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REVIEW —

AUTOIMMUNE CAUSES OF RECURRENT PREGNANCY LOSS

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ABSTRACT

Recurrent pregnancy loss (RPL) is the loss of 3 or more spontaneous and consecutive pregnancies. There are many causes, such as genetic, anatomic, hormonal, medical and immunologic causes. Two theories, the alloimmune and the autoimmune theories, explain the immunologic cause. The Antiphospholipid Antibody (APA) Syndrome is considered as the autoimmune cause of RPL. It involves two antibodies, Lupus anticoagulant (LAC) and the anti-cardiolipin antibody (ACA). The rate of LAC is 7% and of ACA is 15%, among pregnant women. These two antibodies are believed to cause thrombosis in the maternal circulation, leading to the events that lead to the fetal losses. Women with these antibodies, along with other factors, are believed to be at high risk for RPL. The diagnostic criteria for the APA syndrome include elevated LAC or ACA serum levels and clinical findings of thrombosis, thrombocytopenia and RPL. Presently, the medical treatment of the APA syndrome includes heparin, low-dose aspirin, and immunoglobulins. There must also be an active attempt to search for other causes of RPL among patients with APA syndrome, such as anatomic, endocrinologic, anatomic and medical problems. Management of RPL should also include extensive counseling for the patient and her family.

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INTRODUCTION

Recurrent pregnancy loss (RPL) is both a deep personal tragedy for the prospective parent and a dilemma to their physician. With advances in various fields of medicine, new insights into this condition have been established. This problem is now the concern of obstetrician-gynecologists, immunologists, geneticists, clinicians, and social scientists that the management requires a team effort.

RPL is defined as the loss of three or more spontaneous and consecutive pregnancies, occurring before the period of viability. Usually they occur as abortions, with ages of gestation less than 20 weeks or fetal weights of less than 500 grams. If the patient has never had carried a pregnancy to viability, it is labeled a *primary RPL*. If a viable pregnancy has been attained before the series of losses, the condition is a *secondary RPL*. If all losses take place before 12 weeks, these are early losses. After 12 weeks but less then 20 weeks, they are labeled as late losses (Kutteh and Pasquarette, 1995).

There have been changes in the measurement of the incidence of RPL. Based on clinically evident gestations, the rate of single losses during pregnancy ranges from 10-15 percent of pregnancies lasting at least 8 weeks. With the advent of better diagnostic techniques such as hCG beta assays, rates of RPL ranged from 24 to 43% of biochemically diagnosed pregnancies. This is often interpreted as a higher estimate than expected because many of these women were never clinically identified as being pregnant. For RPL, the estimated rate ranges from 1.01 to 1.4% of pregnancies (Kutteh and Pasquarette, 1995).

While RPL seems to be a relatively rare problem, it is a major cause of concern for patients and for physicians. The management of a single fertility problem is challenging enough; the management of recurrent infertility problems compounds the problem several times over. With new advances in the study of RPL, there are new insights in the cause and detection of this problem. This paper attempts to review the common causes of RPL. It will focus on the immunologic causes of RPL, particularly on the autoimmune causes, because of the recent increase in interest in this topic.

CAUSES OF RPL

There are many causes of RPL, with varying rates among patients (Table I).

Table I. Causes of RPL.

Chromosomal (parental)	1.8- 4.6 %
Anatomic	1 - 28 %
Immunologic	6 - 65 %
Unexplained	15 - 50 %
Hormonal	5 - 29 %

From Kutteh and Pasquarette, 1995.

As much as half of cases of RPL may be due to unknown causes. This group includes those patients who have tested negative in the work-up searching for genetic, anatomic, hormonal, and immunologic causes. Many of the present tests available, though much improved over those in the past, may not be sensitive enough to identify the cause for the RPL.

Fetal or placental villi karyotyping, by studying chromosomal patterns, has established the possibility of genetic causes of failed pregnancies. Genetic analysis of single-miscarriage abortuses has discovered abnormalities in as much as 60% of cases. Some of the common causes identified include aneuploidy, most commonly trisomy, monosomy, and polyploidy (Stephenson, 1996). Chromosomal analysis on the products of abortive pregnancies between patients with and without a history of RPL, however, showed no difference in the rates of abnormal karyotypes between the two groups (Stern et al, 1996). Losses of more than two due to a chromosomal cause may be much less than this rate.

Anatomic abnormalities include uterine congenital anomalies, intra-uterine adhesions or synechiae, leiomyomata, and cervical incompetence. Surgical correction procedures, whenever possible, have been attempted in the past. Success rates have variable results because of the inability to perform randomized clinical trials on these cases. Endocrinologic causes include the luteal phase deficiency, thyroid disease, and diabetes (Stephenson, 1996).

There are also certain medical conditions that have been historically associated with an increased risk of pregnancy loss. They are listed in Table Ⅱ. Many if not all of these conditions are now believed to be autoimmune in pathophysiology (Gleicher, 1994). Thrombo-embolic disease is leading cause of obstetric complications and is closely associated to the immunologic causes. It is characterized by a high risk of recurrence when the woman becomes pregnant (Barbour et al, 1995).

Table Ⅱ. Medical conditions associated with pregnancy loss.

1. Collagen Vascular Diseases
a. Systemic Lupus Erythematosus
b. Mixed connective tissue disease
c. Systemic sclerosis
2. Dermatitis herpetiformis
3. Coeliac disease
4. Herpes gestationis
5. Ulcerative colitis
6. Chron's disease
7. Chronic active hepatitis
8. Thyroid disease
9. Diabetes mellitus
10. Endometriosis
11. Pelvic Infection
12. Thrombo-embolic diseases

Modified from Gleicher, 1994.

IMMUNE THEORIES OF RPL

Immunologic causes are now identified as an important cause for RPL. While they may be the cause in a small minority of the identified cases, it may also be the possible cause of the large majority of presently unknown cases. There are two main theories on the immune nature of RPL. In the alloimmune theory state, the maintenance of normal pregnancy requires the immune system to recognize the implanting embryo as foreign. This allows the production of blocking antibodies to protect the embryo from maternal immune defenses. The autoimmune theory state, in which women's immune systems may produce phospholipid antibodies, is thought to have varied deleterious effects on pregnancy.

ALLOIMMUNE THEORY

The alloimmune theory may be the explanation for the RPL for more than half of patients. Mouse studies showed a high pregnancy resorption rate in cases of shared parental MHC. Increasing uterine suppressor cells by pre-immunization with lymphocytes resulted in lower pregnancy resorption rates. This is supported by studies which showed that humans having less diverse and more homozygous histo-compatibility antigen complexes have stronger signals to stimulate production of these blocking antibodies which leads to pregnancy losses (Kutteh and Pasquarette, 1995). The diagnosis of an alloimmune factor contributory to RPL has in the past depended on the results of:

1. Maternal and paternal HLA comparison
2. Assessment of maternal serum cytotoxic antibodies to paternal leukocytes
3. Assessment of maternal serum for blocking factors for maternal-paternal mixed leukocyte reactions.

The alloimmune testing consisted of human leukocyte antigen typing of both partners, the mixed leukocyte culture, and assessment of maternal immunoglobulins G (IgG) and M (IgM) against paternal T and B lymphocytes, using both the complement-dependent cytotoxicity assay and the complement- independent flow cytometric cross-match (Stephenson, 1996). An alloimmune disorder occurs if there is significant HLA type homology or if there are minimal antipaternal antibodies in the mother. The goal of therapy is to increase maternal immune system recognition of paternal cell antigens by the administration of paternal leukocytes or by immunoglobulin infusion to provide passive "blocking" antibodies.

There are criticisms on the alloimmune theory. Human HLA sharing does not preclude successful pregnancies. Comparative studies of the HLA sharing frequency between couples with RPL and without RPL show no statistically significant differences among groups. There are still many studies being conducted on the alloimmune causes of RPL.

AUTOIMMUNE CAUSES

Recent autoimmune studies have determined that approximately 10% of patients with RPL have recognized autoimmune factors. These factors are antibodies that have specificity against negatively charged phospholipids. Anti-phospholipid antibodies are closely related phospholipid-binding autoantibodies that are, respectively, measured by their capacity to prolong phospholipid dependent coagulation assays or via their capability to bind to cardiolipin, immobilized in a microtiter plate (Arnout et al, 1995). These are detected by determining the activity of lupus anticoagulant (LAC) and of anti-cardiolipin antibody (ACA) activity (Kutteh and Pasquarette, 1995).

LAC and ACA are strongly associated with a diverse set of clinical manifestations, including venous and arterial thrombosis, neuro-psychiatric disorders, thrombocytopenia and recurrent fetal loss, which together comprise the "anti-phospholipid antibody (APA) syndrome" (Love and Santoro 1990, Arnout et al, 1995)(TableⅢ).

Table Ⅲ. Criteria for the anti-phospholipid antibody syndrome.

Laboratory Finding - persistently elevated antiphospholipid antibodies:
Lupus anticoagulant (LAC)
Anti-cardiolipin antibody (LAC)
Clinical Findings
Thrombosis - venous or arterial
Recurrent fetal or pregnancy loss
Thrombocytopenia

From Arnout et al,1995.

One of the associated clinical outcomes among patients with antiphospholipid syndrome is RPL. A woman with a high ACA level may suffer as much as 70% of miscarriage recurrence. The mean rates for LAC and ACA are 7 and 15%, respectively, as described by Kutteh et al. Kwak et al reported a 15% increase in the incidence of these antibodies with each successive pregnancy that is lost. This suggests that the failing feto-placental unit may release phospholipid antigens that are auto-antigenic to the women. The incidence of antiphospholipid antibodies is 41.2% at the time of the third pregnancy loss in these women.

In a study by Lim, Festin and Andaman, the rates of APA among Filipino pregnant women were 13% among non-hypertensives and 50% among hypertensives. Increased IgM anti-cardiolipin and prolonged Kaolin clotting time do not seem to be correlated with hypertension. There is however a significant association with IgG anti-cardiolipin. The outcome of pregnancy in these patients did not seem to be related to the level of these antibodies.

Lupus anticoagulant is an immunoglobulin (either IgG or IgM, or both) that interferes with one or more of the phospholipid dependent tests of in vitro coagulation. The term lupus anticoagulant is a misnomer, because it is involved in thrombo-embolic events, and it may be found among patients

who do not meet the criteria for SLE. LAC may be determined by any of the following coagulation assays:

1. Activated partial thromboplastin time (APTT). This is the most commonly used screening test for LAC. LAC prolongs coagulation (usually less than 30 seconds) by binding to negatively charged phospholipids essential for normal coagulation. It is also prolonged in iatrogenic use of heparin.
2. Dilute Russell viper venom time (dRVTT). This is used for screening and as a definitive test, particularly in pregnancy.
3. Kaolin clotting time (KCT),
4. Plasma clotting time (PCT). The last two tests are only considered as screening tests for LAC.

The second type of antibodies includes the APA or ACA. These are acquired antibodies, usually IgG, IgA, or IgM that are targeted against a phospholipid. These are linked to thrombosis and infarction, and are clinically identified by the VDRL, and the enzyme-linked immunosorbent assay or ELISA. VDRL uses the beef heart cardiolipin and has been used extensively in the patients with LAC. The ELISA is more sensitive and specific, using cardiolipin, which is an inner mitochondrial membrane phospholipid. The use of phosphatidylserine increases the sensitivity and specificity of the test (Kutteh and Pasquarette, 1995).

Phospholipid molecules are components of every cell membrane and play a role in cellular signal transduction mechanism that regulates cell division. The regulatory effects of APA on signal transduction have been studied. The amniophospholipids, such as phosphatidylserine and phosphatidylethanolamine are fusogenic lipids and are involved in cellular fusion mechanisms. Phosphatidylinositol is involved in amniotic cell proliferation (Kwak et al, 1994). They are "natural antibodies" which are present in virtually every individual, male or female, but in higher levels in females (Gleicher, 1997). During early pregnancy, autoantibodies to these fusogenic phospholipids may interfere with the fusion mechanism for cytotrophoblasts to syncitiotrophoblast development and amnion development, resulting in reproductive failure. APA may interfere at the very early level in the feto-placental development (Kwak et al, 1994).

The rate of ACA in patients with SLE is high to be around 42-44%, while that in non-SLE patients is only 0-7.5%, depending on the presence of other complications, such as intake of drugs or presence of infections. In general, the patients with non-SLE disorders were older than patients with SLE, and the male to female ratio is around 1, in contrast to 1 : 4 in cases of SLE. Patients with non-SLE disorders who had LAC, were also more likely to have anti-nuclear antibody, anti-DNA, and a positive direct Coomb's test. It must be remembered that non-SLE patients also make up a significant fraction of the anti-cardiolipin population (Love and Santoro, 1990).

There are many theories on the mechanism of action of APA. One theory is the inhibition of prostacyclin (PGI_2) production by endothelial cells. This is a potent vasodilator and inhibitor of

platelet aggregation. This is the antagonist of thromboxane A_2, which is produced by platelets. Humans with APA may have low PGI_2 production thus facilitating a thromboxane-dominant setting towards thrombosis. The other theory postulates the inhibition of protein C by APA to predispose to coagulation events. Protein C is a circulating protein which complexes with a membrane glycoprotein called thrombomodulin that exerts a local anticoagulant effect. In APA, there is inhibition of protein C activation, leading to clotting (Kutteh and Pasquarette, 1995).

El-Roeily (1990) prospectively studied the level of various antibodies present in the non-pregnant state and at various times during pregnancy. The samples included 43 healthy pregnant women and 50 non-pregnant healthy controls matched for age, race and various medical and obstetrical indices. The results of his studies are listed in TableIV.

Table IV. Immunoglobulin antibodies throughout gestation.

Antibody	Non-pregnant	16	20	24	28	32	Delivery
Total IgG	1220	930	970	916	1010	974	939
Phospholipids							
Cardiolipin	24	11	8	16	14	7	7
Phosphatidylserine	16	10	6	8	7	6	7
Phosphatidylglycerol	26	19	10	16	11	25	34
Phosphatidyl-ethanolamine	5	9	3	4	5	11	12
Phosphatidylinositol	18	45	10	31	12	10	8
Phosphatidic acid	15	15	11	13	15	21	22
Total IgM	180	155	151	161	153	158	151
Phospholipids							
Cardiolipin	24	23	11	15	29	22	24
Phosphatidylserine	29	14	8	14	14	35	39
Phosphatidylglycerol	32	33	34	23	16	39	42
Phosphatidyl-ethanolamine	5	2	3	3	3	4	5
Phosphatidylinositol	26	38	13	39	41	20	22
Phosphatidic acid	20	32	19	14	15	20	22
Total IgA	165	165	164	160	167	158	159
Phospholipids							
Cardiolipin	6	9	4	4	6	4	4
Phosphatidylserine	25	4	4	3	5	8	9
Phosphatidylglycerol	8	11	16	15	3	7	8
Phosphatidyl-ethanolamine	4	9	2	12	3	3	3
Phosphatidylinositol	7	13	16	14	25	17	19
Phosphatidic acid	9	10	10	11	10	10	11

Modified from El Roeiy et al, 1990.

Total IgG decreased significantly in pregnancy. The majority of autoantibody levels were within normal nonpregnant ranges. Only a few autoantibodies showed an increase in early pregnancy, including IgG anti-phosphatidyl-inositol and IgM anti-phosphatidyl inositol and

phosphatidic acid, and IgA anti-phosphatidyl-inositol. Most autoantibodies although increased at term, still had values within the normal non-pregnant range. This increase is attributed to fetal antigenic determinants, which enter the maternal circulation through a highly increase volume of fetal maternal cell traffic at term (El-Roiey et al, 1990).

In a review of published studies, 91% of women with LAC had more fetal losses (Scott et al, 1987). There were also strong associations described with fetal distress, intra-uterine growth retardation (IUGR) and preeclampsia. Among patients with recurrent fetal loss or autoimmune disease, the prevalence of LAC is about 65% while that of ACA is up to 61%. In a population of normal pregnant women the prevalence of LAC is 0.27 to 1.2 % while that of ACA is 1.0 to 2.2%. The fetal mortality rate for women with antibodies was 167/1000 (Pattison et al, 1993).

Studies on the placentas from patients with antiphospholipid (aPL) positive sera are relatively few. De Wolf et al (1982) showed decidual vasculopathy and extensive placental infarction in a patient with repeated thrombo-embolic events, RPL and serum lupus anti-coagulant. Out and co-workers (1991) also reported that thrombosis or infarction may be prominent features in placentas with patient with aPL and intra-uterine fetal demise (IUFD) or SLE. However, Lyden et al (1992) suggested that the trophoblastic layer reacts with aPL and thus, direct damage might occur through a mechanism unrelated to thrombosis. Chamley et al found antinuclear and ACA, and their co-factor β2-glycoprotein I, from the placenta of patients with a poor obstetric outcome. Ailus et al (1996) focused on β2-glycoprotein I and found higher levels (along with prothrombin) in habitual abortion patients with gestational diabetes.

Katano et al (1995) investigated the binding of specific aPL to placental tissues in patients with aPL positive sera who had a history of IUFD or SLE. Focusing on the possible mechanisms on the placenta, they detected IgG-APL in the placental eluates of 57% of patients who had a history or RPL, and whose pregnancy resulted in either IUFD or fetal growth retardation. The other antibodies, IgM-aPL or IgG-aPL were absent in the cord blood, probably removed with elution methods. The placentas which were positive for IgG-aPL showed pathologic findings such as infarction, degeneration, thrombus formation and fibrinoid deposits. It is suggested that this may be bound to placental tissues causing direct damage leading to utero-placental insufficiency.

Rand et al (1997) found that trophoblasts and endothelial cells exposed to antiphospholipid antibody IgG had reduced levels of Annexin V, a phospholipid-binding protein with potent anti-coagulant activity, compared to controls. Annexin V was previously known as placental anticoagulant protein I or vascular anticoagulant alpha, and its anti-coagulant properties are based on its high affinity for anionic phospholipids and its capacity to displace coagulation factors from phospholipid surfaces. Trophoblasts and endothelial cells also had faster mean plasma coagulation times compared to controls. The anti-thrombotic role may be at the interface of trophoblasts and

endothelial cells with circulating blood. These further support the presence of thrombosis and subsequent pregnancy loss among patients with aPL levels (Rand et al, 1997).

The levels of aPL antibodies are significantly higher among patients with recurrent abortions and have been found to increase if they had a miscarriage in the present pregnancy. In women who had a live born infant, the titers remained stable or decreased during pregnancy. Down-regulation of these antibodies may have a role in the success of these pregnancies (Kwak et al, 1994).

Out and co-workers (1994) prospectively followed up a group of patients with aPL antibodies, comparing them with a control group. They found that the presence of LAC and a history of three spontaneous abortions could predict a fetal loss. The levels of ACA were similar in both groups. The pregnancies with LAC ended with spontaneous abortions (15%) and in IUFD (20%). All the placentas of these cases showed signs of thrombosis or infarction. In live born infants, low birth weight could be predicted by ACA, a history of a prior IUFD and steroid treatment. No relationships were seen between aPL antibodies and small for gestation age newborns and hypertensive complications in pregnancy (Out et al, 1991).

The most common type of pregnancy loss among women with LAC or aPL antibody was fetal death, which was in 50% of cases, compared to less than 15% of women who tested negative. More than 80% of women with aPL antibodies had at least one fetal death compared to less than 25% of women without (Oshiro et al 1996). These results are similar to those of Yetman et al (1996) who found positive ACA in 17.3% of patent with RPL, compared to only 4% in the control population. 10.1% of women were negative for ACA but were positive for other aPL antibodies, particularly those in the IgG class of phosphatidylinositol, cardiolipin, and phosphatidylethanolamine.

Fetal loss occurred in all stages of pregnancy among patients with aPL antibodies. Among patients with the LAC, there seems to be no particular tendency to an increase in any trimester. For ACA, there is a trend for fetal loss to take place during the late stage, second trimester for SLE and third trimester for non-SLE patients. This study clearly showed the association between aPL antibodies and a history of thrombosis (Love and Santoro, 1990).

What is the relevance of the titer and isotype of the antibodies to recurrent fetal loss? It is suggested that IgG has a higher association with thrombosis compared to IgM. Reports have shown that thrombosis and fetal loss are more frequent among patients with high levels of positive aPL antibody titers. The recommendations of the Second International Anti-cardiolipin Standardization Workshop are that only moderately positive (16 to 80 GPL units) and highly positive (> 80 GPL units) anticardiolipin levels are to be considered as clinically relevant. Since that time, however, more cases that do not fall within these categories still developed good pregnancy outcomes (Arnout et al, 1995).

Roberts et al in 1996 have also shown that recurrent abortion cases appeared to be associated with increased numbers of $CD5/20^{+}$ positive cells and an increased incidence of thyroid antibodies.

The exact mechanism responsible for the increased incidence of the thyroid antibodies is still unclear but it may reflect a general activation of the immune system.

CLINICAL DIAGNOSIS

The evaluation of a patient with RPL should attempt to work up for all possible etiologies, starting with a good clinical history and physical examination. The strict definition of RPL requires that a patient should have had at least 3 consecutive pregnancy losses. However, so much distress is associated with each pregnancy loss that advanced patient age and anxiety may push one to proceed with the work up even with less than the required number of losses. Patients may have more than one cause and may need to be treated with several modalities. Counseling in such a distressful condition almost seems mandatory and may need to involve the couple and the family (Kutteh and Pasquarette, 1996). Thus a multi-disciplinary approach involving the social scientist may be important to deal with the other factors related to the social and psychological development of the problem, if the primary physician is not familiar with counseling techniques.

A summary of diagnostic tests and proposed therapies is presented in Table V.

Table V. Diagnosis and management of RPL.

Etiology	Diagnostic Work-up	Therapy
Genetic	Karyotype partners	Genetic counseling, Donor gamete
Anatomic	Hysterosalpingogram Laparoscopy Hysteroscopy	Septum transection Cervical cerclage
Endocrinologic	Endometrial biopsy Midluteal progesterone levels Thyroid stimulating hormone Prolactin	Prosgesterone Clomiphine citrate Thyroid hormones GnRH analogues
Immunologic	Activated PTT VDRL Lupus anticoagulant Antiphospholipid antibodies	Prednisone Heparin Aspirin Immunoglobulins
Mircrobiologic	Cervical culture Endometrial culture	Antibiotics
Metabolic	As indicated	As Indicated
Medical	As indicated	As indicated
Iatrogenic	Tobacco Ethanol abuse History of exposure	Eliminate consumption Eliminate exposure

Modified from Kutteh and Pasquarette, 1996.

The determination of LAC and aPL in the clinical setting may be very expensive in terms of time, money and personnel. Most laboratories test for LA with the activated partial thromboplastin time (APTT) which is neither specific nor sensitive for LA. However, this is readily available in most centers. More specific tests for LA include the dilute Russel's viper venom time (dRVVT) or tissue thromboplastin inhibition time. However, there are many errors with these two procedures. These errors may be corrected by investigating mixtures of test and normal plasmas at least initially (Exner et al, 1991).

Care is required to prevent platelet activation in the blood samples. High-speed centrifugation is suggested (10 min at 5000 g) and/or filtration through 0.22 micron screens to remove platelets prior to freezing both patient and normal plasmas in mixing tests. If a sensitive test to LA is required, such as in pregnant women, the Kaolin Clotting Time (KCT) is suggested. If specific test is important, as in acute clinical cases with marked coagulation abnormalities or for distinguishing a Factor VIII inhibitor from LA, one may use either the dRVVT or an APTT, followed by a phospholipid neutralization procedure confirmatory schedule (Exner et al, 1991).

Listed below are the revised scientific subcommittee's recommended criteria for LAC. The laboratory diagnosis of a LAC should follow these:

1. Prolongation of phospholipid-dependent clotting tests (KCT, dRVVT, TTI, plasma PRCT, or a sensitive APTT).
2. Clotting time of a mixture of test and normal plasma should be significantly longer than that of normal mixed with various non-LA patient plasmas.
3. There should be a relative correction of the defect by the addition of lysed, washed platelets, or preferably phospholipid liposomes containing phosphatidyl serine or hexagonal phase phospholipids.
4. Other criteria include: nonspecific for any individual clotting factor, rapidly losing apparent activity on dilution of test plasma with saline, usually fast acting and associated with positive aPL antibody ELISA's (Exner et al, 1991).

The specific tests are summarized in Table VI.

To distinguish transient LAC, frequently found in association with infectious diseases, and persistent LAC, as in the aPL syndrome, the diagnosis should be confirmed with a second sample after 6-8 weeks (Arnout et al, 1995).

Should the general obstetric population be screened for aPL antibody levels? The prevalence of aPL antibodies in the general obstetric population is low, and thus would not be cost effective to screen them for these antibodies (El-Roiey et al 1990 , Arnout et al, 1995). Moreover, most aPL antibody levels in normal women seem to be transient. The search for these antibodies should only be part of

the work-up of a high risk population, such as those with a history of RPL, thrombo-embolic disease, connective tissue diseases, or severe preeclampsia (Arnout et al, 1995).

Table VI. Laboratory diagnosis of lupus anticoagulants.

1.	Screening Tests - phospholipid-dependent clotting tests should be prolonged.
a.	Dilute prothrombin time (dPT)
b.	Kaolin clotting time (KCT)
c.	Dilute activated partial thromboplastin time (aPTT)
d.	Dilute Russell viper venom time (dRVVT)
1.	Mixing Studies - the presence of anticoagulant is demonstrated when the clotting time remains prolonged upon addition of normal plasma to the patient or test plasma
2.	Phospholipid deficiency - lupus anticoagulants are differentiated form other coagulation inhibitors by performing coagulation tests in the presence of excessively high phospholipid concentrations. Phospholipids used for this are:
a.	Platelet lyses
b.	Platelet derived microvesicles
c.	Phospholipid liposomes
d.	Hexagonal phospholipids.

From Arnout et al, 1995.

TREATMENT

The treatment of RPL is more complicated than the diagnosis. Some of the treatment options are previous presented in Table VI. There are still many controversial and unresolved issues with regards the causes of RPL. For metabolic and medical etiologies, it may be logical to control the underlying disease or defect to allow possible fertility. However, other issues, such as the timing of metroplasty, role of immunotherapy and the management of unexplained RPL remain dilemmas. These options should be properly discussed with the patient and her husband. Appropriate counseling should be made before, during and after any treatment regimen is started.

Treatment of autoimmune causes of RPL involves the use of steroids and low dose aspirin, or subcutaneous heparin with or without low-dose aspirin. Branch and co-workers (1992) followed 54 women with LAC or medium to high levels of IgG anticardiolipin with 82 pregnancies. These patients were treated during pregnancy with 1) prednisone and low-dose aspirin, 2) heparin and low-dose aspirin, 3) predisone, heparin, and low-dose aspirin, or 4) other combinations of these medications or immunoglobulin. There were no significant differences in the outcome among the four treatment groups. Preeclampsia and fetal distress were in half of all pregnancies, and fetal growth retardation in a third. Slightly more than a third of cases had to be delivered preterm because of fetal or maternal indications. Patients treated appear to have better outcomes (less fetal deaths), as much as 75%, if spontaneous abortions are excluded. However, this is not totally successful because fetal loss still occurs despite treatment (Branch et al, 1992).

Steroids have also been attempted in the treatment of RPL among patients with aPL antibodies. However, the practice is not widely used because steroids, particularly prednisone was found to be possible associated with premature rupture of membranes, preterm delivery, and preeclampsia in the only randomized clinical trial using this in RPL (Cowchock et al, 1992).

The recommended dose of heparin given is 10,000 - 24,000 units/day, and one tablet of children's aspirin is recommended for these patients with RPL (Barbour et al, 1995). These medications should be continued under the close supervision of the attending physician, particularly watching out for problems such as bleeding disorders, which are very common among patients receiving these forms of therapy.

Cowchock and co-workers (1992) also studied women who are considered low-risk because they had none of the associated signs and symptoms of the aPL antibody syndrome. They studied the effect of low-dose aspirin taken during pregnancy compared to a control group. There were few obstetric complications recorded in either group, thus recommending that treatment of such a low risk group cannot be justified based on the evidence (Cowchock et al, 1992).

The treatment options for patients with the aPL syndrome are in Table Ⅶ.

Despite all of the new diagnostic and therapeutic modalities present, many patients will still continue to experience RPL. Not any of these tests and treatments guarantees complete success. Appropriate counseling should be given before, during and after any diagnostic and therapeutic regimen is instituted.

Table Ⅶ. Treatment of the antiphospholipid syndrome.

1. Antiphospholipid antibodies are a fortuitous finding - do not fulfill criteria, no treatment needed
2. Patients with a history of thrombosis
Non-pregnant - depending on severity, may need to receive lifelong oral anticoagulation
Pregnant - Aspirin is given, eventually with prophylactic doses of heparin, depending on severity of thrombotic episodes
3. Patients with a history of fetal losses
Non-pregnant - no treatment recommended, rather follow-up closely
Pregnant - May be treated with aspirin, heparin, or immunoglobulins

From Arnout et al, 1995.

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