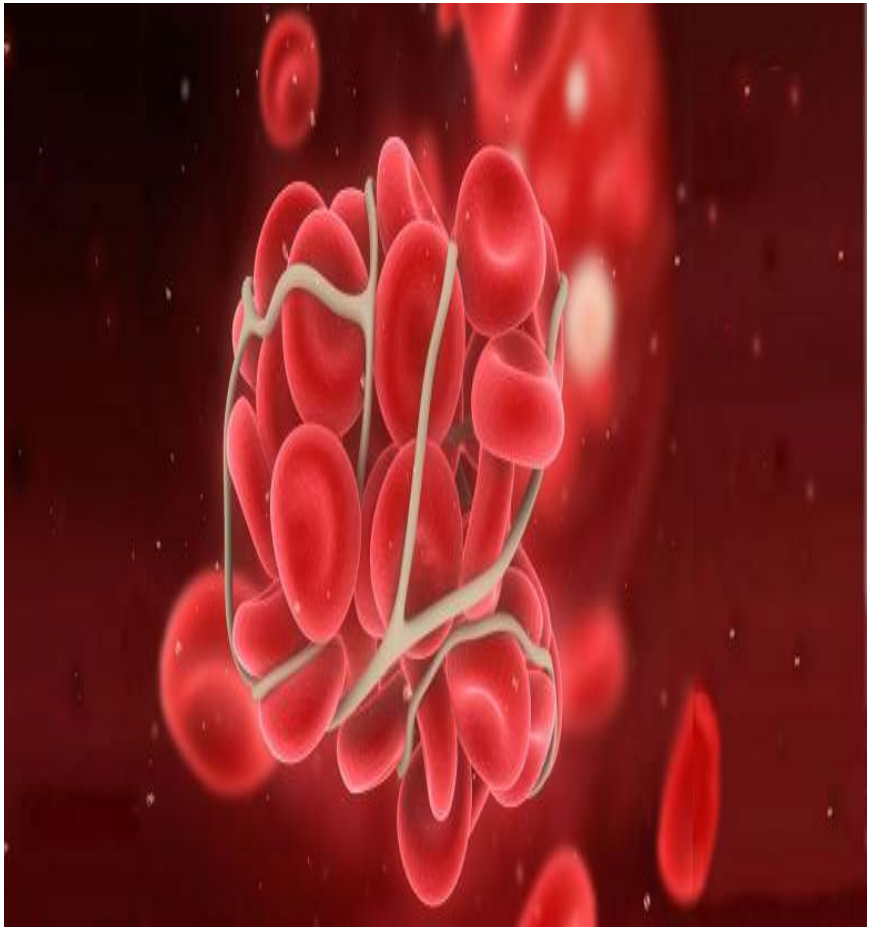
OLGULARLA ANTİFOSFOLİPİD SENDROMU

Uz.Dr. Nesrin ŞEN

ANTİFOSFOLİPİD SENDROMU



- *Venöz ve/veya arteryal tromboz*
- *Gebelik morbiditeleri*
- *En az 12 hafta fosfolipid ve proteinlere karşı gelişmiş otoantikorların varlığı ile karakterize sistemik ve otoimmun hastalıktır .*
- *lupus-antikoagülan(LA),*
- *antikardiolipin (aCL)*
- *anti-β2-glikoprotein-I (aβ2GPI)*

OLGU 1

- 34 yaşında bayan hasta
- 2010 yılında doğum yaptıktan sonra eklem ağrıları olmuş. Salazoprin başlanmış.
- Haziran 2015 de **ANA:+**, anti ds dna:-

  lupus antikoagülanı:2 ,

  antikardiyolipin Ig M:69

  anti kardiyolipin Ig G<2

OLGU 1

- 6 haftalık gebeyken (Aralık 2015) Romatoloji polikliniğine başvurdu.
- FM:Solunum,kardiyak,nörolojik sistem muayenesi normal. Aktif artrit bulgusu yok. Cilt döküntüsü yok.

- BK:6200 Hb:12.5 PLT:154000
- **ESH:51 mm/h** CRP:3,27 mgr/dl KCFT:N BFT:N TİT:N
- RF:- CCP:-

OLGU 1

- **ANA:Pozitif** Antids DNA: - ENA profili:-
- C3-C4:N
- **Anti- Beta 2 Glikoprotein Ig M>200**
- Anti- Beta 2 Glikoprotein Ig G<2
- Anti kardiyolipin Ig M:19.95
- Anti kardiyolipin Ig G<2
- **Lupus Antikoagülanı:+**

- Antifosfolipid Sendromu???
- Klinik????
- Tedavi???

Sapporo Klasifikasyon Kriterleri

Klinik Kriterler	*Laboratuvar Kriterler*
Vasküler tromboz ≥1 arteriyel, venöz veya küçük damar trombozu	En az 12 hafta aralıkla iki ya da daha fazla durumda
Gebelik morbiditesi •Bir veya fazla sayıda, normal fetal morfolojide 10. haftadan sonra fetal kayıp •Bir veya fazla sayıda, preeklampsi, eklampsi veya plasental yetmezlik nedeniyle 34 hafta öncesinde prematüre doğum •Üç veya daha fazla 10.haftadan önce spontan düşükler (kromozomal anormallikler, maternal anatomik veya hormonal anormallikler dışlanmalı)	•Lupus antikoagülan testi pozitifliği • Antikardiyolipin antikoru (IgG ve/veya IgM) •Anti-β2-glikoprotein-I antikorunun (IgG ve/veya IgM)
Tanı için 1 Klinik ve 1 Laboratuvar Bulgu	

Miyakis S, et al. J Thromb Haemost 2006; 4: 295–306

Antifosfolipid Sendromu

Klinik Tutulum	Sıklık		
	Primer AFS	AFS-SLE	
Trombositopeni	%20-25	%30-40	
Kalp kapak tutulumu	% 12-33	%40	Kapakta kalınlaşma,vejetasyon, regurjitasyon
Cilt Tutulumu			
Livedo retikülaris	%20-25	%35	
Ülser	%33	%7-10	Pretibial alanda
Süperfisial tromboflebit	%9		
Böbrek Tutulumu			
Renal arter stenozu	%26		
Nefropati	%35	% 39-67	Arteriol,glomeruler kapiller tutulumu

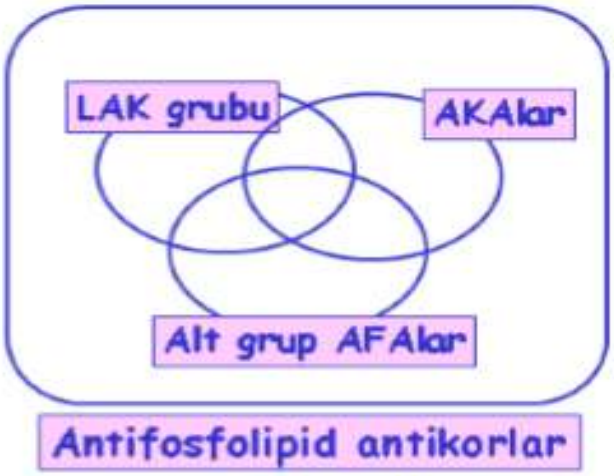
Antifosfolipid Sendromu

Klinik Tutulum	Sıklık Primer AFS AFS-SLE		
S.S.Tutulumu			
Migren/başağrısı	% 20	%25	
Epilepsi	%6-7	%14	
Kognitif bozukluk	%38	%48	
Demans	%25-56		Kronik rekurren iskemik ataklar nedeniyle
Göz Tutulumu	%15-88		Amarosis fugax, retinal damar trombozu(arter/ven)
Transver miyelit		%1	
Pulmoner hemoraji	%1		

Anti Fosfolipid Antikorları

SLE gibi otoimmun hst.larda, enf ve malignite seyrinde ve bazı ilaçlara bağlı ortaya çıkabilen heterojen antikorlardır. Normal kişilerde de bulunabilirler.

- Anti-kardiyolipin
- Anti-fosfotidilserin
- Anti-fosfotidil inozitol
- Antifosfatidil kolin
- Anti-fosfatidil etanolam
- LAK pozitifliği yapanlar



Ruiz-Irastorza G, et al: LANCET, 2010

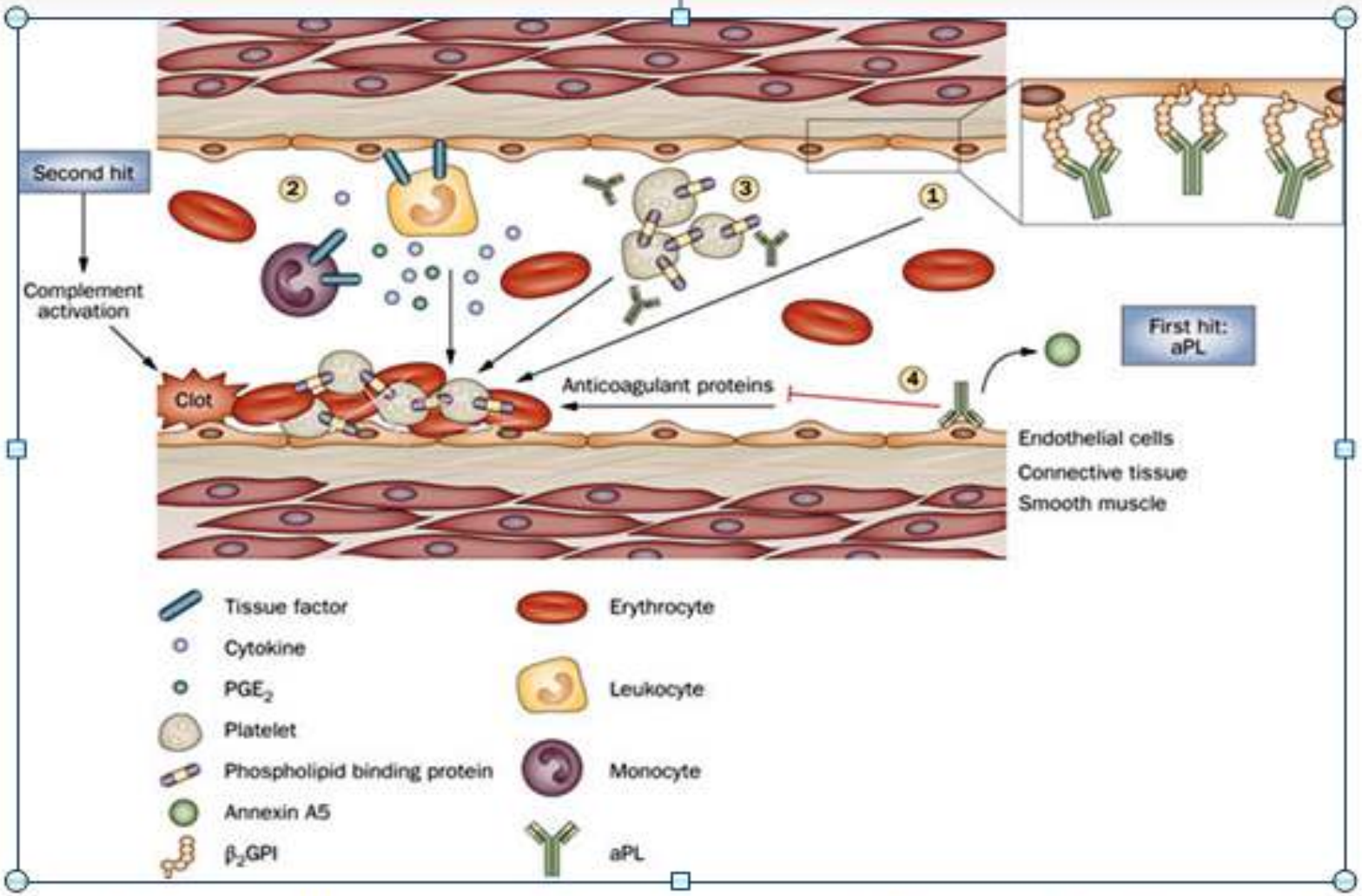
Lupus Antikoagülanı

- Lupus antikoagülan testi, aFL'in protrombinin trombine dönüşümünü inhibe etme yeteneğini ölçmesi açısından fonksiyonel bir koagülasyon testidir.
- İnvitro olarak antikoagülan etkili olmasına rağmen invivo olarak koagülasyonu etkiler.
- Doğrulama basamakları olmaksızın pozitif bir tarama testi pozitif LA testi değildir.

Anti Fosfolipid Antikorları

Antikardiolipin antikoru (aCL) IgG/M **Anti-β2-glikoprotein-I antikoru (aβ2GPI) IgG/M**	**≥40 U >40 GPL veya MPL veya 99 persentil üzerinde**
12 hafta ara ile	

Figure 1 Pathogenic clotting mechanisms mediated by aPL



Meroni, P. L. *et al.* (2011) Pathogenesis of antiphospholipid syndrome: understanding the antibodies *Nat. Rev. Rheumatol.* doi:10/1038/nrrheum.2011.52

nature REVIEWS RHEUMATOLOGY

β2-Glikoprotein I – A Proteini

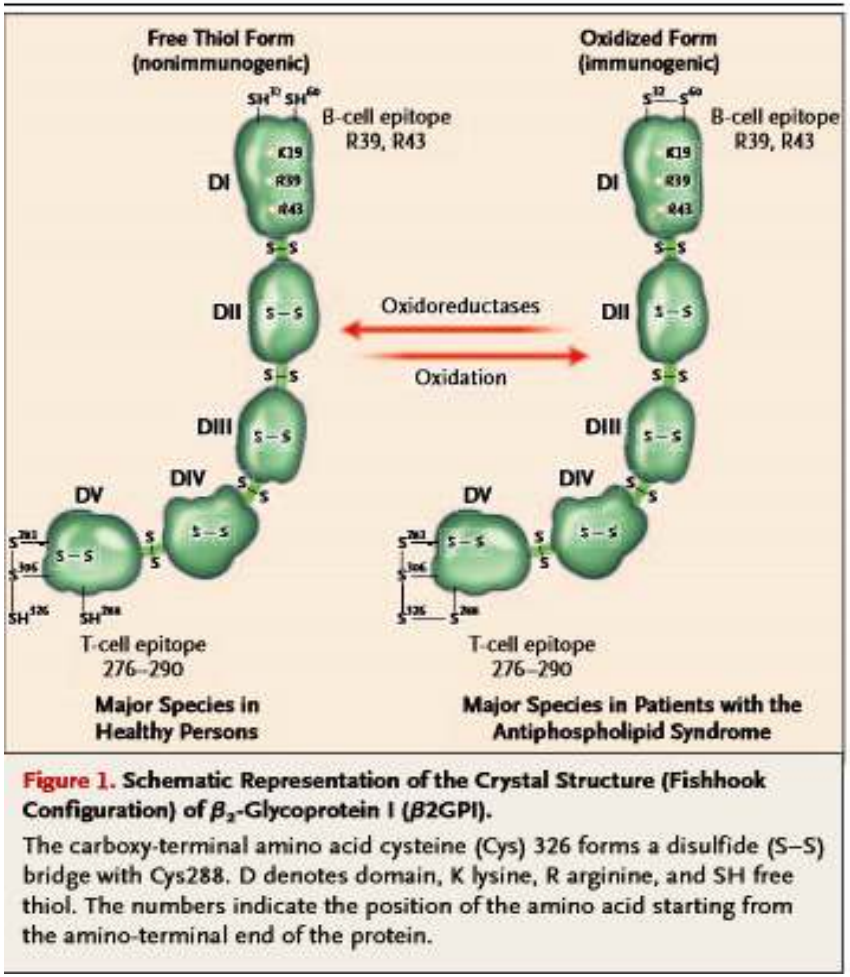


Figure 1. Schematic Representation of the Crystal Structure (Fishhook Configuration) of β_2-Glycoprotein I (β2GPI).

The carboxy-terminal amino acid cysteine (Cys) 326 forms a disulfide (S–S) bridge with Cys288. D denotes domain, K lysine, R arginine, and SH free thiol. The numbers indicate the position of the amino acid starting from the amino-terminal end of the protein.

- β2-glikoprotein I , lipid bağlayıcı protein (50-kDa) olup dolaşımdaki plazma konsantrasyonu 4 µM (200 µg/ml).
- ‘’Kompleman Kontrol Proteini’’
- β2-glikoprotein I hücre membranına penetre olur. Ek olarak aniyonik fosfolipidler, sulfatide , heparin, comp. C3 , annexin A2 , platelet glycoprotein Ib , megalin , apolipoprotein receptor 2 , von Willebrand factor vb ligandlara bağlanır.

Trombosit ve Endotel Hücreleri

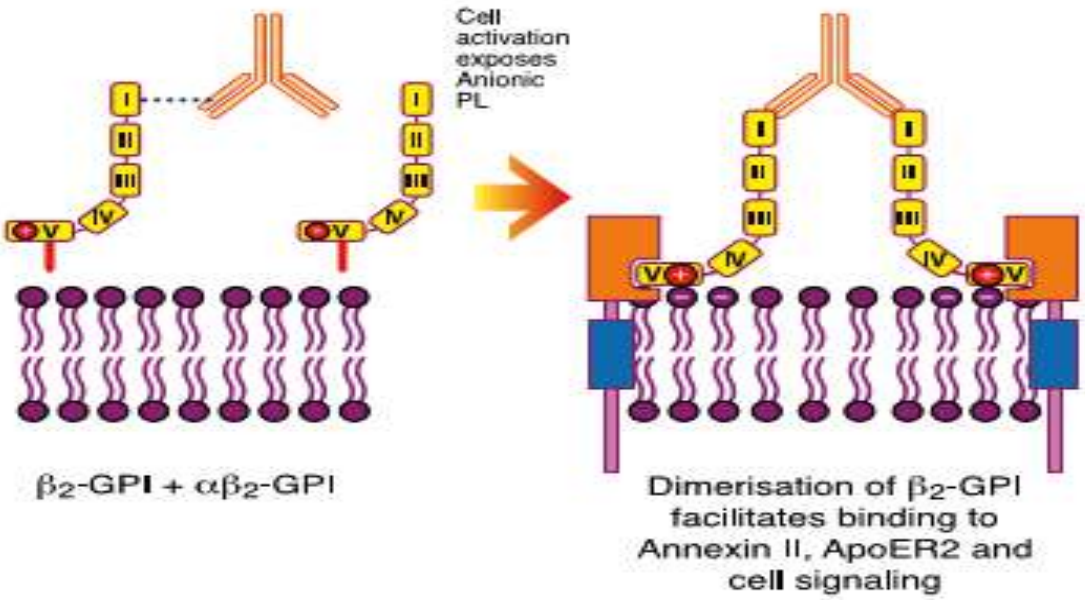


Figure 1. Schematic representation of how anti–β_2-GPI Abs in complex with β_2-GPI may interact with certain surface receptors on platelets (eg, ApoER2′) and endothelial cells (eg, annexin II, also known as annexin A2) to induce cellular activation. Reprinted from Miyakis et al[17] with permission.

Bill Giannakopoulos et all. Blood.2007;109:422-430

PLT TxA2 üretimi

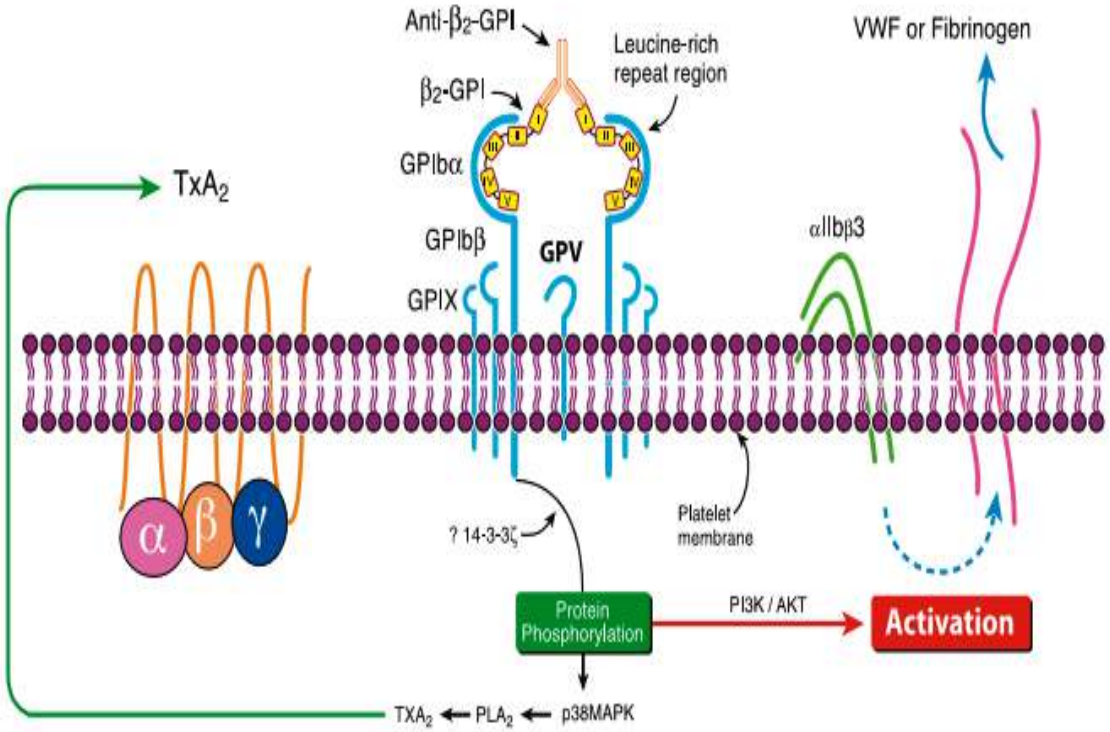


Figure 2. Proposed mechanism of how anti–β_2-GPI Abs in complex with β_2-GPI may crosslink the GPIbα subunit of the GPIb-IX-V receptor on platelets to induce activation of the p38 MAPK/PLA_2 and the PI3K/Akt intracellular pathways, potentially leading to thromboxane A_2 production and the activation of $\alpha_{IIb}\beta_3$. TxA_2 indicates thromboxane. Reprinted from Shi et al[27] with permission.

Bill Giannakopoulos et all. Blood.2007;109:422-430

CD4 T hücrelerin oto-reaktivasyonunun uyarılması

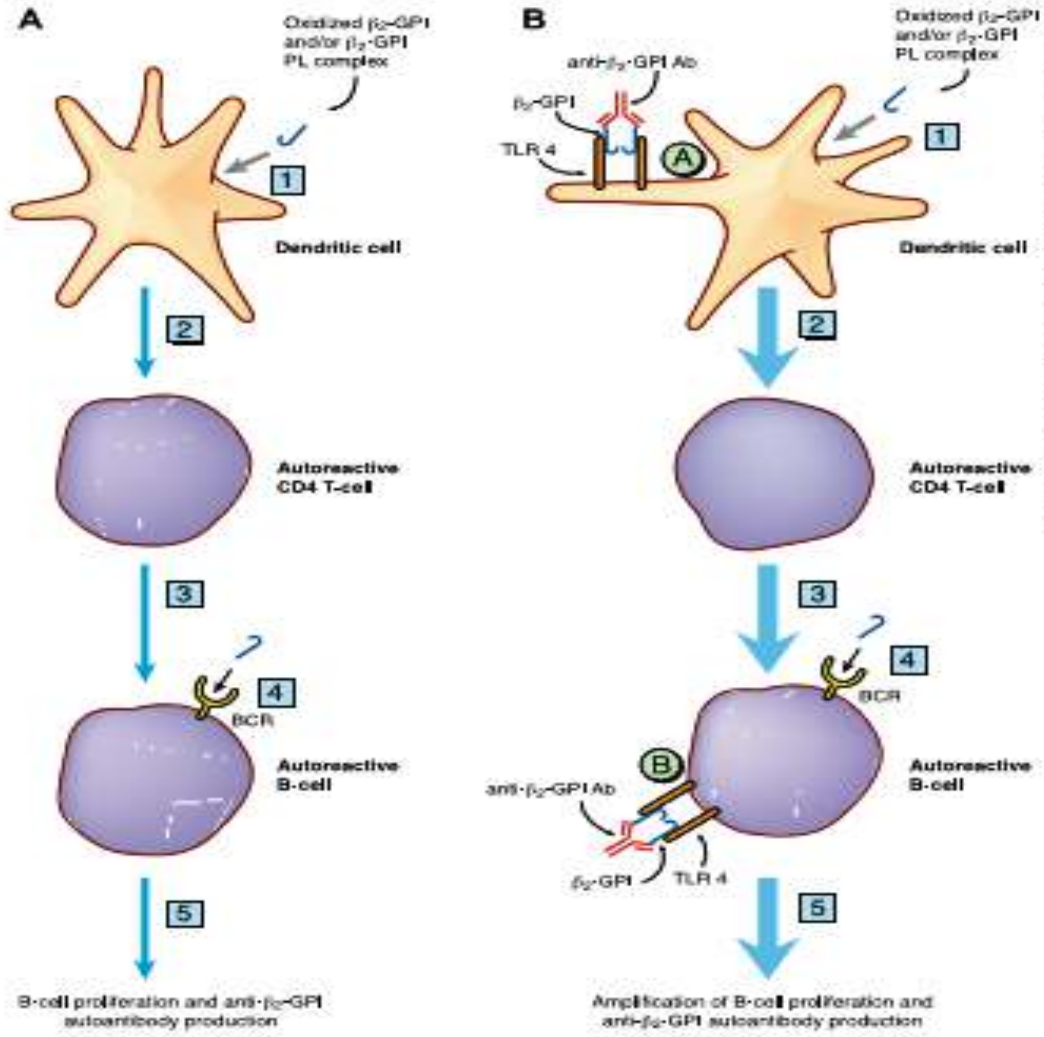
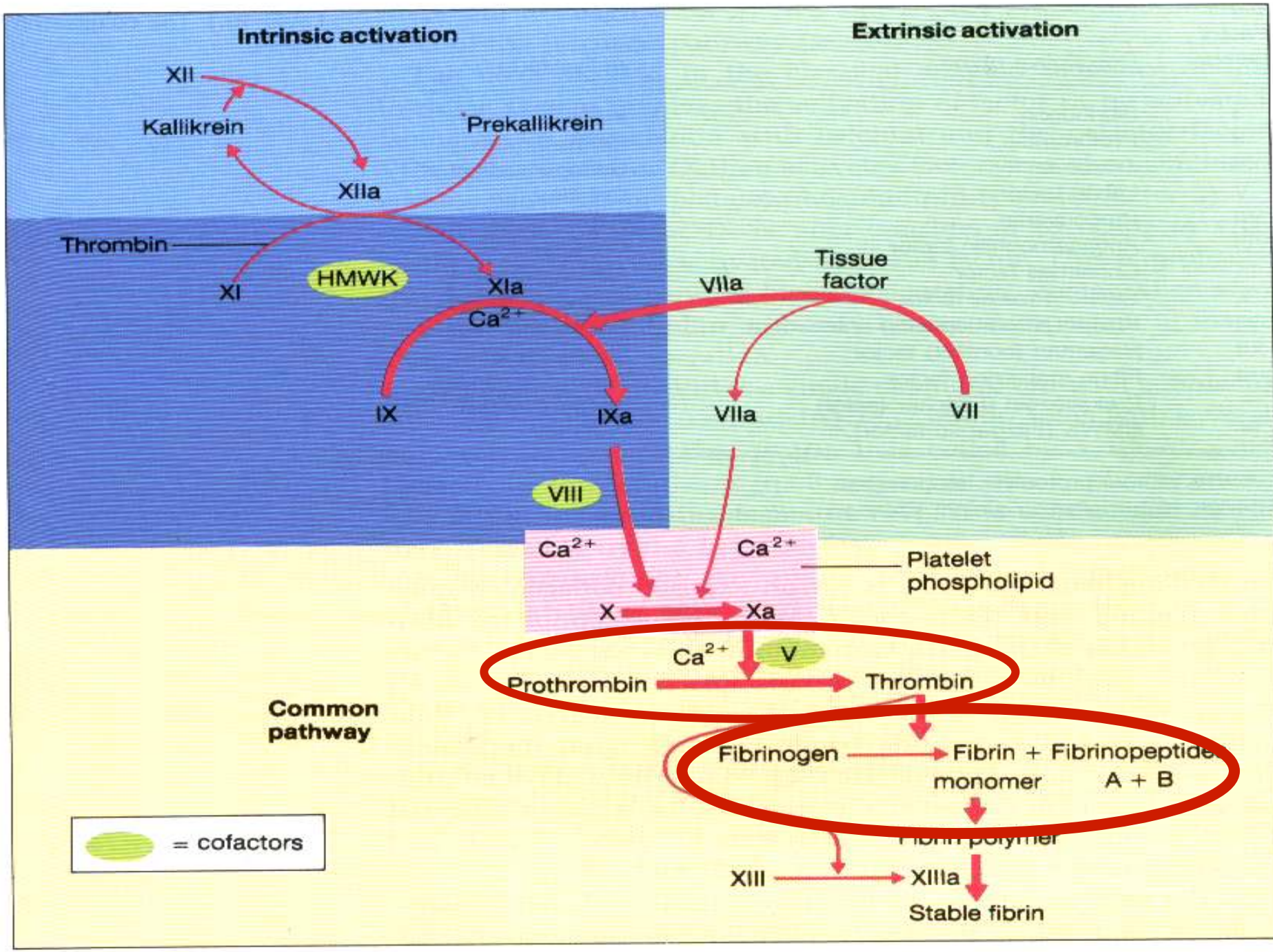


Figure 4. Schematic representation of the hypothesis that anti–β_2-GPI Abs in complex with β_2-GPI may be able to amplify the production of autoantibodies via their ability to bind and crosslink TLR4. (A) The steps that have been delineated in in vitro experiments to be important in the generation of autoantibodies directed against β_2-GPI. Step 1: the uptake and intracellular processing of the autoantigen β_2-GPI (complexed to phospholipid or in the oxidized form) via as yet poorly delineated mechanisms. Step 2: the presentation (by activated DCs) of the β_2-GPI cryptic epitope to autoreactive CD4$^+$ HLA class II–restricted T cells. DCs have been shown to release an array of cytokines that lead to Th1 polarization. Step 3: activated autoreactive CD4$^+$ T cells providing help to autoreactive B cells, which have also received a signal via the B-cell receptor (BCR) (see step 4). Step 4: the ligation by β_2-GPI of the B-cell receptor on autoreactive B cells. Step 5: anti–β_2-GPI autoantibody production. (B) It is hypothesized that oxidized β_2-GPI or the anti–β_2-GPI Ab/β_2-GPI complex may function as an immunologic adjuvant by providing a costimulatory signal via TLR4 on DCs (circled A) and B cells (circled B), leading to the amplification of the signals delineated in panel A. The thick blue line denotes the amplification of steps 1 to 5.

Bill Giannakopoulos et all. Blood. 2007;109:422-430


Intrinsic activation
Extrinsic activation
XII
Kallikrein
Prekallikrein
XIIa
Thrombin
XI
HMWK
XIa
Ca^{2+}
VIIa
Tissue factor
IX
IXa
VIIa
VII
VIII
Ca^{2+}
Ca^{2+}
Platelet phospholipid
X
Xa
Ca^{2+}
V
Prothrombin
Thrombin
Common pathway
Fibrinogen
Fibrin + Fibrinopeptide
monomer
A + B
XIII
XIIIa
Stable fibrin
= cofactors

Tromboz Patogenezi

- Kompleman Aktivasyonu,
- Endotelyal Disfonksiyon,
- Monositlerden proinflamatuar sitokinlerin salınması,
- PLT protrombotik mekanizmaların aktivasyonu,
- CD4 T hücrelerin otoreaktivasyonunun uyarılması,
- Fibrinolitik Sistemin bozulması,
- Apoptotik hücre klerensinin bozulması,
- Doğal antikoagülanlara (Protein C) direnç gelişmesi,
- Makrofajlarca alınan oksidize düşük dansiteli lipoproteinlerin (ox-LDL) endotel hasarına yol açması ve oluşan anti-oxLDL antikor ile AFA arasında çapraz reaksiyonu……

Bill Giannakopoulos et all. ,Blood.2007;109:422-430

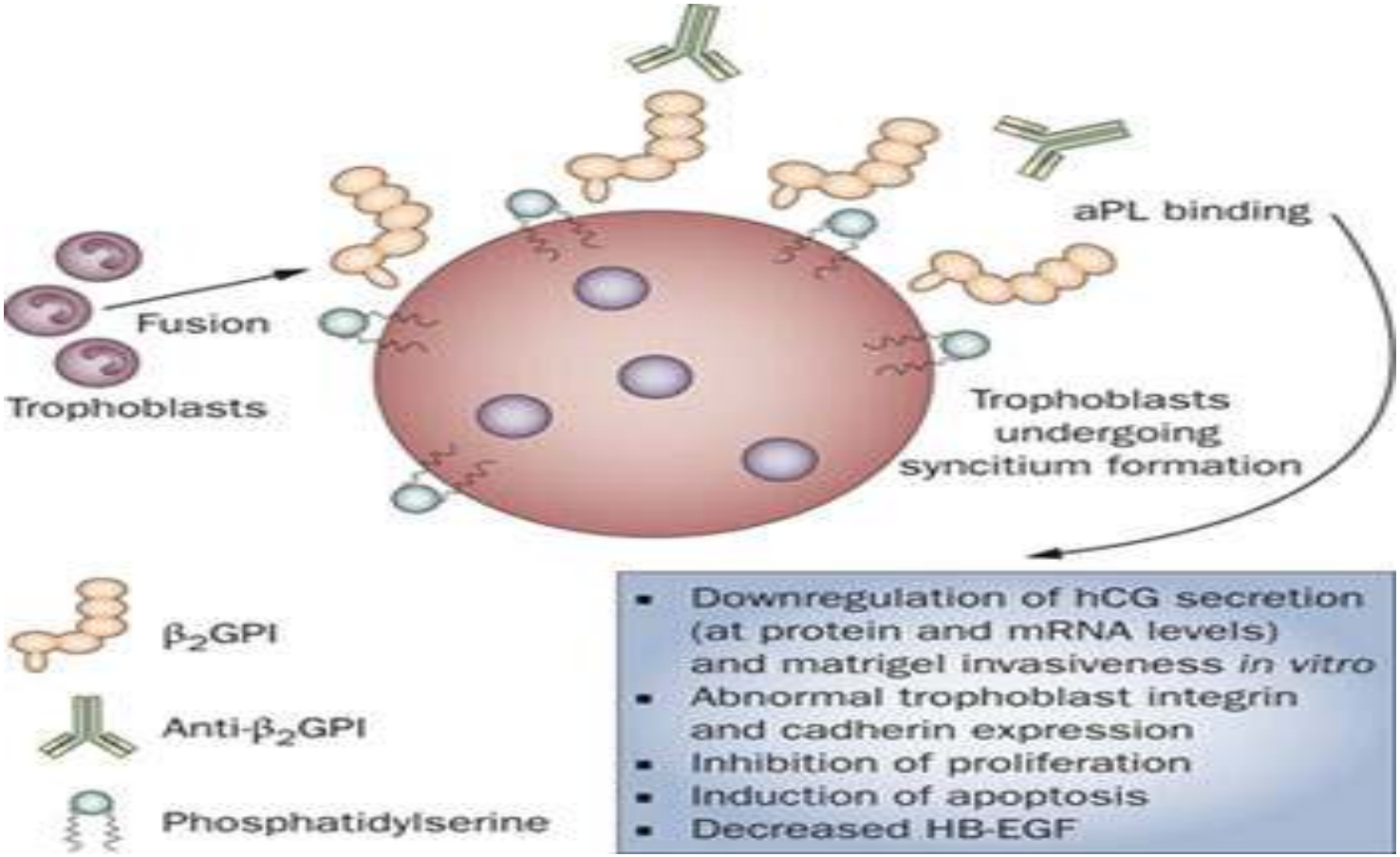
AFS Gebelik

- Bir veya fazla sayıda, normal fetal morfolojide 10. haftadan sonra fetal kayıp
- Bir veya fazla sayıda, preeklampsi, eklampsi veya plasental yetmezlik nedeniyle 34 hafta öncesinde prematüre doğum
- Üç veya daha fazla 10. hf.dan önce spontan düşükler (kromozomal anormallikler, maternal anatomik veya hormonal anormallikler dışlanmalı)

AFS Gebelik Patogenez

- Trombotik değişiklikler,
- hCG salınımının supresyonu,
- Kompleman aktivasyonunun indüksiyonu ve plasental injuri,
- Direkt trofoblastların büyüme ve farklışmasına etkisi (defektif plasentasyon)

aPL effects on trophoblasts



Meroni, P. L. *et al.* (2011) Pathogenesis of antiphospholipid syndrome: understanding the antibodies *Nat. Rev. Rheumatol.* doi: 10/1038/nrrheum.2011.52

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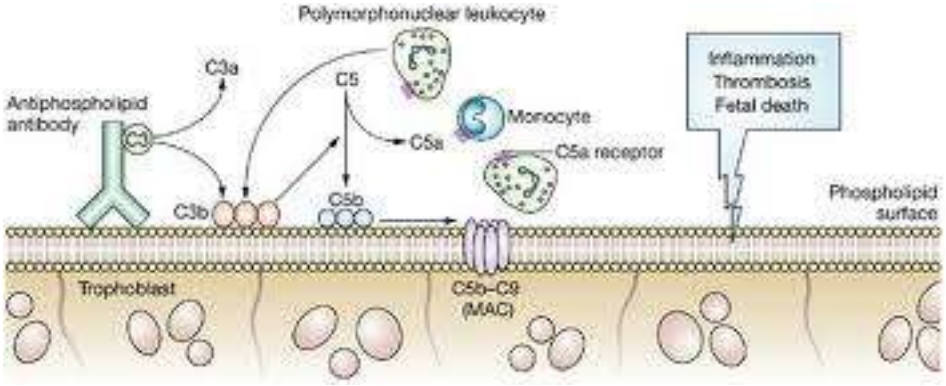
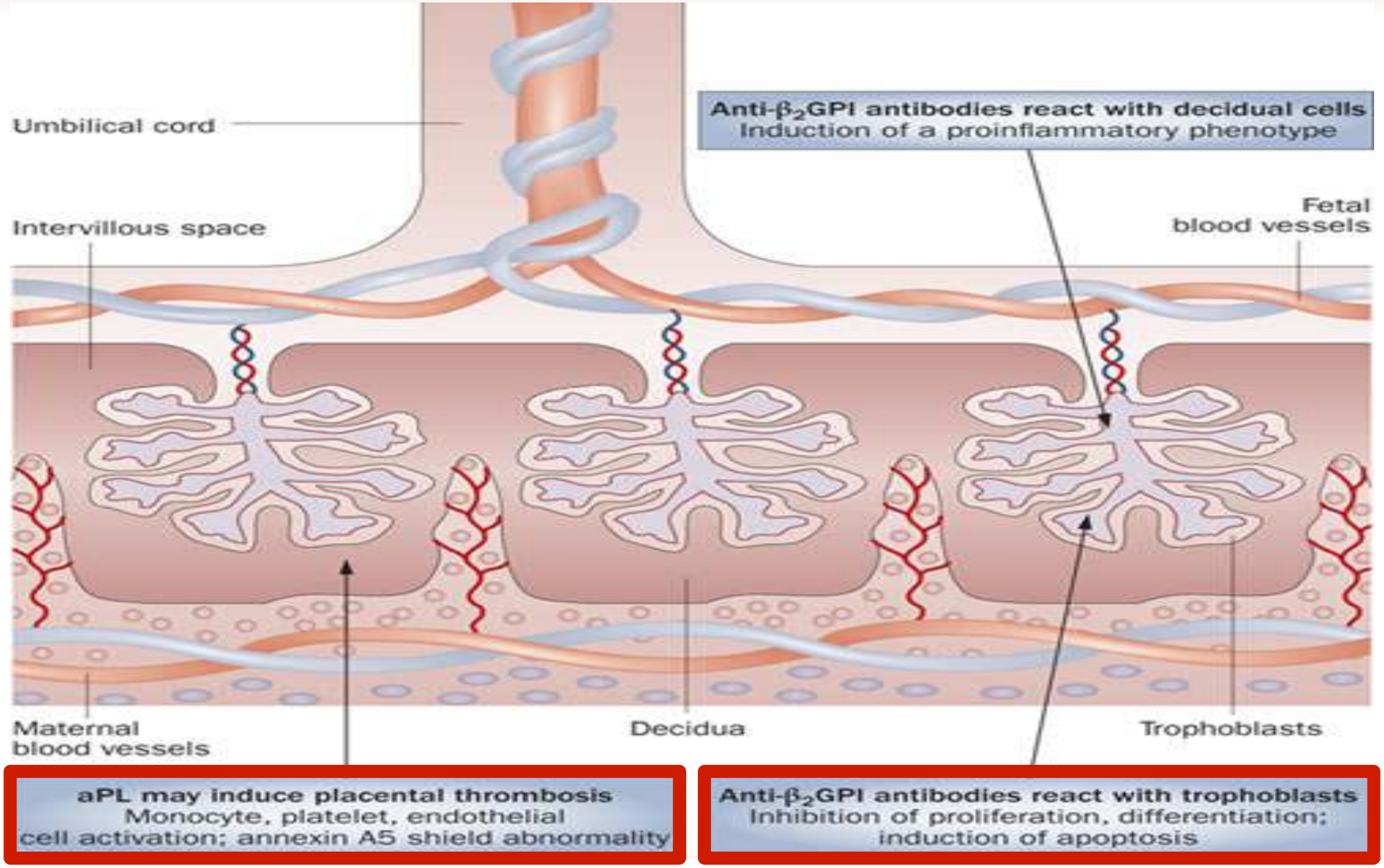
Antifosfolipid Antikorlar- Patofizyoloji



- Antifosfolipid antikorlar ⚡ trofoblastlar
  - Villöz sitotrofoblast farklılaşmasının inhibisyonu
  - Desiduaya doğru ekstravillöz sitotrofoblast invazyonunun inhibisyonu
  - Sinsityotrofoblast apoptozunun indüklenmesi
  - Sinsityotrofoblast yüzeyde kompleman aktivasyonu ile maternal enflamatuar yolakların başlaması

Girardi G Mole Immunol 2006

Main effects of aPL on placenta



Meroni, P. L. *et al.* (2011) Pathogenesis of antiphospholipid syndrome: understanding the antibodies
Nat. Rev. Rheumatol. doi:10/1038/nrrheum.2011.52

nature REVIEWS RHEUMATOLOGY

Tekrarlayan gebelik kayıpları dışında, aFL antikorlar başka obstetrik patolojiler de yapabilir:

- Utero-plasenter yetmezlik,
  - İntrauterin fetal büyüme geriliği
  - Fetal distres
  - 34. hf öncesi erken doğum
- HELLP sendromu
- Preeklampsi, eklampsi
- Ablasio plasentae
- İnfertilite

(Carp HJ, Shoenfeld Y: Clin Rev Allergy Immunol. 2007;32(2):159-61)

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journal homepage: www.elsevier.com/locate/autrev

Review

The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS): A survey of 247 consecutive cases☆

Jaume Alijotas-Reig [a,b,*,aa], Raquel Ferrer-Oliveras [c,aa], Amelia Ruffatti [d], Angela Tincani [e], Elmina Lefkou [f], Ma. Tiziana Bertero [g], Emmanuel Coloma-Bazan [h], Sara de Carolis [i], Gerard Espinosa [h], Patrizia Rovere-Querini [j], Anna Kuzenko [g], Enrique E. Valverde [k], Angel Robles [l], Ricard Cervera [h], Valentina Canti [g], Micaela Fredi [e], Antonio Gil-Aguado [l], Krista Lundelin [m,1], Elisa Llurba [c], Taisiya Melnychuk [c], Cecilia Nalli [e], Elisa Picardo [n], Erika Silvestro [g], Teresa del Ross [d], Inmaculada Farran-Codina [c], (EUROAPS Study Group Collaborators)

Table 2
Detailed current* obstetric complications in this OAPS series (N=247).

Complications	N (%)
No	118 (47.8)
Yes	129 (52.2)
Prematurity	61 (47.3)
Stillbirth & Fetal Loss	29 (22.5)
Miscarriage (latest)	21 (16.3)
FGR early onset	18 (14.0)
Preeclampsia early onset	17 (13.2)
Preeclampsia late onset	16 (12.4)
Prematurity & Preeclampsia early onset/HELLP	15 (11.6)
Prematurity & FGR early onset	9 (7.0)
HELLP	7 (5.4)
Abnormal uterine blood flow	7 (5.4)
Cord blood flow restriction	4 (3.1)
Abruptio placentae	5 (3.8)
Prematurity & FGR & Preeclampsia/HELLP	4 (3.1)
Abnormal middle cerebral artery blood flow	4 (3.1)
FGR late onset	2 (1.6)
Placental haematoma	1 (0.8)

* Latest pregnancy. The majority of women were under any treatment.

AFS-YÜKSEK RİSKLİ GEBELİK

- Antikorların üçününde pozitifliği,
- Öyküde tromboz hikayesinin olması,
- SLE gibi primer hastalığa sekonder olması.

Hannah L. Rose et all.J Thromb Thrombolysis (2014) 38:453–456

Gebelikte Antifosfolipid Antikor Sendromu Tedavi

- Kumadin 1. trimestr yan etkileri;teratojenik
  - Embryopati
  - Mental retardasyon
  - Optik atrofi
  - Nasal hipoplazi
  - Iskelet anomalileri
  - CNS anomalileri
  - Fetal hemoraji

Hayes E et al. LMWH, the most cost effective treatment of VTE. Presented at SMFM Meeting, 2006

Gebelikte Antifosfolipid Antikor Sendromu Tedavi

- LMWH daha az maternal yan etki, fetus'a geçmez, daha efektif, faktor Xa inhibisyonu
- Profilaktik dozaj icin seviye ölçümüne gerek yok
  - *Tinzaparin 4500 IU q gun
  - *Enoxaparin 40 mg q gun
  - *Dalteparin 5000 IU bid
- Terapotik anti-faktor Xa pik seviye hedefi 0.8-1.2 IU/ml
  - *Tinzaparin 175 IU/kg q gun
  - *Enoxaparin 1 mg/kg bid
  - *Dalteparin 100 IU/kg q bid

Autoimmunity Reviews 13 (2014) 795–813

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Review

14th International Congress on Antiphospholipid Antibodies Task Force Report on Obstetric Antiphospholipid Syndrome☆

Guilherme R. de Jesus [a,*], Nancy Agmon-Levin [b,c], Carlos A. Andrade [d], Laura Andreoli [e], Cecilia B. Chighizola [f,g], T. Flint Porter [h,i], Jane Salmon [j,k,l], Robert M. Silver [h], Angela Tincani [e], D. Ware Branch [h,i]

[a] Department of Obstetrics, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil

Live birth rates in groups with recurrent early miscarriage (REM) and antiphospholipid antibodies (aPL) treated with low dose aspirin (LDASA) alone.

Author, year	N	SAB	Anticardiolipin thresholds		LA	% live births
			IgG	IgM		
Cowchock, 1992 [59]	19	≥2	>30	>11	Yes	68.4
Kutteh, 1996 [60]	25	>3	>27	>27	No	44.0
Rai, 1997 [61]	45	≥3	>5	>5	Yes	42.2
Pattison, 2000 [62]	20	≥3	≥5	≥5	Yes	80.0
Farquharson, 2002 [63]	47	≥3	>9	>5	Yes	72.3
Goel, 2006 [65]	39	≥2	>18	No	No	61.5
Laskin, 2009 [67]	21	≥2	>15	>25	Yes	76.2

SAB: Spontaneous abortion.
LA: lupus anticoagulant.

Live birth rates in groups with recurrent early miscarriage (REM) and antiphospholipid antibodies (aPL) treated with heparin and low dose aspirin (LDASA).

Author, year	N	SAB	Anticardiolipin thresholds		LA	Type	% live births
			IgG	IgM			
Cowchock, 1992 [59]	26	≥2	>30	>11	Yes	UFH	73.1
Kutteh, 1996 [60]	25	≥3	≥27	≥27	No	UFH	80.0
Rai, 1997 [61]	45	≥3	>5	>5	Yes	UFH	71.1
Farquharson, 2002 [63]	51	>3	>9	>5	Yes	LMWH	78.4
Goel, 2006 [65]	33	≥2	>18	No	No	UFH	84.8
Laskin, 2009 [67]	22	≥2	>15	>25	Yes	LMWH	77.3
Dendrinos, 2008 [66]	40	≥3	M/H	M/H	Yes	LMWH	72.5
Triolo, 2003 [64]	19	≥3	≥40	No	No	LMWH	84.2

SAB: Spontaneous abortion.
LA: lupus anticoagulant.
LMWH: Low molecular weight heparin.
UFH: Unfractionated heparin.
M/H: Medium/High

Comparison of live birth rates in groups with recurrent early miscarriage (REM) and antiphospholipid antibodies (aPL) treated with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) plus low dose aspirin (LDASA) and LDASA alone.

Author	Intervention	Heparin LDASA		LDASA		*p* value
		N	Live births (%)	N	Live births (%)	
Kutteh [60]	UFH/LDASA	25	80	25	40	<0.05
Rai [61]	UFH/LDASA	45	72	45	42	0.01
Farqharson [63]	LMWH/LDASA	51	78	47	72	NS
Goel [65]	UFH/LDASA	33	85	39	62	0.04
Laskin [67]	LMWH/LDASA	22	77	21	76	NS

Trials comparing live birth Rates in women with recurrent early miscarriage (REM) and antiphospholipid antibodies (aPL) treated with low molecular weight heparin (LMWH) and low dose aspirin (LDASA) to those treated with intravenous immune globulin (IVIG).

Author	LMWH/LDASA		IVIG		p-Value
	N	Live births (%)	N	Live births (%)	
Triolo, 2003 [64]	19	84.2	21	57.1	0.06
Dendrinos, 2009 [67]	40	72.5	38	39.5	0.003

Gebelikte Antifosfolipid Antikor Sendromu Tedavi

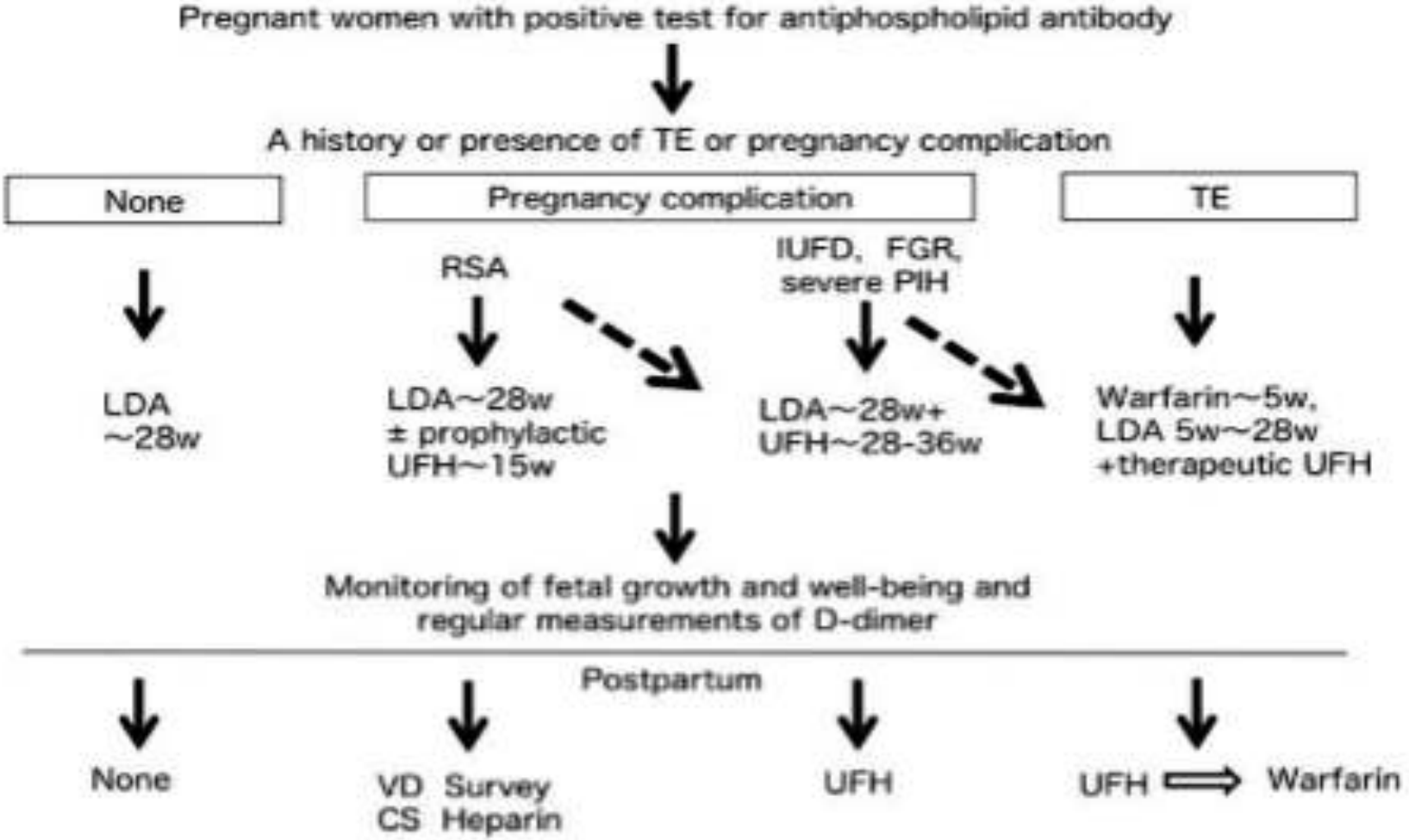
- aFL + tekrarlayan düşük,preeklampsi,IUGG ve tromboz öyküsü yok

  Düşük doz aspirin(100 mgr/gün)
- aFL+ tekrarlayan düşük öyküsü mevcut

  Düşük doz aspirin+ DMAH
- aFL+ tromboz

  Düşük doz aspirin+Teropotik dozda heparin
- SLE eşlik ediyorsa **Hidroksiklorokin+Azatiopürin**
- Katastrofik AFS **IVIG**

Hannah L. Rose J Management of very high risk pregnancy with secondary anti-phospholipid syndrome and triple positivity to the anti-phospholipid antibodies Thromb Thrombolysis (2014) 38:453–456
David Keeling et al. Guidelines on the investigation and management of antiphospholipid syndromeBritish Journal of Haematology, 2012, 157, 47–58



Antiphospholipid antibodies include lupus anticoagulant, anticardiolipin antibody, anti-β2 glycoprotein-I antibody, and β2–glycoprotein I dependent anticardiolipin antibody. If women yield multi-positive tests or a high titer of antiphospholipid antibody, more intensive treatment should be considered as presented by dotted arrows.

TE, thromboembolism; RSA, recurrent spontaneous abortion; IUFD, intrauterine fetal death; FGR, fetal growth restriction; PIH, pregnancy-induced hypertension; LDA, low dose aspirin; UFH, unfractionated heparin; VD, vaginal delivery; CS, cesarean section

Antithrombotic effects of hydroxychloroquine in primary antiphospholipid syndrome patients

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Several studies have shown an important risk of thrombosis relapse in antiphospholipid syndrome (APS) [1,2], and the need for secondary prophylaxis [3]. Hydroxychloroquine (HCQ) is such a treatment, showing a positive balance between benefits and risks, and a low economic cost. The goals of this first prospective study in primary APS patients were to assess the efficacy of HCQ as a new therapeutic approach, and to evaluate its effectiveness relative to standard oral anticoagulants (OAs) for the prevention of recurrent thrombosis.

We report a preliminary prospective non-randomized study approved by the institutional review board in

by

mostasis
University of

fusion affected

Anti-β2GP1
on via TLR4.
s therapeutic

hrome; beta
a; pregnancy;

doi:10.1111/aji.12184

may explain why migration was only partially restored.

Conclusion
Hydroxychloroquine reversed the aPL-inhibition of trophoblast IL-6 secretion and partially limited aPL-inhibition of cell migration. Thus, some form of combination therapy that includes HCQ may be beneficial to pregnant APS patients.

entiation by using ELISA-measured β-human choronic gonadotropin hormone (β-hCG) secretion. We used three types of aPL to study their effect on cell fusion and differentiation: aPL derived from obstetric APS patients and

ion

antiphospholipid syndrome (APS) is an association of thromboembolic complications and/or obstetric pathologies and the presence of antiphospholipid antibodies (aPL) [1]. Obstetric APS treatment combines low-dose-aspirin with low molecular weight heparin [2]. Unfortunately, it is inefficient in about 30% of cases, reinforcing

CONCISE REPORT

A prospective open-label pilot study of fluvastatin on proinflammatory and prothrombotic biomarkers in antiphospholipid antibody positive patients

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ABSTRACT

Objective To determine if proinflammatory and prothrombotic biomarkers are differentially upregulated in persistently antiphospholipid antibody (aPL)-positive patients, and to examine the effects of fluvastatin on these biomarkers.

Methods Four groups of patients (age 18–65) were recruited: (a) primary antiphospholipid syndrome; (b) systemic lupus erythematosus (SLE) with antiphospholipid syndrome (APS) (SLE/APS); (c) persistent aPL positivity without SLE or APS (Primary aPL); and (d) persistent aPL positivity with SLE but no APS (SLE/aPL). The frequency-matched control group, used for baseline data comparison, was identified from a databank of healthy persons. Patients received fluvastatin 40 mg daily for 3 months. At 3 months, patients stopped the study medication and they were followed for another 3 months. Blood samples for 12 proinflammatory and prothrombotic biomarkers were collected monthly for 6 months.

Results Based on the comparison of the baseline samples of 41 aPL-positive patients with 30 healthy

in otherwise healthy individuals as well as in 30%–40% of systemic lupus erythematosus (SLE) patients. aPL-mediated clinical events occur due to complex interaction of proinflammatory and prothrombotic cells. *First*, aPL increase endothelial cell (EC) expression of the cellular adhesion molecules (CAMs) such as intracellular CAM-1 (ICAM-1), vascular CAM-1 (VCAM-1) and E-selectin (E-sel).[2–6] *Second*, tissue factor (TF) upregulation is an important mechanism of the prothrombotic effects of aPL.[7–9] *Third*, aPL induce significant increase in proinflammatory cytokines (interleukin (IL)-6, IL-8 and tumour necrosis factor-α (TNF-α)) on EC.[8 9] Fluvastatin diminishes aPL-mediated upregulation of adhesion molecules and TF in vitro in ECs, as well as the in vivo thrombogenic and proinflammatory effects of aPL in mice.[10–12]

Given the relationship between thrombosis and increased expression of CAMs, TF activity and proinflammatory cytokines in APS, we hypothesise that patients with persistently positive aPL have increased levels of proinflammatory and prothrom-

Journal of Thrombosis and Haemostasis, **2**: 1558–1563

IN FOCUS

Fluvastatin inhibits up-regulation of tissue factor expression by antiphospholipid antibodies on endothelial cells

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Global effects of fluvastatin on the prothrombotic status of patients with antiphospholipid syndrome.

López-Pedrera C[1], Ruiz-Limón P, Aguirre MÁ, Barbarroja N, Pérez-Sánchez C, Buendía P, Rodriquez-García IC, Rodriquez-Ariza A, Collantes-Estevez E, Velasco F, Khasmahta M, Cuadrado MJ.

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Abstract

OBJECTIVE: Numerous mechanisms have been proposed to explain the thrombotic/proinflammatory tendency of antiphospholipid syndrome (APS) patients. Prothrombotic monocyte activation by antiphospholipid antibodies involves numerous proteins and intracellular pathways. The anti-inflammatory, anticoagulant and immunoregulatory effects of statins have been aimed as a therapeutic tool in APS patients. This study delineates the global effects of fluvastatin on the prothrombotic tendency of monocytes from APS patients.

METHODS: Forty-two APS patients with thrombosis and 35 healthy donors were included in the study. APS patients received 20 mg/day fluvastatin for 1 month. Blood samples were obtained before the start, at the end and 2 months after the end of treatment.

RESULTS: After 1 month of treatment, monocytes showed a significant inhibition of tissue factor, protein activator receptors 1 and 2, vascular endothelial growth factor and Flt1 expression that was related to the inhibition of p38 mitogen-activated protein kinase (MAPK) and nuclear factor kappa B/Rel DNA-binding activity. Proteomic analysis showed proteins involved in thrombotic development (annexin II, RhoA and protein disulphide isomerase) with altered expression after fluvastatin administration. In-vitro studies indicated that the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase by fluvastatin might inhibit protein prenylation and MAPK activation.

CONCLUSION: The data from this study support the belief that fluvastatin has multiple profound effects in monocyte activity, which might contribute to thrombosis prevention in APS patients.

OLGU 2

- Kırk yaşında erkek hasta,
- Şikayeti:15 gündür olan nefes darlığı ve göğüs ağrısı
- Hikayesi: 4 yıl önce arteriyel tromboz nedeni ile sağ alt ekstremite trombektomi ameliyatı

  2 yıl önce iskemik serebrovasküler olay

OLGU 2

- Pulmoner tromboemboli ön tanısıyla çekilen ventilasyon/perfüzyon sintigrafisi, pulmoner tromboemboli açısından yüksek riskli bulundu.
- Hastanın tam kan sayımında pansitopeni saptandı. Periferik yaymasında, fragmente eritrositler gözlenirken, atipik hücre saptanmadı. Vitamin B12 ve folik asit değerleri normal sınırlarda bulundu. Laktat dehidrogenaz değeri, laboratuvar normallerinin üst sınırından dört kat yüksek bulundu. Hastada hemolitik anemi olduğu kabul edildi.

OLGU 2

- Daha önce bilinen böbrek problemi bulunmayan hastanın kreatinin değeri: 1.7 mg/dl

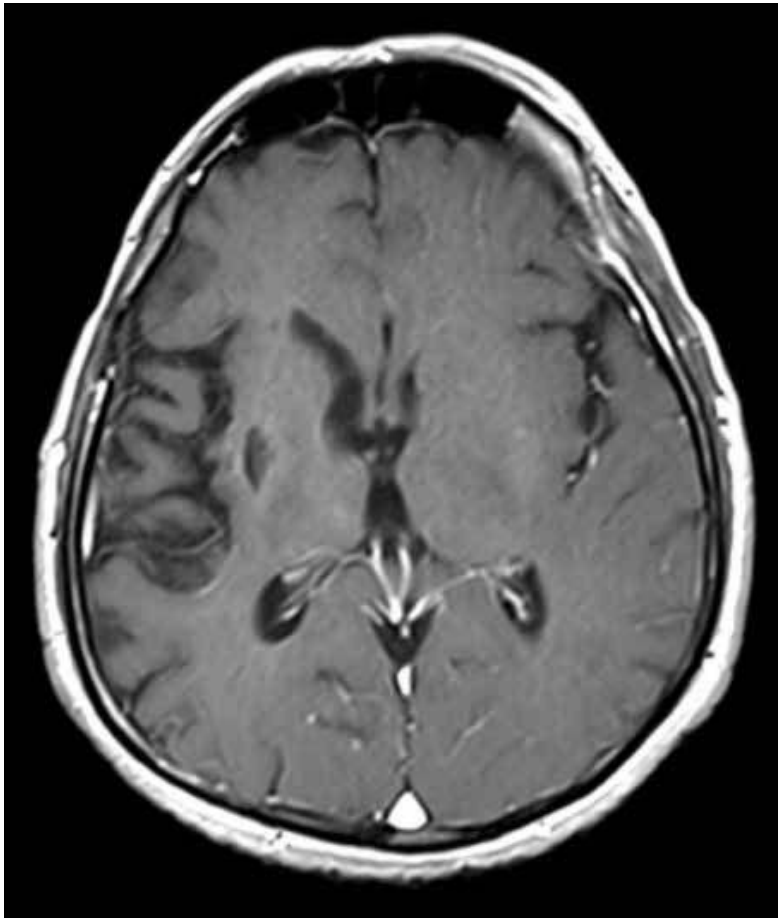
  idrar sedimentinin aktif.

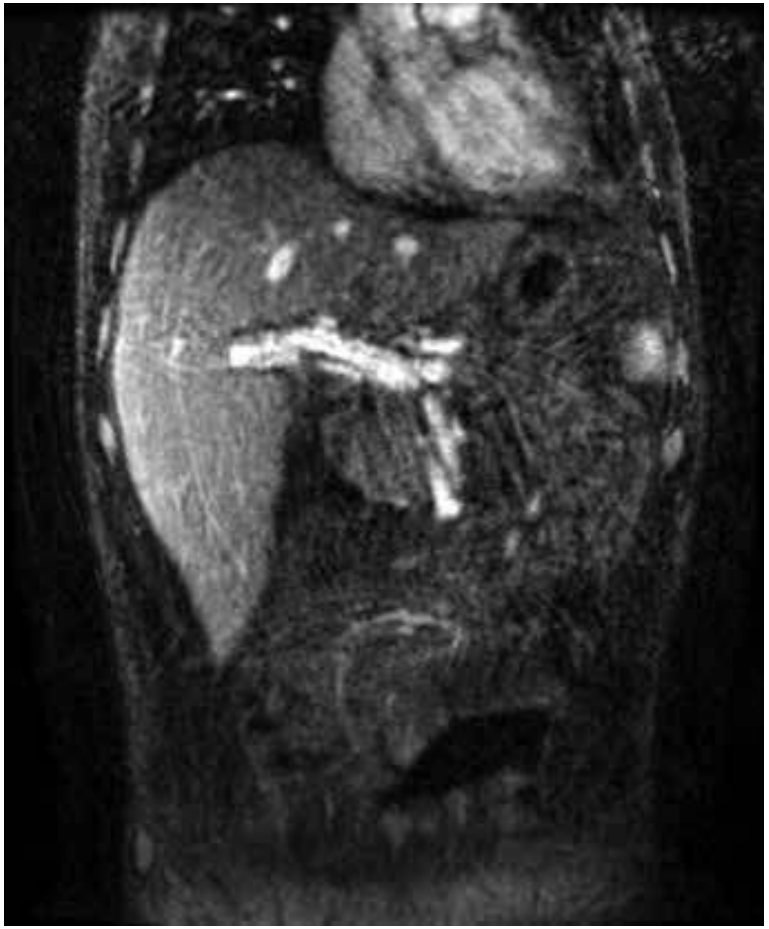
  24 st.lik idrar proteini:4 gram/gün

Hastanın genel durumu ve kanama riski göz önüne alınarak böbrek biyopsisi yapılamadı.

- Hepatosplenomegali ve transaminaz yüksekliği gözlenen hastanın yapılan portal sistem manyetik rezonans (MR) anjiyografisinde,portal vende parsiyel tromboz saptandı.

Şekil 1. (a) Geçirilmiş serebrovasküler olaya bağlı kronik serebral enfark alanı. (b) Manyetik rezonans anjiografi'de saptanan parsiyel portal ven trombüsü.





OLGU 2

- Antikoagülan tedavi öncesi bakılan bazal aktive parsiyel tromboplastin zamanı ve protrombin zamanı uzun olarak tespit edildi. Bu bulgu üzerine AFS ön tanısı ile

  Lupus antikoagülanı: İki kez pozitif

  Antikardiyolipin Ig G ve M: Negatif
- Diğer trombofili nedenlerinin araştırılmasında Faktör V Leiden mutasyonu, protrombin gen mutasyonu ve, MTHFR C677T mutasyonu negatif olarak bulundu. Protein C ve S, antitrombin ve homosistein seviyesi normal sınırlarda tespit edildi.
- Hastada mevcut bulgularla bağ dokusu hastalığı olabileceği de düşünülerek,

  antinükleer antikor testi (ANA), anti-dsDNA, antisentromer ab:+
- Enfektif etyolojilerinin araştırılması için alınan kan ve idrar kültüründe üreme gözlenmedi. Fizik muayene ve sorgulamada enfeksiyon odağı gözlenmedi.

OLGU 2

- Hastada aynı anda tespit edilen ve akut gelişen, ikisi görüntüleme yönteminde gösterilmiş tromboz ile karakterize,
- Üç ayrı organ sisteminde tutulum olması, lupus antikoagülan testi pozitifliği
- ve diğer muhtemel etkenlerden enfeksiyon ve herediter trombofili ekarte edilmesi sonrası, olası KAFS kabul edilerek tedaviye başlandı.

OLGU 2

- Hastaya trombosit sayımına göre düşük moleküler ağırlıklı heparin
- Yatışının 10, 11 ve 12. günlerinde Metilprednizolon 1 gr/gün/3 gün İ.V Takiben 1 mgr/kg/gün prednisolone eşdeğer dozundan oral olarak devam edildi.
- Yatışının 24. gününde intravenöz immünglobulin (IVIG) 2 gr/kg/gün, plazma değişimi eşliğinde başlandı. Toplam üç gün IVIG alan ve 11 seans plazma değişimi uygulanan hastanın, pansitopenisinin devamı üzerine yatışının 37. gününde, bir kez daha üç gün metilprednizolon 1 gr/ gün dozundan verildi.
- Hastanın yatışının 46. gününde genel durumunda iyileşme, pansitopenisinde düzelme izlendi. Proteinüri değerinin gerilemesi üzerine, idame takibinde, siklofosfamid aylık 1 gr parenteral, 1 mg/kg/gün prednisolone eşdeğeri oral steroid ve oral antikoagülasyon ile izlenmesine karar verildi.

Katastrofik AFS

1. Üç veya daha fazla organ, sistem ve/veya dokuda tutulum olduğunun kanıtlanması*

2. Bulguların aynı anda veya bir haftadan kısa sürede gelişmesi

3. Küçük damar trombozunun en az bir organ veya dokuda histopatolojik olarak gösterilmesi**

4. Antifosfolipid antikorlarının kalıcı olarak varlığınınn gösterilmesi (lupus antikoagülanı ve/veya antikardiolipin antikorları)***

"Kesin" katastrofik AFS: 4 kriterin aynı anda varlığı

Olası" katastofik AFS:

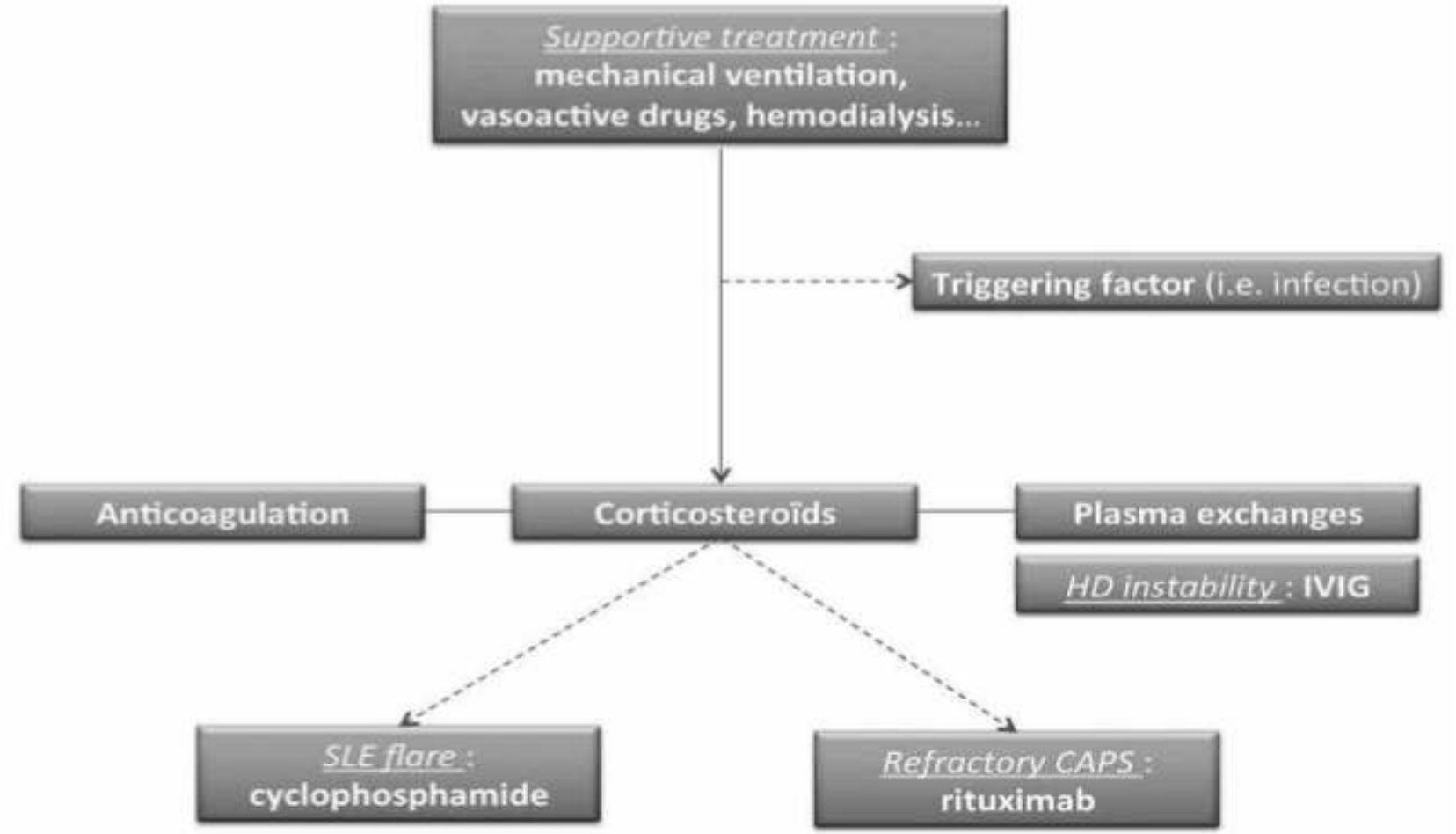
- Kriter 2-3-4 ve sadece iki organ, sistem ve/veya doku tutulumu varlığı
- Kriter 1-2-3 ve hastalarda aFL varlığının en az 6 hafta arayla gösterilememiş olması (örnek: katastrofik AFS öncesinde aFL test edilmemiş hastanın erken dönemde kaybedilmesi)
- Kriter 1-2-4
- Kriter 1-3-4 ve bir haftadan daha uzun ancak bir aydan daha kısa sürede üçüncü vasküler olayın gelişmesi

Clinical manifestations of CAPS

System involved (frequency)	Clinical symptoms
Renal (71%)	Hypertension (mild to malignant) Proteinuria and microscopic hematuria Acute renal failure Renal vein thrombosis Renal infarction
Pulmonary (64%)	Acute respiratory distress syndrome (ARDS) Pulmonary embolism
Central nervous system (62%)	Lack of awarness Confusion syndrome Neurologic deficit (stroke) Posterior reversible encephalopathy (PRES)
Cardiac (51%)	Cardiac failure Valvular dysfunction (mitral, aortic) Pericardial effusion Myocardial infarction
Skin (50%)	Ischemic necrosis of the extremities Livedo racemosa Subungual hemorrhages flames
Hepatic (30%)	Biological cytolysis by microvascular ischemia
Gastrointestinal (23%)	Ischemic abdominal pain Acalculous cholecystitis Pancreatitis Splenic rupture
Adrenal glands (23%)	Hypotension (atypical in CAPS) Abdominal or lombar pains Electrolyte disorders

J. Guntz et all.Catastrophic antiphospholipid syndrome : case reports and review of the literature.Acta Anaesth. Belg., 2014, 65, 87-94

Katastrofik AFS-Tedavi



J. Guntz et all.Catastrophic antiphospholipid syndrome : case reports and review of the literature.Acta Anaesth. Belg., 2014, 65, 87-94

Katastrofik AFS-Tedavi

- **Ritüksimab**
- **Eculizumab**:Fare kaynaklı, insanlaştırılmış monoklonal antikor. Kompleman protein C5'e bağlanır. Böylece C5 konvertaz ile yıkılmasını önler.Sonuçta membran atak kompleksinin oluşumu engellenir.

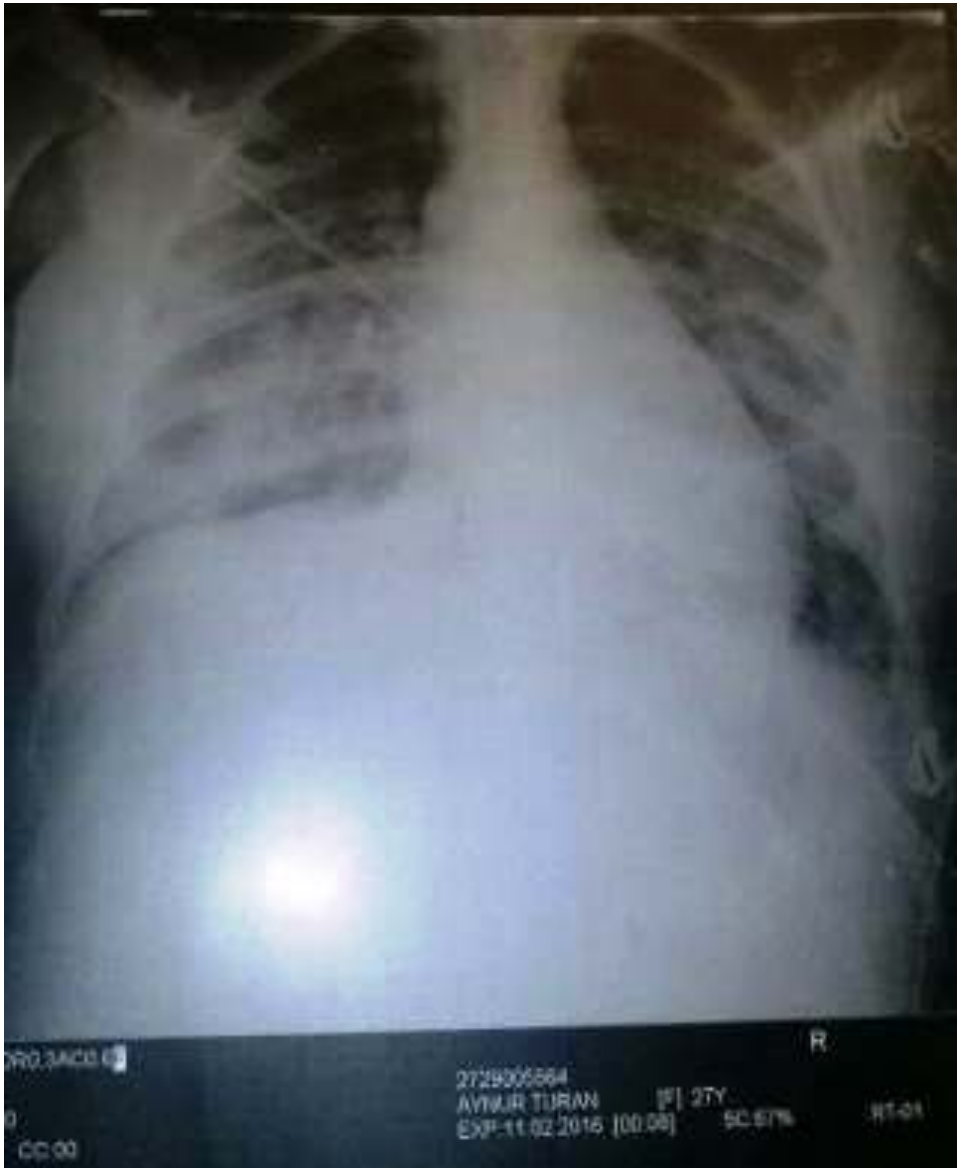
OLGU 3

- 27 yaşında ,bayan ,daha önceden SLE tanısıyla ***Plaquenil*** ve ***Imuran*** tb. kullanıyormuş. Dış merkezde çocuk sahibi olma talebiyle kullandığı ilaçlar kesilerek ovulasyon indüksiyonu yapılmış. Bir hafta sonra karın ağrısıyla O***varyan Hiperstimülasyon Sendromu*** tanısıyla yatarak tedavi olmuş.Birhafta sonra taburcu edilmiş. Nefes darlığı ve göğüs ağrısıyla Koşuyolu Kalp Hast. Hastanesi acil servise başvurmuş.MI? Miyozit ön tanılarıyla Koroner Yoğun Bakım Servisine yatırılmış.

OLGU 3

- BK:5600 Hb:8.6 Plt:273000
- ALT:24 U/L AST:53.4 U/L
- T.Protein:5.99 g/dl (6.4-8.3)
- albumin:2.49 g/dl (3.5-5.2)
- ESH:141 mm/st CRP:8.56 mgr/dl (0-0.34)
- TİT:albumin +

OLGU 3



OLGU 3

- Entübe ,bilinci kapalı
- Koroner anjiografi yapılamadı. Koroner Tromboz??? Miyokardit????
- EF:% 30 Prednol 250 mgr/gün 4 gün →60mgr/gün
- İVİG:0.5 mgr/kg 4 gün verildi.
- Takiplerinde troponin düzeylerinde düzelme??? Akc gr de düzelme
- Kontrol Beyin BT: Diffüz ödem (hipoksik)
- Yatışının 15.günü exitus mortalis

OLGU 3

ANA – ANTİDS DNA – ENA PROFİLİ –

- **lupus antikoagülanı: 4 ,**
- **Anti- Beta 2 Glikoprotein Ig M>123.95** RU/ML
- Anti- Beta 2 Glikoprotein Ig G<2
- Anti kardiyolipin Ig M:28.05 RU/ML
- Anti kardiyolipin Ig G<2

KONTRASEPSİYON

SLE

- Kombine OK ler tromboembolizm riski↑
- Progesteron içeren preparatların nefritli ve ACE inb. kullananlarda K^+ seviyesini arttırdığı gösterilmiş.
- Progesteron içeren transdermal patch SLE hastalarında çalışma yok.
- Levonorgestrel İUA :Enf riskine dikkat
- Bariyer yöntemi

LR Sammaritano Contraception in patients with systemic lupus erythematosus and antiphospholipid syndrome.Lupus (2014) 23, 1242–1245

KONTRASEPSİYON

AFS

- Kombine OK ler tromboembolizm riski↑
- Porgesteron içeren praparatların trombo-embolizm riski çok az. Warfarin kullananlarda menstruel kanamayı azalttığı için yararlı olduğu, uzun dönemde yan etkilerinin kullanımını sınırlıyor.
- Levonorgestrel İUA
- Bariyer yöntemi

LR Sammaritano Contraception in patients with systemic lupus erythematosus and antiphospholipid syndrome.Lupus (2014) 23, 1242–1245

IVF
SLE-AFS

- Hormon manupülasyon ve fertilizasyon tedavileri

aFL + lerde tromboz aktivasyonu
Lupus aktivasyonu

- Ovarian hiperstimulasyon, multifetal gebelik, prematürite ve emosyonel distress.

6 ay boyunca sessiz seyrediyorsa IVF uygulanabilir

AB Levine and MD Lockshin Assisted reproductive technology in SLE and APS
Lupus (2014) 23, 1239–1241

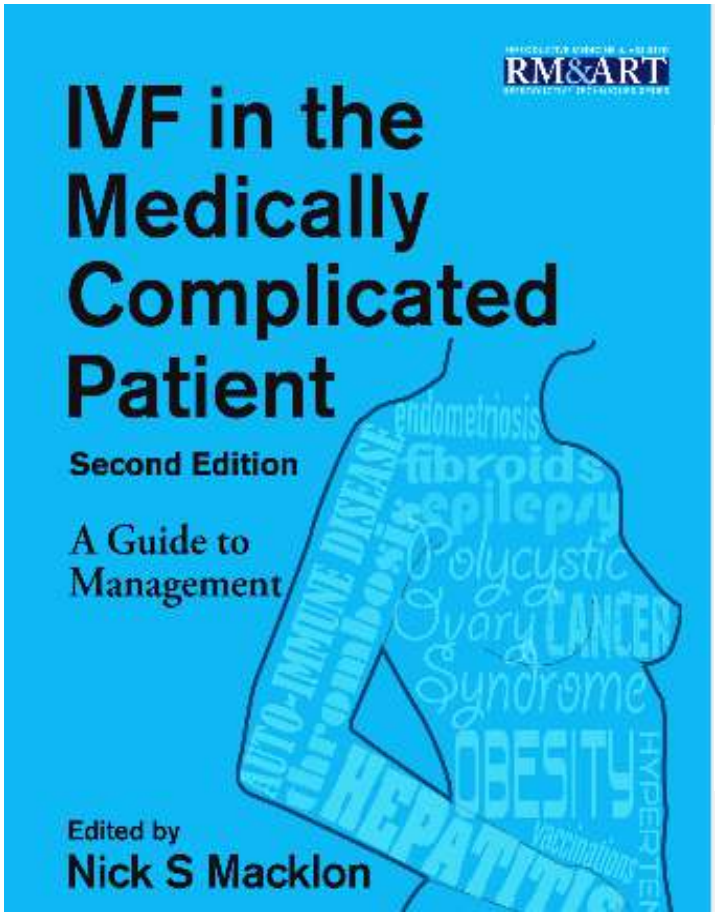


TABLE 4.2

Clinical Situations in which Ovarian Stimulation Should Be Discouraged in Women with SLE

Acute flare (and the following 6–12 months)
Pulmonary hypertension or arterial hypertension
Valvulopathy or heart disease
Previous thromboembolism
Severe renal disease
Antiphospholipid syndrome and anti-Ro/anti-La antibodies

Source: Adapted from Bellver J, Pellicer A. *Fertil Steril* 2009 Dec;92(6):1803–10.

Table 4

Guidelines for use of estrogens in women with SLE.

Clinical criteria	Laboratory criteria
1. Inactive or stable/moderate disease	1. No lupus anticoagulant
2. No history of venous or arterial thrombosis	2. No high titres of any antiphospholipid antibody isotype (IgG >40 GPL, IgM >40 MPL, IgA >50 APL)
3. No history of lupus exacerbation with estrogens	
4. Nonsmoker	
5. Normotensive	
Consider progestogen-only oral contraceptives	
OR	
Use the lowest dose of ethinylestradiol (≤35 μg) in combined oral contraceptives	

José Bellver et all, Ovarian stimulation for ovulation induction and in vitro fertilization in patients with systemic lupus erythematosus and antiphospholipid syndrome. Fertil Steril. 2009 Dec;92(6):1803-10

Table 5 summarizes the guidelines for ovarian stimulation in women with SLE or APS.

Table 5

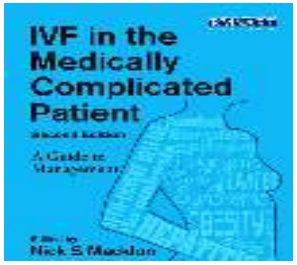
Guidelines for ovarian stimulation in women with SLE or antiphospholipid syndrome.

Friendly ovarian stimulation
Clomiphene citrate: drug of choice in ovulation induction
Prevent ovarian hyperstimulation syndrome
Single embryo transfer
Coadjuvant therapy: anticoagulation, corticosteroids, immunosuppressants
Transfer of frozen embryos and ovum donation
Natural cycles better than treated cycles
Natural E_2 better than synthetic estrogens
Transdermal route better than oral route
Luteal phase support
Progesterone better than hCG
Natural P better than synthetic progestogens
Vaginal route better than oral route

José Bellver et all, **Ovarian stimulation for ovulation induction and in vitro fertilization in patients with systemic lupus erythematosus and antiphospholipid syndrome.** Fertil Steril. 2009 Dec;92(6):1803-10

IVF
SLE-AFS

- **aFL + tromboz öyküsü yok**: Embriyo transferinden sonra LMWH
- **aFL+ tromboz öyküsü +:**Teropatik dozda heparin+ Düşük doz aspirin
- **SLE aFL -**: İmmunsupresan tedavi



Medicine (Baltimore). 2015 Sep;94(37):e1531. doi: 10.1097/MD.0000000000001531.

Successful Pregnancy Following Assisted Reproduction in Woman With Systemic Lupus Erythematosus and Hypertension: A Case Report.

de Macedo JF[1], de Macedo GC, Campos LA, Baltatu OC.

Author information

Abstract

Patients with systemic lupus erythematosus have a poor prognosis of pregnancy, since it is associated with significant maternal and fetal morbidity, including spontaneous miscarriage, pre-eclampsia, intrauterine growth restriction, fetal death and pre-term delivery. We report a case with successful pregnancy in a patient with systemic lupus erythematosus and hypertension. A 39-year-old nulliparous woman presented with systemic lupus erythematosus with antinuclear and antiphospholipid antibodies, hypertension and recurrent pregnancy loss presented for assisted reproduction. The patient responded well to enoxaparin and prednisone during both assisted reproduction and prenatal treatment. This case report indicates that prescription of immunosuppressant and blood thinners can be safely recommended throughout the whole prenatal period in patients with systemic lupus erythematosus. Enoxaparin and prednisone may be prescribed concurrently during pregnancy.

PMID: 26376400 [PubMed - indexed for MEDLINE] PMCID: PMC4635814 Free PMC Article

EXTENDED REPORT

OPEN ACCESS

European registry of babies born to mothers with antiphospholipid syndrome

Arsene Mekinian,[1] Eric Lachassinne,[2] Pascale Nicaise-Roland,[3] Lionel Carbillon,[4] Mario Motta,[5] Eric Vicaut,[6] Catherine Boinot,[7] Tadej Avcin,[8] Philippe Letoumelin,[9] Sara De Carolis,[10] Patrizia Rovere-Querini,[11] Marc Lambert,[12] Sophie Derenne,[13] Olivier Pourrat,[7] Jerome Stirnemann,[1] Sylvie Chollet-Martin,[3] Chiara Biasini-Rebaioli,[5] Rosanna Rovelli,[11] Andrea Lojacono,[5] Ales Ambrozic,[8] Angela Botta,[10] Amelie Benbara,[4] Fabrice Pierre,[7] Flavio Allegri,[5] Monica Nuzzo,[5] Pierre-Yves Hatron,[12] Angela Tincani,[5] Olivier Fain,[1] Marie-Helene Aurousseau,[14] Marie-Claire Boffa[14]

- 134 çocuk , 65 i kız -69 u erkek
- 22 ‘i (%16) preterm doğum ,19 ‘u 2500 gr altında (%14)
- Neonatal komplikasyon 18 olguda (13%), 5 olguda enfeksiyon (4%).
- 5 yıllık takip boyunca thromboz veya SLE tespit edilmedi.
- 3 çocukta davranışsal bozukluk (1çocukta otizm, 1çocukta hiperaktivite, 1 çocukta yeme bozukluğu ve konuşmanın gecikmesi)
- 1 çocukta aksiyal hipotoni ile psikomotor gecikme

Table 4 Offspring's general characteristics, neurodevelopment and follow-up during 5 years

	At birth (n=130)	3 Months (n=110)	9 Months (n=105)	24 Months (n=64)	5 Years (n=27)
Weight (kg)	3±0.5	5.7±1.1	8.8±1.5	12±2	19±5
Weight <2 SD	–	3 (3%)	4 (4%)	0	0
Height (cm)	48±3	58±21	71±5	84±7	111±10
Height <2 SD	–	9 (9%)	9 (9%)	0	0
Cranial perimeter (cm)	34±2	40±2	45±2	48±2	50±2
Cranial perimeter <2 SD	–	0	2 (2%)	0	–
Infections	5 (4%)	6 (5%)	10 (10%)	11 (17%)	–
Atopy	–	8 (7%)	8 (7%)	7 (11%)	1 (4%)
Lupus	0	0	0	0	0
Thrombosis	0	0	0	0	0
Neurodevelopmental abnormality	–	1 (1%)	1 (1%)	3 (5%)	2 (7%)
Neurodevelopmental abnormality description	–	Axial hypotony	Axial hypotony, psychomotor delay	Autism; hyperactive behaviour; feeding disorders, language delay, growth failure	Autism; hyperactive behaviour

Each column represents the number of evaluated children at the check point.

Table 5 Characteristics of children with neurodevelopmental abnormalities

Case	Mother's age	APS features	Pregnancy outcome	Pregnancy treatment	Gestational age (weeks)	Sex	Birth weight (g)	Clinical features	APL
1	32	Obstetrical (IUGR/IUD)	Gestational diabetes	LWMH	38	M	2790	Autism	Negative
2	23	Obstetrical (RFL)	–	LWMH	36	M	2500	Hyperactive behaviour	Negative at birth; ACL IgG 12 U at 2 years
3	44	Obstetrical (RFL)	Gestational diabetes	LWMH-aspirin	37	F	2900	Feeding disorders, language delay, growth failure	Negative at birth; transient anti-β2GPI IgG 3–9 months
4	33	Obstetrical (IUGR/IUD)	IUGR	LWMH	37	F	1570	Axial hypotony, psychomotor delay	Negative

ACL, anticardiolipin antibodies; anti-β2GPI, anti-β_2 glycoprotein-I antibodies; APL, antiphospholipid antibodies; APS, antiphospholipid syndrome; F, female; IUD, intrauterine fetal death; IUGR, intrauterine growth restriction; LWMH, low-weight molecular heparin; M, male; RFL, recurrent fetal loss.

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