Bidirectional effects on autoimmunity and reproduction

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BACKGROUND: Autoimmune diseases may selectively affect women in their reproductive years, and conversely, pregnancy may affect the expression of autoimmune disease. This review addresses the impact of abnormal autoimmunity on female fertility, premature ovarian failure (POF) and recurrent pregnancy loss, as well as the influence of pregnancy in systemic lupus erythematosus (SLE). METHODS: From a PubMed search, citations were selected for their immunological and gynecological relevance. RESULTS: The presence of antiphospholipid antibody (aPL) does neither correlate with the type of female infertility diagnosis nor affect outcomes, and treatment is not indicated. Autoimmunity as a cause of POF is probably limited to the cases associated with the autoimmune thyroid diseases. With respect to recurrent spontaneous abortion, there is no consensus on the mechanisms of an autoimmune effect, although vasculopathy of the terminal spiral arteries may be implicated, but there is a general consensus to screen for aPL when recurrent spontaneous abortion is unexplained. Well-designed diagnostic studies are needed to estimate the true association between specific autoantibodies and recurrent spontaneous abortion. With respect to SLE, pregnancy should be avoided when the disease is active, and the potentially harmful impact of pregnancy can be minimized by multi-disciplinary care. CONCLUSIONS: Autoimmunity may impair female fertility and, in particular, the antiphospholipid syndrome is associated with recurrent spontaneous abortion. Integration of mechanistic and clinical information by multi-disciplinary teams is needed to manage reproductive issues in women with autoimmune diseases.

Keywords: infertility; pregnancy loss; systemic lupus erythematosus; antiphospholipid antibodies

Introduction

The relationship between autoimmunity and reproduction has long been recognized. As most autoimmune disturbances have a predilection for women in their reproductive years, the clinical impact of abnormal autoimmune function on reproductive processes has a paramount importance. Furthermore, this relationship is bidirectional and includes many diverse issues, such as the influence of autoimmunity in infertility, premature ovarian failure (POF) and recurrent pregnancy loss (RPL), on one way, or the impact of pregnancy on the outcome of autoimmune diseases, on the other way. In this review article, we will focus on whether abnormal autoimmunity reduces female fertility and which autoimmune disturbances are the basic causes of POF and RPL in patients with autoimmune diseases. Additionally, we will analyze the influence of pregnancy in systemic lupus erythematosus (SLE), the most representative of the autoimmune diseases. A number of other issues, such as the autoimmune mechanisms involved in endometriosis-related infertility, the potential induction of autoimmune disturbances by assisted reproductive technologies, the fetal complications produced by some autoantibodies (i.e. congenital heart block by anti-Ro/SSA and anti-La/SSB antibodies), the influence of estrogen–progestogen hormonal therapy in the development of SLE flares, or the role of autoimmunity on unexplained male infertility, stay significant but are beyond the scope of this article.

Methods

The decision to focus on the specific topics was taken due to their common and high interest for both obstetricians/gynecologists and internists/rheumatologists. The literature search was performed using Pubmed (keywords: infertility, pregnancy loss, pregnancy AND autoimmunity, autoimmune diseases, SLE), the citations were selected for their immunological and gynecological relevance and the discussion of the retrieved articles followed a multi-disciplinary (internist/gynecologist) approach.
Influence of autoimmunity on reproduction

Autoimmunity and infertility

A key controversial question is whether fertility is impaired in female patients with autoimmune diseases. Except for drug-induced (e.g. cyclophosphamide) ovarian failure, primary infertility is not prominent among patients with systemic autoimmune diseases, such as SLE (Lockshin, 2004). However, discrepancies exist about the role of several autoantibodies that have been described in women with unexplained infertility, either with or without a known underlying autoimmune disease. Conversely, organ-specific autoimmune diseases producing ovary, adrenal and thyroid failure (endocrine autoimmune diseases) may cause female infertility due to POF (Hoek et al., 1997).

Several studies have detected a higher prevalence of antinuclear, anti-dsDNA, anti-smooth muscle, anti-parietal cell, anti-thyroid microsomal, anti-reticulin, anti-mitochondrial, anti-liver/kidney microsomal, anti-carbonic anhydrase, antigonadotrophin and, more commonly, antiphospholipid antibodies (aPLs) in women with unexplained infertility (Wilson et al., 1975; Taylor et al., 1989; Blumenfeld et al., 1993; Roussev et al., 1996; Reimand et al., 2001; Marai et al., 2004; Shatavi et al., 2006; Shoenfeld et al., 2006; Abalovich et al., 2007). Although the published series support the conclusion that some autoantibodies are present more often in infertile patients compared with control women (Table I), it is unclear which antibodies, if any, are associated with an altered prognosis for the infertile women and, therefore, the question of which antibodies should be measured remains unsolved (van Voorhis and Stovall, 1997; Shoenfeld et al., 2006).

However, special attention should be paid to the aPL. One of the greatest controversies in the field of autoimmunity and reproduction in recent years has been whether the presence of aPL has a role in the pathogenesis of female infertility, thus influencing reproductive outcome in infertile women undergoing in vitro fertilization (IVF) (Carp and Shoenfeld, 2007). In fact, several laboratories offer panels of serum autoantibody assays to screen patients including unexplained infertility. Additionally, a report investigating the possible association between aPL and spontaneous abortion after the first IVF and embryo transfer treatment has shown low and similar aPL positivity rates in abortion (4.8%) and term pregnancy (4.8%) groups, thus indicating that aPL testing should not be considered in an infertile general population reaching an IVF program (Balasch et al., 1998). A meta-analysis of seven eligible studies on aPL and IVF outcome involving 2053 patients, of whom 703 (34%) had at least one abnormal aPL result, showed that there was no significant association between aPL and either clinical pregnancy or live birth (Hornstein et al., 2000).

Additional evidence for the lack of association between the presence of aPL and female infertility comes from therapeutical studies performed on aPL-positive infertile women undergoing IVF (Table II). The first such study (Birkenfeld et al., 1994) employed the use of 80 mg of aspirin daily and 10 mg of prednisone daily starting 2 weeks before initiation of IVF cycles. Subjects were 15 women who had failed to conceive during their latest embryo transfer cycle using either fresh or frozen embryos and who had presented at least one positive result for lupus anticoagulant, anticardiolipin antibodies (aCL) or antinuclear antibodies at some unspecified time in the past. Seven (47%) women established ongoing pregnancies. The non-randomized study design, the lack of any controls and the small number of patients preclude any comment about efficacy of treatment. In another non-randomized study (Kutteh et al., 1997), the authors found that 9.9% of 191 infertile women undergoing IVF had aCL and an additional 8.9% were positive for the aPL. There were 19 women with antibodies who were empirically treated with heparin and aspirin and 10 achieved pregnancies (52.6%), whereas eight of 17 (47%) untreated women achieved pregnancies. These differences were not significantly different. In a third study (Schenk et al., 1996), the authors found that 43 of 90 (48%) IVF patients were positive for two or more aPL in a panel of immunoassays testing for IgG and IgM antibodies to six phospholipid antigens. These women were treated with heparin (5000 U s.c., twice daily) and low dose aspirin (81 mg, Hornstein et al., 2000) have been unable to find differences in aPL positivity rates between infertile women and fertile controls or between different diagnostic categories of infertile female patients including unexplained infertility.

### Table I. Summary of studies on autoantibodies in a general infertility population.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Population</th>
<th>ASMA (%)</th>
<th>ATA (%)</th>
<th>ANA (%)</th>
<th>aPL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson et al. (1975)</td>
<td>Ovulatory dysfunction (n = 77)</td>
<td>35*</td>
<td>10</td>
<td>20*</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Fertile controls (n = 77)</td>
<td>3</td>
<td>14</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Taylor et al. (1989)</td>
<td>Unexplained infertility (n = 41)</td>
<td>49*</td>
<td>—</td>
<td>10</td>
<td>17*</td>
</tr>
<tr>
<td></td>
<td>Pregnancy women (n = 351)</td>
<td>17</td>
<td>—</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Roussev et al. (1996)</td>
<td>Unexplained infertility (n = 45)</td>
<td>—</td>
<td>9*</td>
<td>10</td>
<td>42*</td>
</tr>
<tr>
<td></td>
<td>Normal controls (n = 15)</td>
<td>—</td>
<td>0</td>
<td>—</td>
<td>7</td>
</tr>
<tr>
<td>Reimand et al. (2001)</td>
<td>Unexplained infertility (n = 34)</td>
<td>35*</td>
<td>6</td>
<td>12*</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Normal controls (n = 392)</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Marai et al. (2004)</td>
<td>Unexplained infertility (n = 20)</td>
<td>—</td>
<td>0</td>
<td>—</td>
<td>65*</td>
</tr>
<tr>
<td></td>
<td>Fertile controls (n = 15)</td>
<td>—</td>
<td>0</td>
<td>—</td>
<td>7</td>
</tr>
<tr>
<td>Shoenfeld et al. (2006)</td>
<td>Unexplained infertility (n = 69)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>12*</td>
</tr>
<tr>
<td></td>
<td>Normal controls (n = 120)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2</td>
</tr>
</tbody>
</table>

ASMA, anti-smooth muscle antibodies; ATA, anti-thyroid antibodies; ANA, antinuclear antibodies; aPL, antiphospholipid antibodies; aPT, anti-prothrombin antibodies. *P < 0.05.
Orally, daily). The per embryo implantation rate of 12.9% in the treated, seropositive women was not significantly different from that in the untreated, seronegative women (7.7%). Moreover, neither the clinical nor ultimate ongoing pregnancy rates differed according to aPL status or treatment. Finally, in the largest treatment study (Sher et al., 1994), the authors found a higher prevalence of aPL in women with confirmed pelvic pathology (pelvic inflammatory disease, iatrogenic abdominal/pelvic adhesions or endometriosis) than in those with unexplained infertility. For treatment (heparin, 3000 U s.c., twice daily and 81 mg of aspirin p.o. daily), only selected women with pelvic pathology were included. Although how women were selected for treatment is unclear, 49% of those treated had clinical pregnancies compared with 16% of the 25 women not treated (P < 0.05). The relatively high rates of aPL in women with pelvic pathology differ from those of many other studies where no increase in aPL in women with tubal factor infertility was found. It is also crucial to recognize that a 49% clinical pregnancy rate in the aPL positive, treated women is similar to the results of most experienced centers for comparable young patients (tubal factor, endometriosis) who are not treated with heparin and aspirin, whereas the reported 16% clinical pregnancy rate for the untreated patients in the same good prognosis categories is low compared with most programs. Also, when pregnancy rates of untreated aPL negative and positive women were compared, the confidence limits of the ratio of the pregnancy rates (aPL negative/aPL positive) were 0.58–4.72, suggesting that aPL status had little effect on IVF outcome. Thus, it is possible that the apparently improved IVF pregnancy rates seen in treated infertile patients were independent of aPL status. An additional reason for these discrepancies among the studies could be the different cut-off for aPL positivity.

Therefore, on the basis of the above evidence, it is well accepted at present that aPL are not related with female infertility and do not affect IVF success, thus therapy for aPL is not justified.

Autoimmunity and POF

Another important issue concerning autoimmunity and infertility is the role of autoantibodies directed against ovary, adrenal and thyroid glands in the development of POF, a primary ovarian defect affecting ~1% of women less than 40 years old (Coulam et al., 1986; Beck-Peccoz and Persani, 2006). Despite the fact that many cases of POF have been effectively linked to chromosomal, genetic, enzymatic, toxic, infectious and iatrogenic causes, the underlying etiopathogenic mechanism causing most POF cases remains unsolved (Davis, 1996). However, several studies have suggested that some cases of POF may be the direct result of autoimmune-mediated destruction of the ovaries (La Barbera et al., 1988; Blumenfeld et al., 1993; Hoek et al., 1997; van Voorhis and Stovall, 1997; Tuohy and Altuntas, 2007).

One of the reasons to suspect the autoimmune etiology of POF is its frequent association with some endocrine autoimmune diseases, mainly autoimmune thyroid diseases (Poppe and Velkeniers, 2004; Poppe et al., 2006) and Addison’s disease (Botazzo et al., 1996). The autoimmune thyroid diseases are also frequently associated with endometriosis and the polycystic ovarian syndrome (Poppe et al., 2006)—two conditions where infertility is common. In patients with Addison’s disease, two main types of autoantibodies are detected: cy–Ad antibodies, directed against adrenal cell cytoplasm, and St–C antibodies, which also react with a variety of steroid-producing cells, including adrenal cortex, testes, trophoblast and different types of ovarian cells such as follicular and luteal cells. Of patients with Addison’s disease and POF, 60% present St–C antibodies, which are also present in 15–20% of patients with Addison’s disease but without amenorrhea, but 40% of them will develop POF during the ensuing 10–15 years of follow-up. These autoantibodies show some specificity for enzymes involved in steroid production, such as p450-17a-hydroxylase and the p450 side chain cleavage product of p450-17a-hydroxylase (Forges et al., 2004).

The frequency of POF in other endocrine autoimmune diseases varies between different study populations, but it often occurs as part of an autoimmune polyglandular syndrome with high frequencies of hypothyroidism, insulin-dependent diabetes mellitus and adrenal abnormalities (Ahonen et al., 1988; Kalantaridou et al., 1998).

POF may also occur as an isolated ovarian-specific disorder independent of any polyglandular or global systemic autoimmune disorder. Several autoantibodies have been described in isolated POF: (i) antibodies against zona pellucida: they have been described in 5.6% patients with isolated POF (Kamada et al., 1992) and, in experimental animal models, these antibodies have been able to inhibit the follicular development (Smith and Hosid, 1994); (ii) antibodies against FSH and LH receptors: some investigators have described the presence of these antibodies in patients with isolated POF (Austin et al., 1979; Tang and Faiman, 1983; van Weissenbruch et al., 1991; Wheatcroft et al., 1994; Anasti et al., 1995), but they have also been detected in patients with iatrogenic ovarian failure (Hoek et al., 1997); (iii) antibodies against other endocrine systems: anti-thyroid antibodies are found in some patients with isolated POF as well as autoantibodies against gastric wall cells, Langerhans cells and

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**Table II**. Summary of studies on medical treatment of aPL-positive women undergoing in vitro fertilization procedures.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No. treated</th>
<th>Treatment</th>
<th>Treatment criteria</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birkenfeld et al. (1994)</td>
<td>15</td>
<td>Aspirin+Prednisone</td>
<td>&gt;1 of 4 autoantibody assays positive; last fresh or frozen embryo transfer unsuccessful</td>
<td>7/15 (46.6%) ongoing pregnancies</td>
</tr>
<tr>
<td>Sher et al. (1994)</td>
<td>169</td>
<td>Heparin+Aspirin</td>
<td>&gt;1 of 18 aPL assays positive; organic pelvic pathology</td>
<td>82/169 (49%) clinical pregnancies</td>
</tr>
<tr>
<td>Schenck et al. (1996)</td>
<td>35</td>
<td>Heparin+Aspirin</td>
<td>&gt;2 of 12 aPL assays positive; unselected candidates</td>
<td>39.7% clinical pregnancies compared to 33.3% for untreated seronegatives (N.S.)</td>
</tr>
<tr>
<td>Kutteh et al. (1997)</td>
<td>19</td>
<td>Heparin+Aspirin</td>
<td>&gt;1 of 3 assays for aCL isotypes positive; unselected patients</td>
<td>No differences for clinical pregnancies (52.6%) from untreated cycles (47%)</td>
</tr>
</tbody>
</table>

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acetyl-choline receptor; (iv) antinuclear and anti-DNA antibodies: anti-DNA antibodies have been found in 10.5% of women with POF while in a control group of healthy fertile women only 3.3% presented such antibodies (Blumenfeld et al., 1993); and (v) novel autoantibodies: recent studies on POF patients implicate the ubiquitous expressed glycolytic enzyme, alpha-enolase, as a potential antigenic target (Sundblad et al., 2006), and the ovarian-specific maternal-effect protein, Mater, whose expression is essential for fertility (Tong et al., 2004; Tuohy and Altuntas, 2007). However, against the autoimmune origin of POF in these patients is the fact that it is very uncommon to find oophoritis in cases with isolated POF.

Therefore, an abundance of evidence indicates that autoimmunity is primarily responsible for POF mainly in cases associated with autoimmune thyroid diseases, Addison’s disease and with other polyendocrine autoimmune diseases, but in patients with isolated POF the evidence favoring an autoimmune origin is not so strong.

Autoimmunity and RPL

Pregnancy loss in humans is very high, approaching a rate up to 75% of fertilized ova and 15% of well-confirmed pregnancies (Miller et al., 1980; Wilcox et al., 1988; Boklage, 1990). RPL, usually defined as two or more consecutive losses, affects 2–5% of women in reproductive age (Hatasaka, 1994). Although no uniform classification of pregnancy losses has been used in the literature, at present, it seems appropriate to use the classification recently proposed by the European Society of Human Reproduction and Embryology (ESHRE) (Farquharson et al., 2005). Several studies have reported the presence of various autoantibodies in patients with RPL (Roussev et al., 1996). However, the questions arise as to which antibodies are predictive of pregnancy losses in patients with known autoimmune diseases (i.e. SLE), and which autoantibodies should be sought in women with unexplained RPL.

The antiphospholipid syndrome (APS)—either primary or associated to SLE—is the autoimmune disease most commonly associated with RPL in affected patients. A large number of studies have found that in women with SLE, those with aPL are at an increased risk for RPL (reviewed in Carmona and Balasch, 2002). However, the incidence of pregnancy loss in the APS has been reported as varying from as high as 90% (Rai et al., 1995) to as low as 15% (Empson et al., 2002). Controversy still remains over the type of pregnancy loss more closely related with aPL. A retrospective study in a group of 366 women with RPL compared the type of prior pregnancy loss between women with and without aPL. A total of 79 women included in the study tested positive for aPL, whereas 290 did not. The rate of prior pregnancy loss was similar in both groups (>80%). However, those patients with aPL had 50% of prior late pregnancy losses compared with <25% late pregnancy loss rate in women without aPL. The specificity of late pregnancy loss for the presence of aPL was 76% compared with only 6% for two or more early pregnancy losses, thus suggesting that late pregnancy loss is the most frequent type of loss associated with APS. In contrast, another group (Rai et al., 1995) found a high prospective rate of pregnancy loss in 20 untreated pregnancies of women with RPL and aPL, when compared with a cohort of 100 consecutive women with RPL, in whom no underlying cause to account for their pregnancy loss was found. Of the 20 women with aPL, 18 (90%) presented a subsequent pregnancy loss, compared with 34 of the 100 women (34%) with normal investigations (P < 0.001). Interestingly, early pregnancy loss was the most common type of loss in women with aPL. This is consistent with other studies that have found that most of the aPL-related pregnancy losses were biochemical pregnancy losses or early pregnancy losses in nature (Parazzini et al., 1991; Parke et al., 1991; MacLean et al., 1994; Yetman and Kutteh, 1996). Experimental data using APS animal models further support the evidence that any type of pregnancy loss (including pre-implantation embryos), but mainly embryo resorption, is associated with aPL (Sthoeger et al., 1993; Ikematsu et al., 1998; Shoefeld et al., 1998; Ziporen and Shoenfeld, 1998).

These discrepancies between studies can be explained by the differences in the patient selection criteria. In some studies, only patients with aCL were included; patients with SLE were included in some studies but not in all. The nature of the population included in the study and the diverse severity of the disease can also influence in the observed differences. So, it is very important that all studies include a very clear definition of the selection criteria in order to allow adequate comparisons.

The association of aPL with RPL in patients with SLE and the APS suggests a causative role but by no means does it prove it. The major pregnancy-related target for aPL is the placenta, and uteroplacental insufficiency is often attributed to vasculopathy of the terminal spiral arteries, which nourish the placental intervillous space. These vessels have smaller diameter and showed intimal thickening, fibrinoid necrosis and intraluminal thrombosis (De Wolf et al., 1982). In other cases, the infarcted region may show villous congestion and hemorrhage and early trophoblastic necrosis (Benden et al., 1987). In addition to placental infarction and thrombosis, perivillous fibrin deposition and evidence of decidua vascular atherosclerosis, indicative of spiral artery vasculopathy, are seen in some APS cases (Gharavi et al., 2001). In a large study, 47 placentae from 45 women (16 of whom had APS) who had had fetal death at 16–39 weeks’ gestation were analyzed. Placentae from patients with the APS showed a decrease in vasculo-syncytial membranes; additionally, hypovascular villi and thrombosis and infarction were seen more often than in placentae from women with aPL (Out et al., 1991). All these findings are secondary ischemic-hypoxic changes caused by thrombosis/decidual vasculopathy (Magid et al., 1998); however, they are not specific to APS and do not always correlate with the fetal outcome. Furthermore, the conventional histopathologic studies could not distinguish between placentae from women with APS and from women with pre-eclampsia (Levy et al., 1998) and placental thrombosis is not always present in women with APS and pregnancy losses (Sebire et al., 2003).

The mechanisms by which aPL cause the above described changes are not completely understood and several hypotheses have been proposed (Table III). The earliest one is eicosanoid balance alteration mediated by aPL. Inhibition of endothelial cell production of PGI2 (a potent inhibitor of platelet aggregation and vasodilator) and enhancement of placental TXA2 production by plasma from aPL-positive women have been demonstrated by some investigators (Table I) (Carreras et al., 1981; Schorer et al., 1992). Another possible mechanism for thrombosis in
APS is the cross-reactivity between aPL and glycosaminoglycans, a family of heparin-like substances related with the non-thrombotic properties of the vascular endothelium. The inhibition of this function by aPL may in part explain the thrombosis associated with them. In one study, the aPL inhibited the heparin-dependent activation of antithrombin III by up to 80% (Chamley et al., 1993). Additionally, aPL may interfere with the function of natural inhibitors of coagulation such as placental anticoagulant proteins (PAP) and others. PAP are a group of four calcium-dependent phospholipid-binding proteins that inhibit phospholipid-dependent steps of coagulation by making phospholipid inaccessible to clotting factors (Walker et al., 1992). The major component of the PAP family is the PAP-1, also called annexin V, which is most abundant in the placenta. Annexin V and aPL compete for phospholipids in coagulation assays (Sammaritano et al., 1992). It has been shown that the distribution of annexin V over the intervillous surface was significantly lower in patients with APS than that in women with RPL (Rand et al., 1994). Furthermore, in another study, IgG fractions from patients with APS were incubated with cultured trophoblasts and human umbilical vein endothelial cells. Cells exposed to aPL had reduced levels of annexin V and increased procoagulant activity (Rand et al., 1997). These findings suggest that reduced annexin V production and inhibition of its anticoagulant function by aPL may play a role in pregnancy loss in APS patients.

However, other non-thrombotic mechanisms have been implicated, and interference with the embryonic implantation is the mechanism that has received most attention. The aPL have been found to react directly with third trimester villous trophoblast cells (Lyden et al., 1992; Di Simone et al., 2000), prevent proliferation of trophoblast derived from chorionic carcinoma cells (Chamley et al., 1998), inhibit in vitro chemotaxis and differentiation of villous trophoblast isolated from third trimester placentae (Di Simone et al., 1999), decrease trophoblast invasion (Sebire et al., 2002; Bose et al., 2005) and inhibit extravillous trophoblast differentiation (Quenby et al., 2005). Furthermore, aPL can induce pregnancy loss in mice by impairing the embryonic implantation capacity, likely because of a direct interaction with the trophoectoderm cells (Sthoeger et al., 1993).

Additionally, aPL may impair the placental production of chorionic gonadotrophin during the early phases of pregnancy, thus determining the embryonic evolution (Shurzt-Swirski et al., 1993) and, in the mice model, APS is associated with a diminished secretion of interleukin-3, which is positively related with pregnancy (Fishman et al., 1992) and the pregnancy loss is prevented by in vitro administration of recombinant interleukin-3 (Fishman et al., 1993).

Recently, the role of complement activation by the aPL has also received a great deal of attention. Several studies have suggested that activation of the complement cascade is necessary for aPL-mediated thrombophilia and fetal loss (Holers et al., 2002; Salmon et al., 2002; Girardi et al., 2004; Pierangeli et al., 2005). It was found that inhibition of the complement cascade in vivo, using the C3 convertase inhibitor complement receptor 1- related gene protein y (Cryy)-Ig, blocks aPL-induced fetal loss and growth retardation and reverses aPL-mediated thrombosis (Holers et al., 2002). Furthermore, mice deficient in complement C3 and C5 (C3 – / – and C5 – / –, respectively) were resistant to thrombosis, endothelial cell activation and fetal loss induced by aPL. Additionally, an anti-C5 monoclonal antibody reversed thrombogenic properties of aPL in vivo, thus confirming the involvement of C5 complement activation in aPL-induced thrombosis (Holers et al., 2002; Pierangeli et al., 2005). It has also been shown that the interaction of complement component 5a (C5a) with its receptor (C5aR) is necessary for thrombosis of placental vasculature (Girardi et al., 2003).

Another important issue is the role of autoimmunity in unexplained RPL. In addition to aPL, several other autoantibodies have been associated with unexplained RPL, including anti-annexin V (Rand et al., 1998), anti-prothrombin (von Landenberg et al., 2003), anti-nuclear (Kutteh, 2002), anti-laminin (Inagaki et al., 2001, 2003), and anti-gliadin type IgA and IgG anti-transglutaminase antibodies related with celiac disease (Bustos et al., 2006). Marai et al. (2004) analyzed 38 women with unexplained RPL and 28 control parous women and found a significant association between unexplained RPL and antithyroid peroxidase antibodies and a combinatorial panel of autoantibodies, including those against thyroid peroxidase, thyroglobulin and extractable nuclear antigens, but not with aPL. Shoenfeld et al. (2006) analyzed a group of 109 patients with RPL and 120 healthy volunteers. In RPL, aPL, anti-prothrombin and anti-Saccharomyces cerevisiae antibodies (ASCA) were more prevalent than in controls, with odd ratios (ORs) of 4.8, 5.4 and 3.9 for each antibody, respectively. Therefore, although there is a general consensus to screen for aPL in patients with unexplained RPL, larger cohort studies are necessary to determine the true incidence of RPL in the presence of each autoantibody or combinations of autoantibodies. In addition, these cohort studies should either be corrected for the

Table III. Summary of proposed mechanisms of aPL-mediated RPL.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombotic mechanisms</td>
<td></td>
</tr>
<tr>
<td>Eicosanoid balance alteration</td>
<td></td>
</tr>
<tr>
<td>Cross-reactivity with glycosaminoglycans</td>
<td></td>
</tr>
<tr>
<td>Interference with the function of natural inhibitors of coagulation</td>
<td>(i.e. placental anti-coagulant proteins such as annexin V)</td>
</tr>
<tr>
<td>Interference with the embryonic implantation</td>
<td></td>
</tr>
<tr>
<td>Interaction with the trophoectoderm cells</td>
<td></td>
</tr>
<tr>
<td>Direct reaction with villous trophoblast cells</td>
<td></td>
</tr>
<tr>
<td>Hormonal imbalance</td>
<td></td>
</tr>
<tr>
<td>Impairment of the placental production of chorionic gonadotrophin</td>
<td></td>
</tr>
<tr>
<td>Cytokine imbalance</td>
<td></td>
</tr>
<tr>
<td>Diminished secretion of interleukin-3</td>
<td></td>
</tr>
<tr>
<td>Complement activation</td>
<td></td>
</tr>
</tbody>
</table>

Table IV. Summary of studies on the influence of pregnancy on the course of SLE.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>No. of pregnancies</th>
<th>SLE flare (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nossent et al. (1990)</td>
<td>39</td>
<td>74</td>
</tr>
<tr>
<td>Petri et al. (1991)</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Wong et al. (1991)</td>
<td>29</td>
<td>45</td>
</tr>
<tr>
<td>Derksen et al. (1994)</td>
<td>35</td>
<td>18</td>
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<td>Ruiz-Irastorza et al. (1996)</td>
<td>78</td>
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<td>Lima et al. (1995)</td>
<td>108</td>
<td>57</td>
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<td>Carmona et al. (1999)</td>
<td>60</td>
<td>28</td>
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subsequent spontaneous abortions caused by fetal chromosomal aberrations, or should use multi-variate analysis to correct for the effect of confounding factors such as maternal age.

**Influence of pregnancy on SLE**

SLE is the autoimmune disease that most commonly can be compromised by pregnancy because of its fluctuant nature that alternates periods of clinical activity with others of remission, with hormonal changes being some possible triggers of reactivation. The influence of pregnancy in other autoimmune diseases is less notorious, either because they rarely appear in young women (Sjögren’s syndrome, systemic vasculitis) or because their outcome is scarcely influenced by hormonal changes.

At present, as therapy has helped more SLE patients to feel well enough to have families, the topic of the influence of pregnancy on SLE is a matter of great interest. However, there is no agreement about the exact influence of pregnancy on the course of SLE. Thus, several prospective and retrospective recent studies (Nossent and Swaak, 1990; Petri et al., 1991; Wong et al., 1991; Tincani et al., 1992; Derksen et al., 1994; Lima et al., 1995; Ruiz-Ifaorosta et al., 1996; Carmona et al., 1999) have shown contradictory results with a reported frequency of lupus flare ranging from 18 to 74% (Table IV). This wide range in lupus flare during pregnancy among different studies may be explained by several factors, such as different entry criteria, methodological differences in the study design, small numbers of patients included, criteria used to diagnose and quantify flare, and routine steroid administration (Urowitz et al., 1993; Khamashita et al., 1997). Additionally, there could be many difficulties in the differential diagnosis between SLE flare and some pregnancy symptoms (facial rash, arthralgia, fatigue and edema in the legs) as well as between renal flare and pre-eclampsia.

The use of prophylactic steroids during pregnancy is a matter of controversy. Some authors recommend the use of prednisone throughout pregnancy for all pregnant lupus patients (Petri et al., 1991) but others disagree (Wong et al., 1991; Derksen et al., 1994; Khamashita et al., 1997). Our group (Carmona et al., 1999) has found that the majority of SLE flares (46.6%) occurred during late pregnancy or the postpartum period despite the fact that, initially, most women were prophylactically given prednisone from 36 weeks pregnancy until 1 month after delivery, thus suggesting that prednisone does not prevent lupus flare and causing us to abandon such practice. Therefore, pregnancy does not cause SLE to worsen, provided that the disease is clinically inactive at conception and patients are managed according to a careful multi-disciplinary monitoring and treatment schedule. This contention is also supported by experimental evidence showing that pregnancy, parturition and suckling have no negative effects on variables of disease activity in the mouse model of SLE (McMurray et al., 1993).

The clinical take-home messages are that SLE patients should be advised to become pregnant when the disease is inactive, strict obstetrical/medical care should be performed during pregnancy and, although prophylactic steroids are not required, several drugs, such as hydroxychloroquine, prednisone and azathioprine, can be safely used in case of an SLE flare (Ostensen et al., 2006).

**Final remarks**

This review article has analyzed several of the most clinically relevant issues implying the bidirectional relationship between autoimmunity and reproduction. It can be concluded that autoimmunity may impair female fertility and reproductive outcome. Special attention should be paid to the presence of aPL due to their close association with RPL. In turn, pregnancy may adversely affect autoimmune conditions, mainly SLE. This stresses the need for well-coordinated, multi-disciplinary teams, including obstetricians/gynecologists, internists/rheumatologists and hematologists/immunologists, to manage reproductive issues in females affected by autoimmune diseases.

**References**


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