainly in patients having systemic lupus erythematosus or the antiphospholipid syndrome. These autoantibodies include "classical" antiphospholipid antibodies such as anticardiolipin, anti-β2-glycoprotein-I, antiphosphatidylserine, and antiphosphatidylethanolamine. There are also some "nonclassical" antiphospholipid antibodies directed to prothrombin, thromboplastin, or mitochondrial antibodies of M5 type, which were also found in patients with reproductive failure. Moreover, animal models as well as some human studies support a role for other autoantibodies in these clinical manifestations including antithyroglobulin, antilaminin-1, anti-corpus luteum, antiprolactin, anti-poly(ADP-ribose), and lymphocytotoxic antibodies.
***Conclusions*:** Even though there is not enough data currently to support a firm association between some of these autoantibodies and reproductive failure, future studies are likely to help us determine and expand the number of autoantibodies screened in these patients.

KEY WORDS: Antilaminin antibody; antiphospholipid syndrome; reproductive failure; systemic lupus erythematosus; thyroglobulin.

INTRODUCTION

Reproductive failure complicates many autoimmune diseases such as systemic lupus erythematosus (SLE), and it is also a major manifestation of the antiphospholipid syndrome (APS). APS is characterized by various aspects of reproductive failure such as recurrent abortions at various stages, intrauterine growth retardation, pre-eclampsia, and possibly also infertility (1). Even though recurrent pregnancy loss and other features of reproductive failure might result from various factors, autoimmune factors provide a major etiology for at least unexplained recurrent pregnancy loss. Herein we briefly review the association of autoantibodies with reproductive failure, with special emphasis on autoantibodies other than antiphospholipid antibodies (aPL). This association is evident from either (and sometimes both) human studies or murine models.

"CLASSICAL" ANTIPHOSPHOLIPID ANTIBODIES

aPL are the hallmark of APS, and one of the two major clinical manifestations of APS include various aspects of reproductive failure. Thorough and comprehensive discussion of the role of aPL in reproduction is beyond the scope of this review. Nonetheless,

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some remarks are provided regarding the groups of autoantibodies that are known as the classical aPL.

Anticardiolipin

Anticardiolipin is probably the most classical aPL, as it is used for the definition of APS. It is highly associated with recurrent pregnancy loss, but also with other manifestations of APS such as focal CNS involvement (2,3). Animal model support the pathogenic role of anticardiolipin in pregnancy (4). Infusion of anticardiolipin antibodies to pregnant mice resulted in lower fecundity rate, increased resorption index of embryos, lower number of embryos per pregnancy, and lower weights of embryos and placentae than in the control mice (5). Following active immunization with a human pathogenic monoclonal IgM aCL (H-3), primary APS developed in BALB/c mice: the mice had high titers of aCL with clinical manifestations typical for APS, mainly obstetric manifestations (6).

Antiphosphatidylserine

The role of antiphosphatidylserine antibodies in pregnancy loss is evident also from murine studies. Passive induction of APS has been reported in two different studies (7,8). Moreover, active immunization with phosphatidylserine also led to obstetric clinical manifestations typical of experimental APS: lower fecundity rate, lower number of embryos per pregnancy, and lower weights of embryos and placentae, but higher fetal resorption rate than in the control mice (9).

Antiphosphatidylethanolamine

There is evidence in some studies that antiphosphatidylethanolamine are associated with the manifestations of APS such as thrombosis, recurrent fetal loss, neurological features, and livedo reticularis (10,11).

Anti-β2-Glycoprotein-I

β2-Glycoprotein-I is probably the autoantigen in APS. Autoantibodies directed to it are strongly associated with thrombosis, recurrent fetal loss, thrombocytopenia, hemolytic anemia, and heart valve disease (12–14). Immunization with β2-glycoprotein-I also resulted in the induction of the typical manifestations of obstetric APS (15).

"NONCLASSICAL" ANTIPHOSPHOLIPID ANTIBODIES

In addition to the above-mentioned autoantibodies, there are autoantibodies directed to antigens associated with the coagulation system, and some also serve as cofactors for aPL. There are some reports that also provide a link between them and reproductive failure.

Antithromboplastin

Thromboplastin is composed of a complex of phospholipids, lipoprotein, and cholesterol, and it enables activation of coagulation factor VII upon its binding. The presence of these antibodies has been associated with thrombosis, thrombocytopenia, hemolytic anemia, and fetal loss in SLE patients (16). They are also correlated with lupus anticoagulant and anticardiolipin antibody presence.

Antimitochondrial Antibodies of M5 Type

These antibodies are directed toward an unknown antigen located in the inner membranes of mitochondria (50 kDa). They are associated with recurrent fetal loss, hemolytic anemia, and thrombocytopenia, and have a controversial association with thrombosis (17,18). They are found in up to 31% of SLE patients, and correlate with the presence of other classical aPL.

Antiprothrombin

Antiprothrombin autoantibodies are mainly associated with thrombosis in APS and outside the setting of APS. One example would be IgG antiprothrombin and anti-β2GPI antibodies measurement at entry to a 5-year coronary prevention trial, which were compared between 106 patients who experienced nonfatal myocardial infarction or cardiac death and 106 subjects without coronary episodes during the follow-up (19). Antiprothrombin levels were significantly higher in patients than in controls, and level of aPT in the highest third of distribution, predicted a 2.5-fold increase in the risk of cardiac events. The association of these antibodies with pregnancy loss is still controversial, but a recent study emphasizes a significant association between the presence of antiprothrombin antibodies and pregnancy loss in APS, especially early pregnancy loss (manuscript submitted for publication).

OTHER AUTOANTIBODIES

In addition to aPL, there are other autoantibodies reported to be associated with reproductive failure in general or in the setting of APS/SLE.

Antithyroglobulin

Some reports support an association between antithyroglobulin antibodies and pregnancy loss. Even though thyroid dysfunction can explain this association, the increase in miscarriages cannot always be explained by thyroid dysfunction alone as it can be encountered in the presence of normal thyroid function (20,21). This suggests that the higher rate of miscarriages observed in women with autoimmune thyroid disturbances reflect primarily an autoimmune phenomenon, rather than or in addition to a consequence of an overt thyroid hormone abnormalities. Thus, the presence of antibodies to the thyroid could represent a secondary marker of a predisposition for an autoimmune disease rather than the actual cause of pregnancy loss. We have recently conducted a study in which active immunization of mice with thyroglobulin resulted in the production of antithyroglobulin antibodies, with increased rate of fetal resorptions compared with nonimmunized mice (manuscript submitted for publication). No thyroid pathology could be identified in these mice.

Anti-Corpus Luteum

Autoantibodies directed to the corpus luteum glycoprotein were found in 22% of female SLE patients who were under 40 years of age. These antibodies were found associated with early stages of ovarian dysfunction (22). This finding might tentatively link these antibodies and infertility, but this assumption should be further confirmed.

Antiprolactin

Autoantibodies to prolactin have been reported in 5% of SLE patients, but in 41% of SLE patients also having hyperprolactinemia (23). Their presence is associated with decreased disease activity in lupus, but no clear clinical manifestation. They are associated with increased lymphocyte counts and decreased anti-DNA antibody levels. Even though not determined, the association of these antibodies with hyperprolactinemia might signify decreased conception rates in these patients, as hyperprolactinemia can lead to infertility.

Lymphocytotoxic Antibodies

The autoantibodies reacting with lymphocytes are a heterogeneous group of antibodies which target different membranal and intracellular antigens. They are detected in 28–90% of SLE patients, but they also appear in viral diseases, malignancies, and rheumatoid arthritis. Many different clinical associations have been described with these autoantibodies including cognitive dysfunction, lupus nephritis, and also spontaneous abortions (24).

Anti-Poly(ADP-Ribose)

Poly(ADP-ribose) is a branched homopolymer synthesized from the respiratory coenzyme NAD+ at the site of DNA breakage. Autoantibodies against it have been reported in 42–73% of SLE patients, and in these patients they have been associated with obstetric complications including abortion and premature delivery (25).

Antilaminin

IgG antilaminin-1 antibodies were found in more than 30% of 177 recurrent aborters, and the levels of these antibodies were higher in recurrent aborters than in healthy pregnant and nonpregnant women. Accordingly, the live birth rate of subsequent pregnancies in IgG antilaminin-1 positive recurrent aborters was significantly lower than in antilaminin-1 negative recurrent aborters (26). Animal models also support such a role for antilaminin-1. Intravenous injections of laminin antibodies to rabbit induced a high incidence of abortions, fetal death, retroplacental hematomas, and hemorrhages in surviving litters. The antibodies were found in the parietal and visceral yolk sac (27). We have recently conducted a study in which immunization with laminin-1 resulted in the production of antilaminin-1 antibodies and increased fetal resorption rates (manuscript submitted for publication). These findings are not surprising as laminins critically contribute to cell differentiation, cell shape and movement, maintenance of tissue phenotypes, and promotion of tissue survival, and hence they are most important during development of early preimplantation embryos, during the implantation process, and during the organogenesis in postimplantation embryos.

CONCLUSIONS

Autoimmune factors provide one of the differential diagnosis in the etiology of reproductive failure.

Autoantibodies associated with reproductive failure include mainly aPL, but the above-mentioned data suggest that many other antibodies might be at least a marker of such clinical presentation. Unfortunately, regarding most of these nonclassical and other autoantibodies, there is currently not enough data to suggest a firm association between their presence or elevated levels and clinical manifestations of reproductive failure. Development of animal models along with clinical studies would enable us disclose which among autoantibodies could serve indeed as such a marker. Nonetheless, it seems that more autoantibodies would be used in the future for screening patients currently having what is termed "unexplained" reproductive failure.

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