Autoantibodies as predictors of pregnancy complications

H. J. A. Carp¹, P. L. Meroni² and Y. Shoenfeld³

Certain autoantibodies which are found in autoimmune diseases including CTDs can impair fertility. Reproductive failure may present as pregnancy loss, either as miscarriage, intrauterine fetal death or stillbirth. There are also late obstetric complications such as intrauterine growth restriction, pre-eclampsia and pre-term birth. This review summarizes the possible influences of autoantibodies in reproductive failure, and particularly their predictive value (if available). The aPLs detectable by lupus anticoagulant, anti-cardiolipin or anti-ß2 glycoprotein I assays are associated with pregnancy loss and have a positive predictive value (PPV) of 75%. In spite of the general consensus on the management of pregnant aPL-positive women, few well-designed clinical trials have been reported and there is also insufficient data about the PPV of treatment. Anti-thyroid antibodies have been associated with pregnancy loss, and indeed have a PPV of 40%. However, no antibody is pathognomic for pregnancy loss. It may be more appropriate to assess a combination of antibodies rather than one antibody. However, a large meta-analysis of published trials is required in order to determine the prevalence of each particular autoantibody and different combinations of antibodies in different forms of reproductive failure.

**Key words:** Recurrent miscarriage, Pregnancy loss, Autoimmunity, Autoimmune diseases, Autoantibodies.

**Introduction**

Patients with CTD often consult prior to pregnancy requiring advice as to whether their condition predisposes them to various pregnancy complications. CTDs are associated with a large number of autoantibodies. Often the prognosis will depend on the presence of specific autoantibodies. Until now, no autoantibody has been found to be pathognomic for maternal pregnancy complications. However, various autoantibodies have been associated with impaired reproductive outcome.

The aPLs such as lupus anticoagulant (LA), anti-cardiolipin (aCL) and anti-ß 2 glycoprotein I (ß2GP1) have all been reported to be associated with recurrent pregnancy loss (RPL) or as possible factors involved in infertility. Antibodies to thyroid antigens, such as thyroglobulin (aTG) and thyroid peroxidase (aTPO), antibodies to nuclear antigens (ANAs), anti-laminin, anti-prothrombin antibodies (aPTs) and anti-sacchromyces cerevisiae antibodies (ASCA) [1], have also been implicated in pregnancy complications.

The pregnancy complications have included many conditions including miscarriage, intrauterine growth restriction (IUGR), pre-eclamptic toxemia (PET), stillbirth and pre-term labour.

The evidence for associating certain antibodies with impaired reproductive outcome have used animal models, in which active immunization has induced the production of autoantibodies and passive immunization with antibodies in order to reproduce the effects seen in humans. There are prevalence studies, attempting to show an increased prevalence of autoantibodies in patients with impaired reproductive outcomes, and cohort studies showing an increased incidence of pregnancy complications in the presence of antibodies. Prevalence and cohort studies may be based on a single centre, or on a large pool of patients from multiple centres. There are also comparative trials of treatment, examining whether treatment aimed at lowering the level of antibodies, or impeding their action lowers the incidence of pregnancy complications. When these are taken together, it should be possible to quote the positive predictive value (PPV). The PPV is the proportion of patients with positive test results who develop the condition. However, the PPV depends on the prevalence of the antibodies in the general population also. This review will try to look at certain autoantibodies in order to examine their predictive value.

**Anti-phospholipid antibodies**

The aPLs are known to have pathogenic effects on pregnancy outcome in animal models [2]. They may react with fetal trophoblast as well as with maternal decidual cells so directly affecting several cell functions pivotal for inducing a defective placentation [3]. Complement-mediated placental inflammation has also been reported to play a key role in an experimental model of fetal loss induced by passive injection of large amount of aPL after the implantation [4]. However, the real importance of complement activation in human pathology is still a matter of research [5]. In addition, the thrombogenic effect of aPL may cause placental infarctions with the consequent impairment of the blood exchange between maternal and fetal circulation [3]. It has been reported that 5–51% of patients with recurrent spontaneous miscarriage have aCL and 0–20% have LA [6]. Although aPLs are a risk factor for pregnancy loss, they are not pathogenic.

Attempts have been made to find the specific autoantibody responsible for pregnancy loss. There is evidence that the pathogenic antibodies are those directed towards ß2GP1 [3]. Unfortunately, there are no cohort studies examining the natural history of untreated patients with aPL. There is a widespread belief, based on early studies that these antibodies are so pathogenic that they should always be treated. The nearest to a large study on the natural history is Empson et al.’s [7] meta-analysis of 95 patients comparing treatment with aspirin with placebo. There was an 86% live birth rate in the placebo group. Hence, the PPV seems to be only 14%. However, as false-negative rates were not quoted, it is impossible to arrive at a valid conclusion about the PPV. Marai et al. [8] compared the results of autoantibody testing on 38 women with recurrent miscarriages (at least three consecutive miscarriages) in the first trimester of pregnancy, compared with a control group of 28 parous women with normal fertility. There was no association with aPL. However, the small numbers may have masked any difference in the results. A recent meta-analysis study reported that LA, aCL and ß2GP1 all were strong risk factors for pregnancy loss [9]. A larger study of 269 patients [1] showed an increased prevalence of aPL (11% compared with 2.5%), with a PPV of 75%.
Anti-prothrombin antibodies

The aPTs have previously been related to pregnancy loss in APS. Since the higher prevalence of aPT was found in women with recurrent miscarriage and aPL, it is difficult to discriminate between the predictive value of aPT and that of aPL themselves [10]. Shoenfeld et al.’s [1] trial showed a significantly increased level of aPT in women with infertility, [Odds ratio (OR) = 5.15; 95% CI 2.12, 12.74] and in recurrent pregnancy loss, (OR = 5.42; 95% CI 2.4, 12.5), PPV 33%. These antibodies were more closely associated with secondary abortions, (m miscarriages after a live birth) than primary miscarriages (all pregnancies have terminated in miscarriage). The aPTs are not usually assessed in recurrent pregnancy loss. Routine testing for these antibodies may be indicated if other studies also report an increased prevalence of aPT in recurrent pregnancy loss and if their standardization can be improved.

Autoantibodies with anti-trophoblast actions

Testing for LA, aCL and aβ2GP1 is required for supporting the formal diagnosis of APS [11]. It has been suggested that antibodies to other PLs such as phosphatidylycerine (PS), phosphatidyl ethanolamine (PE), phosphatidyl choline (PC), phosphatidyl glycerol (PG), phosphatidyl inositol (PI), etc. may be useful to identify women with RPL negative for LA, aCL and aβ2GP1. However, the diagnostic and prognostic value of some of these antibodies has not been well documented. Moreover, at least in assays that employ anionic PLs, PL-binding proteins (β2GP1, in particular) are present in the plates; so it is difficult to understand whether the positive results in these assays are due to β2GP1-dependent aPL or to antibodies reactive only with other anionic PLs.

Although β2GP1-independent aPS antibodies have been shown in experimental in vitro models to react directly with PS exposed on the surface of the syncytio-trophoblast, their real pathogenic role is still debated. Actually, it has been shown that β2GP1 binds to PS as a cationic molecule and behaves as the main antigenic target expressed on the trophoblast cell membrane for the maternal aPL [3, 11].

The presence of IgG and IgM aPE antibodies was also suggested to be a reliable risk factor for early fetal losses (as they affect trophoblast formation) [12, 13]. Hence, measurement of aPS and aPE antibodies has been said to be indicated in women with early recurrent pregnancy losses, since they represent antibodies that—in addition to aβ2GP1 antibodies—affect cell division during embryogenesis and the normal function of the trophoblast [12–14].

It may be that a full aPL panel should be measured for the diagnosis of autoimmune reproductive failure, particularly in the case of negativity of LA, aCL and aβ2GP1. However, the standardization of these assays is far from being comparable with that we have obtained so far for the standard aPL tests.

Obstetric complications of aPL

In APS, defined as the persistent presence of aPL (LA, aCL, aβ2GP1 antibodies) and the loss of three or more miscarriages prior to 10 weeks, or the loss of one or more fetuses above 10 weeks, there is a higher incidence of obstetric complications including IUGR, PET, stillbirth and pre-term labour. Although there have been follow-up studies of APS, showing an increased incidence of late obstetric complications compared with a healthy control group, there have been no follow-up studies of the obstetric complications in aPL-associated recurrent miscarriage compared with recurrent pregnancy loss without aPL. The incidence of obstetric complications is higher in women with recurrent pregnancy loss than in the general population [15].

Treatment of obstetrical APS

The standard treatment of aPL in pregnancy consists of low-molecular weight heparin and low-dose aspirin [11, 16]. However, there are no comparative studies with which to judge this regimen. Hence, no predictive value can be given about treatment using evidence-based medicine. There are only descriptive reports. Recently, doubt has been cast on the role of aspirin, as a meta-analysis comparing three trials of aspirin compared with placebo showed a non-statistically significant OR of 1.05 in favour of aspirin [6]. Low-molecular weight heparins may lower the fetal loss rate; however, there is no effect on the incidence of late obstetric complications. Hence, when APS presents with late obstetric complications rather than pregnancy loss, no prediction can be made about prognosis with anti-coagulant treatment.

Intravenous immunoglobulin (IVIg), however, actually lowers the titre of autoantibodies. Although it is not an anticoagulant and does not prevent thrombosis, there is some evidence that IVIg may lower the incidence of late obstetric complications [17]. However, there is insufficient data to allow any predictive value to be given.

Anti-thyroid antibodies

Anti-thyroid antibodies (ATAs) have been suggested to be independent markers of ‘at-risk’ pregnancy. Euthyroid women with recurrent miscarriage have increased levels of autoantibodies either against thyroglobulin (aTG) or thyroid peroxidase (TPO) while the probability of abortion in women with ATA has been shown to be greater than in controls [18]. There are animal models in which active immunization of mice with thyroglobulin has raised antibodies to thyroglobulin, and leading to increased fetal wastage and lower fetal and placenta weights [19]. However, the pathophysiological role of these antibodies is still unclear. In recurrent pregnancy loss, the association between pregnancy loss and thyroid antibodies may be a result of: (i) a direct effect of ATAs on fetal tissue or (ii) the thyroid antibodies representing an underlying more generalized defect in autoimmunity. However, the prevalence of ATA has been reported to be 15–20% in normal pregnant women, compared with 20–25% in women with recurrent miscarriages [20]. In Marai et al.’s [8] study, anti-TPO antibodies were the only autoantibodies found to have a significant association with recurrent miscarriage. The aTPOs were found in 21% of the women with recurrent miscarriages (8/38) as compared with 0% in women with infertility and no miscarriages (0/20). However, in Shoenfeld et al.’s [1] larger study, there was no association with recurrent miscarriage as a whole, but anti-TG antibodies were associated with late pregnancy loss compared with controls, (OR 8.44; 95% CI 1.6, 43.8), PPV = 40%. Therefore, the prognostic value of ATA remains uncertain.

Anti-laminin antibodies

Laminin-1 is a major multifunctional glycoprotein that forms an integral part of basement membranes, and is the earliest synthesized component during embryogenesis. IgG anti-laminin antibodies have been associated with infertility and recurrent first-trimester miscarriages in humans [21]. Active immunization of naïve mice with laminin-1 followed by elevated circulating anti-laminin-1 antibodies results in reproductive failure manifested by a higher fetal resorption rate [22]. However, a MEDLINE search failed to identify any cohort studies examining the natural history of pregnancy in the presence of these antibodies. There is little information about the PPV of these antibodies.
Anti-nuclear antibodies

Cubillos et al. [23] found that the incidence of ANAs was 31.8% in patients with a history of miscarriages (110 patients), but only 5.7% in 35 healthy patients with proven fertility and no history of pregnancy loss or autoimmune disease. In previous studies, a high prevalence of low-titre ANA have been reported in the sera of patients with both explained and unexplained pregnancy losses [24]; However, the significance of these findings is still unclear. ANAs were found with a higher prevalence in patients with autoimmune disease in Shoenfeld et al.’s [1] study. However, they were not found to occur with a higher prevalence in patients with infertility or recurrent pregnancy loss.

Anti-sacchromyces cerevisiae antibodies

In Shoenfeld et al.’s [1] series, ASCAs were found to be associated with RPL. ASCAs can predict the development of the Crohn’s disease many years in advance [25]. Crohn’s disease has been reported to be associated with intraterine growth restriction and pre-term labor, and fetal loss has been significantly associated with the activity of Crohn’s disease at the time of conception [26, 27]. In Shoenfeld et al.’s (Shoenfeld) series, the OR for pregnancy loss was 3.9 (95% CI 1.5; 10.6) in the presence of ASCAs, with a PPV of 19.4%.

Comments

Many autoantibodies have been associated with impaired fertility and it is still not completely clear which antibody panel should be assessed in the management of pregnancy complications. In the absence of specific antibodies that are pathognomonic of pregnancy failure, it may be that a group of combined antibodies is more significant than any one antibody, and it may be more appropriate to assess a panel of antibodies rather than one antibody. Marai et al. [8] tried this approach by screening the titres of seven autoantibodies in the sera of women with recurrent miscarriage. Autoantibodies to a combined panel of TPO, TG and ENAs were found to be most predictive. In Shoenfeld et al.’s [1] study, a combination of ASCA, aPL and aPT was found with the most predictive compared with controls with an OR of 5.23 (95% CI 2.8; 2.9) with a PPV of 47.9%.

There is, however, a general consensus to screen for aPL, LA, aCL and aβ2GP1 in recurrent pregnancy loss or obstetric complications such as PET, IUGR or stillbirth. The role of other antibodies such as ATA, aPS, aPE, aPT, etc. remains controversial, due to differing prevalences in different series. A large meta-analysis of published trials is required in order to determine the prevalence of each particular autoantibody in different forms of reproductive failure. Cohort studies are necessary to determine the true incidence of pregnancy loss in the presence of each autoantibody or combinations of auto-antibodies. These cohort studies should either be corrected for the subsequent miscarriages due to fetal chromosomal aberrations, or use multivariate analysis to correct for the effect of confounding factors such as maternal age. Accurate figures will subsequently become available regarding the PPV.

Disclosure statement: The authors have declared no conflicts of interest.

References