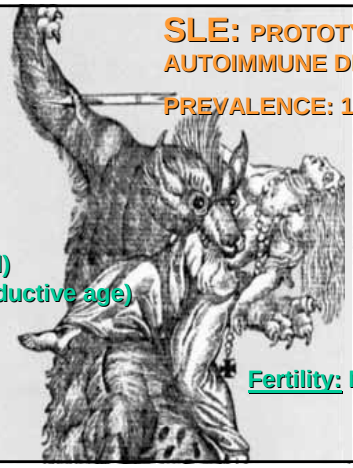
Management of Pregnancy in Patients with SLE and APS: The Need for a Multidisciplinary Approach

Ricard Cervera, MD, PhD, FRCP
Department of Autoimmune Diseases
Hospital Clínic
Barcelona

SLE: PROTOTYPE OF AUTOIMMUNE DISEASE

PREVALENCE: 1/300-700



Ratio F/M:
9/1 (overall)
15/1(reproductive age)

Fertility: Normal

PREGNANCY AND SLE

1. Effect of SLE on pregnancy outcome (fetal/maternal)
2. Effect of pregnancy on SLE flares
3. Effect of the antiphospholipid syndrome

PREGNANCY AND SLE

1. Effect of SLE on pregnancy outcome (fetal/maternal)
2. Effect of pregnancy on SLE flares
3. Effect of the antiphospholipid syndrome

EFFECT OF SLE ON PREGNANCY OUTCOME (FETAL / MATERNAL)

- Pregnancy losses
- Prematurity
- Intra-Uterine Growth Restriction (IUGR)
- Pre-eclampsia

EFFECT OF SLE ON PREGNANCY OUTCOME

The Hospital Clínic of Barcelona Experience

103 pregnancies in 76 SLE patients

Updated from:
Carmona F, Font J, Cervera R, et al.
Eur J Obst Gynecol 1999; 83: 137-142

EFFECT OF SLE ON PREGNANCY OUTCOME

The Hospital Clínic of Barcelona Experience

Obstetric control :

- Prenatal counselling
- Frequent Visits: weekly/fortnightly
- Fetal control
  - Ultrasound / Doppler
  - Echocardiography
  - NST / FCM / Biophysical Profile

EFFECT OF SLE ON PREGNANCY OUTCOME

The Hospital Clínic of Barcelona Experience

LABORATORY DETERMINATIONS

Week	4	8	12	16	20	24	28	32	36	40
Platelets	+	+	+	+	+	+	+	+	+	+
aPL	+	+			+			+		
Ro/La	+									
Urine Alb.	+	+	+	+	+	+	Weekly→			
Creat. Cl.	+		+			+	As indicated →			
Fetal NST						+	Weekly →			
Ultrasonography		+	+		+	As indicated →				
Doppler					+	As indicated →				
Fetal echoc.					+	As indicated →				
ANA/Com	+		+						+	

EFFECT OF SLE ON PREGNANCY OUTCOME

The Hospital Clínic of Barcelona Experience

SAFE

- Acetaminophen
- Low dose aspirin
- Steroids
- Heparin

PROBABLY SAFE

- Hydroxychloroquine
- Azathioprine

NOT INDICATED

- NSAID (3rd trimester)
- Cyclophosphamide
- Methotrexate
- Oral anticoagulants

EFFECT OF SLE ON PREGNANCY OUTCOME

The Hospital Clínic of Barcelona Experience

THERAPEUTIC CONTROL

aPL ⊕:

Aspirin (100 mg/day) or Aspirin + LMWH

Flare:

Prednisone (0.2-1 mg/kg/day)
Azathioprine
Hydroxychloroquine

EFFECT OF SLE ON PREGNANCY OUTCOME

The Hospital Clínic of Barcelona Experience

103 pregnancies in 76 SLE patients

Age (yr.):	28.7± 4.8 (20-42)
Years since diagnosis	
<1	5 (4.8%)
1-5	45 (43.7%)
6-10	25 (24.3%)
>10	19 (18.4%)
Not determined	3 (2.9%)
Active disease at conception	7 (6.8%)

EFFECT OF SLE ON PREGNANCY OUTCOME

The Hospital Clínic of Barcelona Experience

103 pregnancies in 76 SLE patients

Early pregnancy loss	12 (11.7%)
Fetal death	5 (4.9%)
Perinatal death	5 (4.9%)
Congenital Heart Block	1 case
Prematurity	3 cases
Intrauterine	1 case

EFFECT OF SLE ON PREGNANCY OUTCOME

The Hospital Clínic of Barcelona Experience

103 pregnancies in 76 SLE patients

Prematurity	17 (16.5%)
IUGR	8 (7.8%)
Pre-eclampsia	7 (6.8%)

EFFECT OF SLE ON PREGNANCY OUTCOME

The Hospital Clínic of Barcelona Experience

103 pregnancies in 76 SLE patients

Type of delivery	
Vaginal	70 (68%)
Cesarean	33 (32%)

EFFECT OF SLE ON PREGNANCY OUTCOME

The Hospital Clínic of Barcelona Experience

COMPLICATIONS IN PATIENTS ACTIVE AND INACTIVE AT CONCEPTION

	Active (7)	Inactive (78)	p
Pre-eclampsia	2 (28.5)	5 (6.4)	<0.05
Flare	3 (42.8)	16 (20.5)	NS
Prem. Rupt. of Memb.	2 (28.5)	5 (6.4)	<0.04
IUGR	2 (28.5)	6 (7.6)	NS
Pre-term	2 (28.5)	18 (23)	NS
Low birthweigth	3 (42.8)	16 (20.5)	NS
Perinatal Mortality	0	5 (6.4)	NS

EFFECT OF SLE ON PREGNANCY OUTCOME

The Hospital Clínic of Barcelona Experience

COMPLICATIONS IN PATIENTS WITH AND WITHOUT FLARE

	Yes (24)	No (61)	p
Pre-eclampsia	5 (20.8)	1 (1.6)	<0.05
Prem. Rupt. of Memb.	3 (12.5)	2 (3.2)	NS
IUGR	4 (16.6)	4 (6.5)	NS
Preterm birth	3 (12.5)	10 (16.3)	NS
Low-birth weight	4 (16.6)	11 (18)	NS

PREGNANCY AND SLE

1. Effect of SLE on pregnancy outcome (fetal/maternal)
2. Effect of pregnancy on SLE flares
3. Effect of the antiphospholipid syndrome

EFFECT OF PREGNANCY ON SLE FLARES

Flare frequency during pregnancy : 13-60%

Increased frequency of flares :
Petri, 1991; Mintz, 1986; Ruiz-Irastorza, 1996

Not increased frequency of flares during pregnancy:
Lockshin, 1989; Derksen, 1994; Carmona, 1999

EFFECT OF PREGNANCY ON SLE FLARES
Differences between studies

Differences in

- inclusion criteria
- study designs
- number of patients
- steroid administration
- diagnostic criteria

Difficulties in

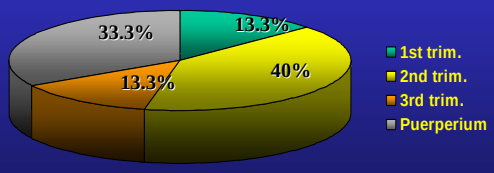
- differential diagnosis between flare and pregnancy symptoms
- differential diagnosis between renal flare and pre-eclampsia

EFFECT OF PREGNANCY ON SLE FLARES
The Hospital Clínic of Barcelona Experience

103 pregnancies in 76 SLE patients

No. of Flares	**24 (23.3%)**
Type	
Cutaneous	13 (54.1%)
Thrombocytopenia	8 (33.3%)
Pericarditis	5 (20.8%)
Arthritis	5 (20.8%)
Renal	4 (16.6%)

EFFECT OF PREGNANCY ON SLE FLARES
The Hospital Clínic of Barcelona Experience
FREQUENCY OF FLARES

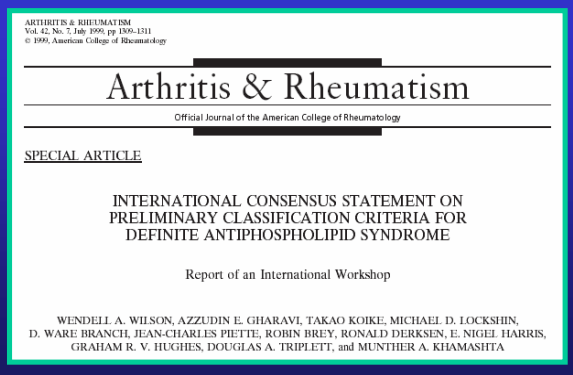


What about prophylactic treatment with prednisone?

Worsening of SLE is uncommon in pregnancy and prophylactic prednisone therapy is not necessary.

PREGNANCY AND SLE

1. Effect of SLE on pregnancy outcome (fetal/maternal)
2. Effect of pregnancy on SLE flares
3. Effect of the antiphospholipid syndrome



ARTHRITIS & RHEUMATISM
Vol. 42, No. 7, July 1999, pp 1309–1311
© 1999, American College of Rheumatology

Arthritis & Rheumatism

Official Journal of the American College of Rheumatology

SPECIAL ARTICLE

INTERNATIONAL CONSENSUS STATEMENT ON PRELIMINARY CLASSIFICATION CRITERIA FOR DEFINITE ANTIPHOSPHOLIPID SYNDROME

Report of an International Workshop

WENDELL A. WILSON, AZZUDIN E. GHARAVI, TAKAO KOIKE, MICHAEL D. LOCKSHIN, D. WARE BRANCH, JEAN-CHARLES PIETTE, ROBIN BREY, RONALD DERKSEN, E. NIGEL HARRIS, GRAHAM R. V. HUGHES, DOUGLAS A. TRIPLETT, and MUNTHER A. KHAMASHTA

Pregnancy morbidity

(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

(b) One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe preeclampsia or eclampsia, or severe placental insufficiency (18,19), or

(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

OBSTETRIC COMPLICATIONS

-Early pregnancy loss
-Fetal deaths
-Premature births
-Pre-eclampsia / Eclampsia

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

PHARMACOLOGICAL TREATMENT

- Aspirin
- Heparin
- Aspirin & Heparin
- Steroids
- IV Immunoglobluins

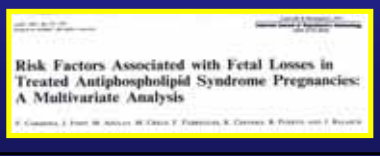
PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME PHARMACOLOGICAL MANAGEMENT

Author, year	*Reference*	*Therapy*	*Pregnancies (n)*	*Live births (%)*
Hasegawa, 1992	74	None	12	8
Many, 1992	75	None	102	7
Rai, 1997	76	None	20	10
Laskin, 1997	77	Placebo	46	52
Pattison, 2000	47	Placebo	20	85
Tchobroutsky, 1988	55	Aspirin	15	87
Out, 1992	78	Aspirin	16	81
Balasch, 1993	16	Aspirin	15	93
Silver, 1993	79	Aspirin	22	100
Kutteh, 1996	80	Aspirin	25	44
Lima, 1996	81	Aspirin	27	74
Granger, 1997	82	Aspirin	37	76
Rai, 1997	76	Aspirin	45	42
Le Thi Huong, 2001	83	Aspirin	17	65
Rosove, 1990	84	Heparin	15	93
Ruffatti, 1997	85	Heparin	53	100
Branch, 1992	49	Heparin + aspirin	19	74
Cowchock, 1992	86	Heparin + aspirin	12	75
Many, 1992	75	Heparin + aspirin	23	69
Kutteh, 1996	80	Heparin + aspirin	50	80
Lima, 1996	81	Heparin + aspirin	7	86
Granger, 1997	82	Heparin + aspirin	16	56
Rai, 1997	76	Heparin + aspirin	45	71
Backos, 1999	87	Heparin + aspirin	150	71

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

The Hospital Clínic of Barcelona Experience

77 pregnancies in 56 APS patients



Risk Factors Associated with Fetal Losses in Treated Antiphospholipid Syndrome Pregnancies: A Multivariate Analysis

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

The Hospital Clínic of Barcelona Experience

Obstetric management as high-risk pregnancies:

- Prenatal counselling
- Close fetal and maternal surveillance:
  - Frequent Visits (weekly/fortnightly)
  - Doppler flow studies
  - Serial ultrasound explorations
  - Fetal wellbeing assessment

Coordinated multidisciplinary team

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

The Hospital Clínic of Barcelona Experience

LABORATORY DETERMINATIONS

Week	4	8	12	16	20	24	28	32	36	40
Platelets	+	+	+	+	+	+	+	+	+	+
aPL	+	+			+			+		
Ro/La	+									
Urine Alb.	+	+	+	+	+	+	Weekly→			
Creat. Cl.	+		+			+	As indicated →			
Fetal NST						+	Weekly →			
Ultrasonography		+	+		+	As indicated →				
Doppler					+	As indicated →				
Fetal echoc.					+	As indicated →				
ANA/Com	+		+						+	

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

The Hospital Clínic of Barcelona Experience

PHARMACOLOGICAL TREATMENT

No previous treatment
Aspirin 100 mg/day
from 1 month before attempting conception

Failure of aspirin in previous pregnancy
Aspirin plus LMW heparin

History of thrombosis
Aspirin plus LMW heparin

Prednisone during pregnancy
Only if required for medical complications

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

The Hospital Clínic of Barcelona Experience

PATIENTS CHARACTERISTICS (I)

77 pregnancies (56 patients)

Age: 29.79 ± 0.49 (range: 16-40)

Previous pregnacies (n=176)

Early pregnancy losses	110 (62.5%)
2nd-3rd trimester pregnancy losses	30 (17%)
Total	140 (79.5%)
Viables pregnancies	*36 (20.5%)*

APS:

Primary	38 (67.9%)
SLE	18 (32.1%)

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

The Hospital Clínic of Barcelona Experience

PATIENTS CHARACTERISTICS (II)

Laboratory findings (n=77)

LA ⊕	*60 cases (77.9%)*
aCL ⊕	*52 cases (67.6%)*
IgG aCL ⊕	*37 cases (48.1%)*
IgM aCL ⊕	*15 cases (19.5%)*
LA ⊕ / aCL ⊕	*34 cases (44.2%)*
LA ⊕ / aCL -	*17 cases (22.1%)*
LA- / aCL ⊕	*26 cases (33.8%)*
antiβ2GP1	*36 cases (46.7%)*

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

The Hospital Clínic of Barcelona Experience

RESULTS (I)

AAS alone (n= 64 patients)

46 (76.6%) starting before conception
18 (23.4%) starting during first trimester

Aspirin plus LMW Heparin (n= 13 patients)

3 (23%) previous treatment failure
10 (77%) associated thrombosis

Prednisone,5-60 mg (n=28 patients)

7 (25%) thrombocytopenia
21 (75%) SLE

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

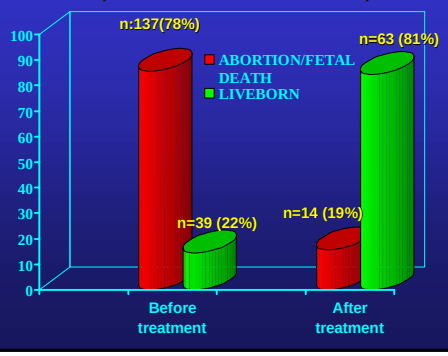
The Hospital Clínic of Barcelona Experience

RESULTS (II)

Early pregnancy loss	7 cases (9%)
Pregnancies > 20 weeks	70 cases
Intrauterine demise	5 cases (6.5%)
Neonatal mortality	2 cases (2.5%)
Normal Liveborn	63 cases (81.8%)

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

The Hospital Clínic of Barcelona Experience



PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

The Hospital Clínic of Barcelona Experience

RESULTS (IV)

	Normal liveborn
AAS only *(n=64 patients)*	53 cases (82.8%)
AAS plus LMW Heparin *(n=13 patients)*	10 cases (76.9%)

p=0.69

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

The Hospital Clínic of Barcelona Experience

RESULTS (V)

	Normal liveborn
AAS before conception *(n=59 patients)*	52 cases (88.1%)
AAS after conception *(n=18 patients)*	11 cases (61.1%)

p=0.01 OR (IC):4.7 (1.3-16.2)

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

The Hospital Clínic of Barcelona Experience

RESULTS (VIII)

Association of several parameters to poor outcome

Preconception use of aspirin	0.04
Primary vs Secondary APS	NS
Number of previous fetal losses	NS
Circulating levels of aCL	NS
Presence of circulating LA	NS
Retrochorial hematoma	NS
Uterine Artery Notch at 20 ws gestation	0.07
Doppler velocimetry: umbilical artery 23-26 ws gestation	0.002
Early mid-trimester level of αfetoprotein and βhCG	NS
Use of Prednisone	NS
Use of Heparine	NS

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

The Hospital Clínic of Barcelona Experience

RESULTS (IX)

Multiple logistic regression

Parameter	Diagnostic accuracy	OR (CI)
AAS before conception	78.71	3.32 (1.04-10.6)
Uterine Artery Doppler	80.83	18.5 (1.6-55.1)

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

The Hospital Clínic of Barcelona Experience

CONCLUSION

Preconceptional treatment with low-dose aspirin and Doppler studies of fetal circulation are, in our opinion, the key points for obtaining positive results in pregnant patients with the APS.

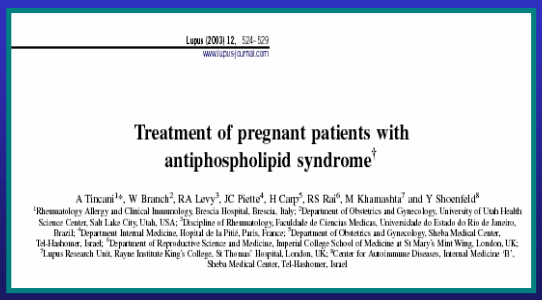
10th International Congress on
Antiphospholipid Antibodies
Giardini Naxos, Taormina, Sicily, Italy
September 29 - October 2, 2002

PRE-CONGRESS SESSION: THERAPY CONSENSUS

Supported by an unrestricted educational grant from American Autoimmune Related Diseases Association, Inc., USA (AARDA)

Chairpersons:	**Y. Shoenfeld,** Israel **M. Khamashta,** UK
	PROPHYLAXIS **D. Alarcon-Segovia**, A.S. Roubey, D. Triplett, W. Wilson, Mexico, USA
	THROMBOEMBOLISM **J.A. McIntyre**, J.M.M.C. Arnout, T. Koike, P.L. Meroni, J-C. Piette, USA, Belgium, Japan, Italy, France
	STROKE **R.L. Brey**, J. Chapman, R. Derksen, T. Exner, E.N. Harris, S.R. Levine, USA, Israel, The Netherlands, Australia
	PREGNANCY **A. Tincani**, D.W. Branch, H.J.A. Carp, M. Khamashta, R.A. Levy, R. Rai, Italy, USA, Israel, UK, Brazil
	OTHER CNS **J.H. Rand**, R.L. Brey, **J. Chapman**, T. Exner, D. Smith, USA, Israel, Australia, Canada
	CARDIAC **M. Lockshin**, L. Carreras, S.A. Krilis, G. McCarty, M. Petri, UK, Argentina, Australia, USA
	CATASTROPHIC **R.A. Asherson**, M-C. Boffa, R. Cervera, P. De Groot, D. Erkan, South Africa, France, Spain, The Netherlands, USA

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME



Lupus (2003) 12, 524–529
www.lupusjournal.com

Treatment of pregnant patients with antiphospholipid syndrome†

A Tincani[1]*, W Branch[2], RA Levy[3], JC Piette[4], H Carp[5], RS Rai[6], M Khamashta[7] and Y Shoenfeld[8]

[1]Rheumatology Allergy and Clinical Immunology, Brescia Hospital, Brescia, Italy; [2]Department of Obstetrics and Gynecology, University of Utah Health Science Center, Salt Lake City, Utah, USA; [3]Discipline of Rheumatology, Faculdade de Ciencias Medicas, Universidade do Estado do Rio de Janeiro, Brazil; [4]Department Internal Medicine, Hopital de la Pitié, Paris, France; [5]Department of Obstetrics and Gynecology, Sheba Medical Center, Tel-Hashomer, Israel; [6]Department of Reproductive Science and Medicine, Imperial College School of Medicine at St Mary's Mint Wing, London, UK; [7]Lupus Research Unit, Rayne Institute King's College, St Thomas' Hospital, London, UK; [8]Center for Autoimmune Diseases, Internal Medicine 'B', Sheba Medical Center, Tel-Hashomer, Israel

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

We found that patients suffering from APS-related pregnancy losses (without thrombosis) are generally treated with heparin and low dose aspirin (75–100mg). The few discordant opinions recorded in the questionnaire mainly related to the treatment of patients with a history of early pregnancy loss, without thrombosis. Some experts in fact suggest, according to previous reports,[2,8] that in these cases aspirin alone can be prescribed while heparin should be added only in cases of aspirin failure.

PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

Finally, although optimal pharmacological treatment is necessary to achieve a successful outcome in APS pregnancy, the pharmacological treatment may not be sufficient. Close surveillance of pregnant patients through repeated clinical, biological and echo-Doppler examinations is required by various specialists (rheumatologists, obstetricians, haematologists and so on) working in close collaboration also with the neonatal intensive care units in order to offer optimal management to preterm infants as preterm delivery is not rare in APS.

CONDENSATION

PREGNANCY AND SLE

"Pregnancy in patients with SLE should not be regarded as an unacceptable high risk condition provided that conception is accurately planned and patients are managed according to a careful multidisciplinary treatment schedule".

Carmona F, Font J, Cervera R, et al. Eur J Obst Gynecol 1999; 83: 137-142

ELSEVIER

Autoimmunity Reviews 1 (2002) 354–359

AUTOIMMUNITY REVIEWS

www.elsevier.com/locate/autrev

Pregnancy outcome in systemic lupus erythematosus: good news for the new millennium

Ricard Cervera[a,*], Josep Font[a], Francisco Carmona[b], Juan Balasch[b]

[a]Department of Autoimmune Diseases, Institut Clínic of Infections and Immunology, Hospital Clínic, Villarroel 170, 08036-Barcelona, Catalonia, Spain

[b]Institut Clínic of Gynecology, Obstetrics and Neonatology, Hospital Clínic, Barcelona, Catalonia, Spain

6th INTERNATIONAL CONGRESS ON
AUTOIMMUNITY
PORTO, PORTUGAL
SEPTEMBER 3-7, 2008

COMMITTEES

Yehuda Shoenfeld, Israel, Chairman
Ricard Cervera, Spain, Co-chairman
Jorge Kalil, Brazil, Co-chairman