Recurrent pregnancy loses and antiphospholipid syndrome

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Definetion

is a systemic autoimmune disorder that is characterized

by the presence of serum aPL and clinical manifestations,

- Arterial thrombosis
- Venous thrombosis
- Obstetrical complications especially RPL

Approximately 20% of women with RPL have autoimmune abnormalities and is the most common aPL

Fifteen percentage of women with three or more RPL were reported to have persistently positive aPL, and the fetal loss rate of these women was reported to be 50–90% if no specific treatment was given.

Rai RS, Hum Reprod 1995

Clinical and laboratory criteria established for the research of definite antiphospholipid syndrome: the Sydney criteria

Note: At least 1 clinical and 1 laboratory criterion must be present for definite APS.

Clinical criteria

1. Vascular thrombosis

   One or more clinical episodes of an arterial, venous, or small vessel thrombosis, confirmed by imaging or Doppler studies or histopathology, without significant evidence of inflammation in the vessel wall.

2. Obstetric morbidity

   a. One or more unexplained demise of a morphologically normal fetus at or beyond 10 weeks of gestation, or

   b. One or more premature births of a morphologically normal neonate at or before 34 weeks of gestation, caused by severe preeclampsia or severe placental insufficiency, or

   c. At least 3 unexplained, consecutive miscarriages of less than 10 weeks of gestation. Known factors associated with recurrent miscarriage, including parental genetic, anatomic, and endocrinologic factors, should be ruled out.

Laboratory criteria

1. aCL IgG and/or IgM in blood, present in medium or high titers (greater than 40 GPL or MPL or greater than the 99th percentile) on 2 or more occasions at least 12 weeks apart, measured by a standardized ELISA.
2. Anti-β2GP1 antibody of IgG and/or IgM isotype in blood (greater than the 99th percentile) on 2 or more occasions at least 12 weeks apart, measured by a standardized ELISA.
3. Lupus anticoagulant present in plasma, on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis, which include the following steps:

   a. Prolonged phospholipid-dependent coagulation using a screening test such as the aPTT, kaolin clotting time, dilute Russell viper venom time, and dilute prothrombin time

   b. Failure to correct the prolonged coagulation time on the screening test by mixing with normal plasma

   c. Shortening or correction of the prolonged coagulation time on the screening test by the addition of excess phospholipid or platelets

   d. Exclusion of other coagulopathies (eg, factor VIII inhibitor) or heparin

aPL

aPLs are acquired antibodies that react directed against negative charged phospholipids.

- Cardiolipin (diphosphatidyl glycerol)
- Phosphatidylserine
- Phosphatidyl inositol
- Phosphatidylglycerol

.

APL effect

They show slow progressive thrombosis and infarction in placenta.

They have been shown to inhibit the release of hcG from human placetal explants; to block in vitro trophoblast migration, invasion and multinucleated cell formatiin. Inhibit trophoblast cell adhesion molecules; and activate complement on the trophoblast surface, inducing an inflammatory response.

β2-glycoprotein I

Apolipoprotein H (Apo-H), previously known as(β2-glycoprotein I), is a multifunctiona lapolipoprotein. One of its functions is to bind cardiolipin. When bound the structure of cardiolipin and Apo-H both undergo large changes in structure.

İnhibitory effects;

- Apo-H appears to completely inhibit **serotonin release** by the platelets and prevents subsequent waves of the **ADP-induced aggregation**.
- Apo-H causes a reduction of the prothrombinase binding sites on platelets.
- Apo-H also inhibits the generation of factor Xa in the presence of platelets.Apo-H also inhibits that activation of Factor XIIa
- In addition, Apo-H inhibits the activation of protein C blocking its activity on phosphatidylserine:phosphatidylcholine vesicles. However once protein C is activated, Apo-H fails to inhibit activity.

Presence of aPLand adverse pregnancy

The presence of aPLs (LAC, aCL) during pregnancy is a major risk factor for adverse pregnacy outcome.

In a large meta-analaysis fo studies of couples with recurrent pregnacy loss the incidence of APS 15%-20% compared with 5% in nonpregnant women without a history of obstetric complications.

Kutteh WH, Am j Reprod Immunol 1999; 41:133-52.

It is not yet understood how aPLs arise in patients with APS.

- Genetic factors?
- Infection?

LAC

LAC is a immunoglobulin that interferes with one or more of the phospholipid-dependent tests of in vitro coagulation.

Name is a misnomer in two ways

-Although it is called an anticoagulant, patients with LAC more frequently have hypercoagulable state.

-Second LAC is frequently found in without SLE

How can we identify presence of LAC

aPTT

The kaolin clot time

dRVVT

Plasma clot time

aPTT

İt is not reliable test in pregnancy because coagulation proteins, which increase during pregnancy

fibrinogen, FVIII, von Willebrand factor, FVII and FX may mask the LAC.

dRVVT

is a sensitive test and, because the snake venom activates FX, the test is less affected by pregnancy.

LAC confirmatory

Regardless of which test is used, there are three step that are necessary to identify an LAC

aPTT +

Confirm is there an inhitor?/ Do mixing test.

Normal platelet poor plasma and patient plasma ratio1:1

if aPTT normal : a factor deficiency

if aPTT not normal : do confirmatory test

Neutrolisation test:

Add frozen-thawed plasma to patient plasma

The LAC is absorbed to phospholipid and test return normal: LAC+

What happened in Sydney criteria

2006 Update of Classification-1

- Clinical criteria were not significantly changed
  - Suggest that clinicians not classify a patient with APS if more than 5 years separate the clinical event and the positive laboratory test
- Laboratory criteria
  - Elevated LA, aCL, or anti-β2GPI must be present on two or more occasions, at least 12 weeks apart
  - Threshold defined for aCL is a "medium to high titer" that equates to greater than 40 GPL or 40 MPL
  - Inclusion of anti-prothrombin antibodies is premature in the classification criteria for APS
  - IgA aCL and IgA anti-β2GPI cannot be considered as laboratory criteria for APS

2006 Update of Classification-2

- A positive LA test better correlates with thrombosis, pregnancy morbidity, and thrombosis in SLE (Systemic Lupus Erythematosus) patients than does a positive aCL test
- Anti-β2GPI antibodies are an independent risk factor for thrombosis
- Subclassification of APS into 4 categories based on aPL assay positivity

Type I APS	More than one laboratory criteria present-in any combination (associated with more severe course of disease)
Type IIa APS	LA present alone
Type IIb APS	aCL antibodies present alone
Type IIc APS	anti-β2GPI antibodies present alone

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healthcare

Contribution of the addition of anti-β2-glycoprotein to the classification of antiphospholipid syndrome in predicting adverse pregnancy outcome

GALIA ORON[1], AVI BEN-HAROUSH[1], RACHEL GOLDFARB[1], YAIR MOLAD[2], MOSHE HOD[1], & JACOB BAR[3]

Abstract

Objectives. Anti-β2 glycoprotein 1 (a-β2GP1) was added to the criteria for antiphospholipid syndrome (APS) in 2005. However, its clinical significance with respect to complications of pregnancy is not well established. The aim of this study was to evaluate the association of laboratory findings of a-β2GP1 with events of thromboembolism or obstetric complications (pregnancy loss, placental dysfunction, intrauterine growth restriction, preeclampsia, fetal death, and preterm delivery) in women with clinical and laboratory evidence of APS.

Methods. A retrospective cohort design was used. Ninety-one patients (total 394 pregnancies) referred to a tertiary medical center for evaluation of clinical features consistent with APS were divided into three groups: group A ($n = 34$), two positive tests for anticardiolipin (ACL) or lupus anticoagulant (LAC), in accordance with original APS classification (1998); group B ($n = 18$), two positive tests for a-β2GP1, in accordance with the revised APS criteria; and group C ($n = 39$), only one positive test for ACL or LAC.

Results. Of the 52 women with APS (group A or B), 36 had primary disease, and 16 had secondary disease. On comparison of the groups, group B was characterized by a significantly higher rate of complicated pregnancy (83.3%) than groups A (47.1%) and C (76.9%), $P = 0.007$, and a higher rate of fetal loss (72.2%) than groups A + C (28.8%, $P = 0.001$).

Conclusions. The findings suggest that the revised APS criteria are preferable to the original classification for the prediction of complicated pregnancy.

Keywords: *Anti-β2 glycoprotein 1, antiphospholipid syndrome, pregnancy, complications*

AOGS
ACTA Obstetricia et Gynecologica Scandinavica

AOGS SHORT RESEARCH REPORT

Anti-β2 glycoprotein I antibodies and pregnancy outcome in antiphospholipid syndrome

The miscarriage rate

in the double-positive group: 46.2%
aCL+/ab2GPI- group: 22.1%
in the Acl-/ab2GPI+ group: 36.4%

Acta Obstetricia et Gynecologica Scandinavica 92 (2013) 234–237

APS/Pregnancy outcome

I-Recurrent Pregnancy loss

II-Fetal loss

III-Severe preeclampsia prior to 34 weeks

IV-Severe placental insufficiency

I-Recurrent Pregnancy loss

RPL has been defined as 2 or 3 or more consecutive losses before the 20th week of gestation and affects up to 2% to 4%of pregnancies.

The risk of miscarriage in subsequent pregnancies is 30% after 2 losses and 45% after 3 losses in patients without a history of live birth,

ASRM accept RPL as 2 or more failed clinical pregnancies as documented by ultrasonography and recommended a thorough evaluation of RPL after two or more clinical losses.

It has been observed that circulating aPLs is the main risk factor in 7% to 25% of early RPL (loss in the first trimester),

whereas prevalence studies show that between 1% and 5% of patients have LAC.

All 3 of the laboratory criteria for diagnosis of APS
the presence of LAC,
increased levels of aCL antibodies,
and increased levels of b2GP1 have been linked with RPL,

Fetal loss

Late fetal loss (after 10 weeks of pregnancy)

with aCL antibodies and b2GP1 antibodies, but not LAC, being strongly associated with intrauterine fetal death.

- Late fetal loss is also more common as the number of aPL antibody tests become positive.
- In a recent report from Italy involving 97 pregnancies in 79 patients with APS and without hereditary thrombophilia, triple positivity conferred a risk of late fetal loss of 52.6% compared with a loss rate of 2.2% when only 2 tests were positive.

Ruffatti A, Thromb Res 2009;123:482–7.

Defective placentation

- Abnormalities of early trophoblast invasion caused by aPLs are a likely pathogenic mechanism in obstetric APS.
- Exposure of trophoblastic cell monolayers to aPLs resulted in an increased rate of programmed cell death (apoptosis) and inhibition of syncytial formation
- Experimental models indicate that aPLs can directly
  - retard trophoblast invasiveness,
  - impair trophoblastic cellular differentiation and maturation,
  - diminish human chorionic gonadotropin secretion

How does heparin prevent pregnancy loss 1

It has anticoagulant effect.

The efficacy of heparin is dose independent.

Studies in the murine model indicate that anticoagulants such as **hirudin and fondaparinux** are ineffective in the treatment of aPL-induced pregnancy loss, despite having anticoagulant effects similar to heparin.

Low-molecular-weight heparin (LMWH) directly impedes aPL binding to trophoblast cells and reinstates normal trophoblast invasiveness and differentiation hindered by aPL.

Heparin also can potentially regulate apoptosis in placental explants by increasing levels of Bcl-2, an antiapoptotic protein.

How does heparin prevent pregnancy loss 2

- Heparins have been shown to prevent complement activation in vitro, an action that would protect normal placentation from inflammatory injury.
- Exposure of trophoblastic cells to LMWH results in an increase in matrix metalloproteinases in trophoblastic cells, an action that would promote trophoblastic invasiveness.
- Heparin sulfate directly binds aPL, providing a novel and alternative mechanism for its therapeutic benefit in treating obstetric APS

MANAGEMENT OF APS IN PREGNANCY

Several treatments have been proposed,

- single low-dose aspirin per day
- aspirin and low-dose or high-dose prednisone,
- aspirin and unfractionated heparin,
- aspirin and LMWH,
- intravenous immunoglobulin.

All treatments seem to improve the live birth rate? however,

Heparin with low-dose aspirin seems to provide the highest success rates

MANAGEMENT OF APS IN PREGNANCY

The management principles are:

- Prevention of thrombosis
- Antenetal surveillance of mother and fetus
- Peripartum care
- Postpartum prophylaxis

Heparin and Aspirin

Heparin with low dose aspirin is the preferred regimen started as soon as a viable pregnancy is documented and continued till 34 weeks.

(Cochrane database 2005)

Aspirin

improves pregnancy outcome by preventing thrombosis and preventing damage to trophoblast.

Heparin

Besides antithrombotic mechanism

Reduce the binding of aPL

Decreasing inflammation

Facilitating implantation

Inhibiting complement activation

Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. Empson M, Cochrane Rew. 2005 Apr 18;(2)

- Unfractionated heparin combined with aspirin (two trials; n = 140) significantly reduced pregnancy loss compared to aspirin alone (relative risk (**RR) 0.46**, 95% confidence interval (CI) 0.29 to 0.71).
- Low molecular weight heparin (LMWH) combined with aspirin compared to aspirin (one trial; n = 98) did not significantly reduce pregnancy loss (RR 0.78, 95% CI 0.39 to 1.57).
- There was no advantage in high-dose, over low-dose, unfractionated heparin (one trial; n = 50).
- Three trials of aspirin alone (n = 135) showed no significant reduction in pregnancy loss (RR 1.05, 95% CI 0.66 to 1.68).

LMWH

Have fewer comlications.

Inhibit FXa and in additon has anticoagulant effect through its action on AT-III and factor IIa.

Conservative therapeutic range is 0.6-1.0 IU/ml and 1.0-2.0 IU/ml in patients treated LMWH once daily.

A number of LMWH are available which have a molecular weight of 4000-6000 daltons.

the various fractions have different pharmacological profiles and the properties and dose of one LMWH can not be explorated to another.

Enoxaparine (Levonox, clexane) in the dose of 20-40 mg/day sc has been used successfully in pregnancy with a live birth rate of 85-95%.

Gestational outcome in thrombophilic women with recurrent pregnancy loss treated by enoxaparin.

Brenner B, Hofmann R

Abstract

Inherited and acquired thrombophilia are associated with recurrent pregnancy loss (RPL). We have evaluated the efficacy and safety of the low molecular weight heparin enoxaparin in 50 women, (mean age 26 +/- 3 years) with RPL (> or =3 losses in 1st, > or =2 losses in 2nd and > or =1 loss in 3rd trimester) who were found to harbor thrombophilia. Twenty-seven had a solitary thrombophilic defect, and twenty-three women had combined thrombophilic defects: 17--two defects and 6--three defects. Following diagnosis of thrombophilia, sixty-one subsequent pregnancies were treated with the low molecular weight heparin enoxaparin throughout gestation until 4 weeks after delivery. Dosage was 40 mg/day in women with solitary defect and 80 mg/day in combined defects. Aspirin, 75 mg daily was given in addition to enoxaparin to women with antiphospholipid syndrome. Forty-six out of 61 (75%) gestations treated by enoxaparin resulted in live birth compared to only 38/193 (20%) of the untreated pregnancies in these 50 women prior to diagnosis of thrombophilia (p <0.00001). In 23 women without a single living child following 82 untreated gestations, antithrombotic therapy resulted in 26/31 (84%) successful deliveries (p <0.0001). In 20 women with a prior living child, antithrombotic therapy improved successful delivery from 33/86 (38%) to 20/21 (95%) (p <0.0001). Enoxaparin dose of 40 mg/day resulted in live birth in 24/35 (69%) of gestations, compared to 19/23 (83%) gestations in women treated with 80 mg/day (p = 0.37). Only one thrombotic episode and one mild-bleeding episode were noticed during enoxaparintherapy. Enoxaparin is safe and effective in prevention of pregnancy loss in women with inherited and acquired thrombophilia.

Thrombos 2000 May;83(5):693-7.

Meta-analysis of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications

Marc A. Rodger,[1-4] Marc Carrier,[1,2,4] Grégoire Le Gal,[1,2,4] Ida Martinelli,[5] Annalisa Perna,[6] Évelyne Rey,[7] J. I. P. de Vries,[8] and Jean-Christophe Gris,[9] on behalf of the Low-Molecular-Weight Heparin for Placenta-Mediated Pregnancy Complications Study Group

A 35-year-old woman with recurrent severe placenta-mediated pregnancy complications in her 2 pregnancies asks: Will low-molecular-weight heparin help prevent recurrent placenta-mediated pregnancy complications in my next pregnancy? We performed a meta-analysis of randomized controlled trials (RCTs) comparing low-molecular-weight heparin (LMWH) vs no LMWH for the prevention of recurrent placenta-mediated pregnancy complications. We identified six RCTs that included a total of 848 pregnant women with prior placenta-mediated pregnancy complications. The primary outcome was a composite of pre-eclampsia (PE), birth of a small-for-gestational-age (SGA) newborn (<10th percentile), placental abruption, or pregnancy loss >20 weeks. Overall, 67 (18.7%) of 358 of women being given prophylactic LMWH had recurrent severe placenta-mediated pregnancy complications compared with 127 (42.9%) of 296 women with no LMWH (relative risk reduction, 0.52; 95% CI, 0.32 to 0.86; $P = .01$; I^2, 69%, indicating moderate heterogeneity). We identified similar relative risk reductions with LMWH for individual outcomes, including any PE, severe PE, SGA <10th percentile, SGA <5th percentile, preterm delivery <37 weeks, and preterm delivery <34 weeks with minimal heterogeneity. LMWH may be a promising therapy for recurrent, especially severe, placenta-mediated pregnancy complications, but further research is required. (*Blood*. 2014;123(6):822-828)

RR reduction: 0.52

Guidelines for prophylactic heparin plus aspirin treatment of patients with RPL without a history of thromboembolism but with APS

1. Baseline nonpregnant studies of aPLs, complete blood count with platelets, PT, PTT, and lupus anticoagulant should be obtained. aPL assay should be confirmed before pregnancy.
2. Aspirin 81 mg should be initiated before conception and discontinued 4 weeks before the expected delivery date. Aspirin 81 mg should be resumed postpartum and continued for life unless otherwise contraindicated or until better recommendations are available.
3. Subcutaneous heparin (5000 units every 12 hours) should be initiated when pregnancy is confirmed unless instructed otherwise. Patients who weigh more than 80 kg (175 pounds) should use heparin 7500 units every 12 hours. Platelets and PTT tests should be checked every week for 2 weeks initially, 1 week following any adjustment in dose, and each trimester throughout pregnancy to evaluate for heparin-induced thrombocytopenia (patients with prior thromboembolic events should be fully anticoagulated).
4. Calcium carbonate (1200–1500 mg) with vitamin D (800–1000 IU) should be taken daily in divided doses once a patient starts heparin to decrease the bone loss associated with pregnancy and heparin therapy.
5. The pregnancy should be documented by ultrasonography by 7 weeks for the detection of fetal heart motion. Further sonography may be performed at 18 to 20 weeks.

6. Antenatal testing should begin at 28 to 30 weeks, based on the possible increased risk of fetal growth restriction and stillbirth. This testing may include kick counts, nonstress tests, and/or serial biophysical profiles. Serial scans for growth rate may be indicated.

7. Heparin should be continued until the patient initiates spontaneous labor or until the night before any scheduled induction or operative delivery. One heparin dose may be skipped the night before amniocentesis. Heparin should be restarted postpartum at the lowest predelivery dosage and continued for 4 weeks (in those patients with previous thromboembolic events, full anticoagulation should continue for 6 weeks postpartum).

8. For prolonged deliveries and operative deliveries, the use of pneumatic sequential compression devices or hose should be considered until the patient is ambulatory.

9. If the patient is fully anticoagulated and delivery is emergent, 1% protamine sulfate can be administered intravenously over 10 minutes (2.5 mg protamine per 1000 U heparin, maximum 50 mg protamine) if coagulation indicators are increased.

10. Patients should not use estrogen-containing birth control pills for contraception. Aspirin 81 mg daily is advised until further recommendations become available. Patients who smoke should be advised to stop.

Thromboprophylsis Regimes

APS without previous thrombosis and RPL	LDA LDA+UFH 5000-7500IUx2 sc.(prophylactic dose)
APS without previous thrombosis and fetal death >10 weeks gestation or previous early delivery (<34 weeks) because of preeclampsia	LDA+UFH 5000-10.000IUx2 sc.(prophylactic dose) Or LMWH prophylactic dose
APS with thrombosis	LDA+UFH 7500-10.000IUx every 8-12 hours(aPTT in theraupatic range) Or LMWH thereupatic dose Enoxaparine 1mg-1.5/kg/day Dalteparine 100-200 U/kg/day

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Review

14th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends

Doruk Erkan [a,*], Cassyanne L. Aguiar [a], Danieli Andrade [b], Hannah Cohen [c], Maria J. Cuadrado [d], Adriana Danowski [e], Roger A. Levy [f], Thomas L. Ortel [g], Anisur Rahman [c], Jane E. Salmon [a], Maria G. Tektonidou [h], Rohan Willis [i], Michael D. Lockshin [a]

1-Older non-heparin/warfarin anticoagulants
2-Hydroxychloroquine
3-Statins
4-B-cell inhibition
5-Complement inhibition
6-Peptide therapy
7-VitaminD

Conclusion

Antiphospholipid antibodies (aPLs) are acquired antibodies directed against negatively charged phospholipids, a group of inner and outer cell membrane antigens found in mammals.

Obstetric antiphospholipid antibody syndrome (APS) is diagnosed in the presence of certain clinical features in conjunction with positive laboratory findings.

Although obstetric APS was originally reported in association with slow progressive thrombosis and infarction in the placenta, it is most often associated with a poor obstetric outcome.

Several pathophysiologic mechanisms of action of aPLs have been described.

The most common histopathologic finding in early pregnancy loss has been defective endovascular decidual trophoblastic invasion.

Treatment with heparin and aspirin is emerging as the therapy of choice, with approximately 75% of treated women with RPL and aPL having a successful delivery, compared with less than 30% without treatment.