Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili
Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

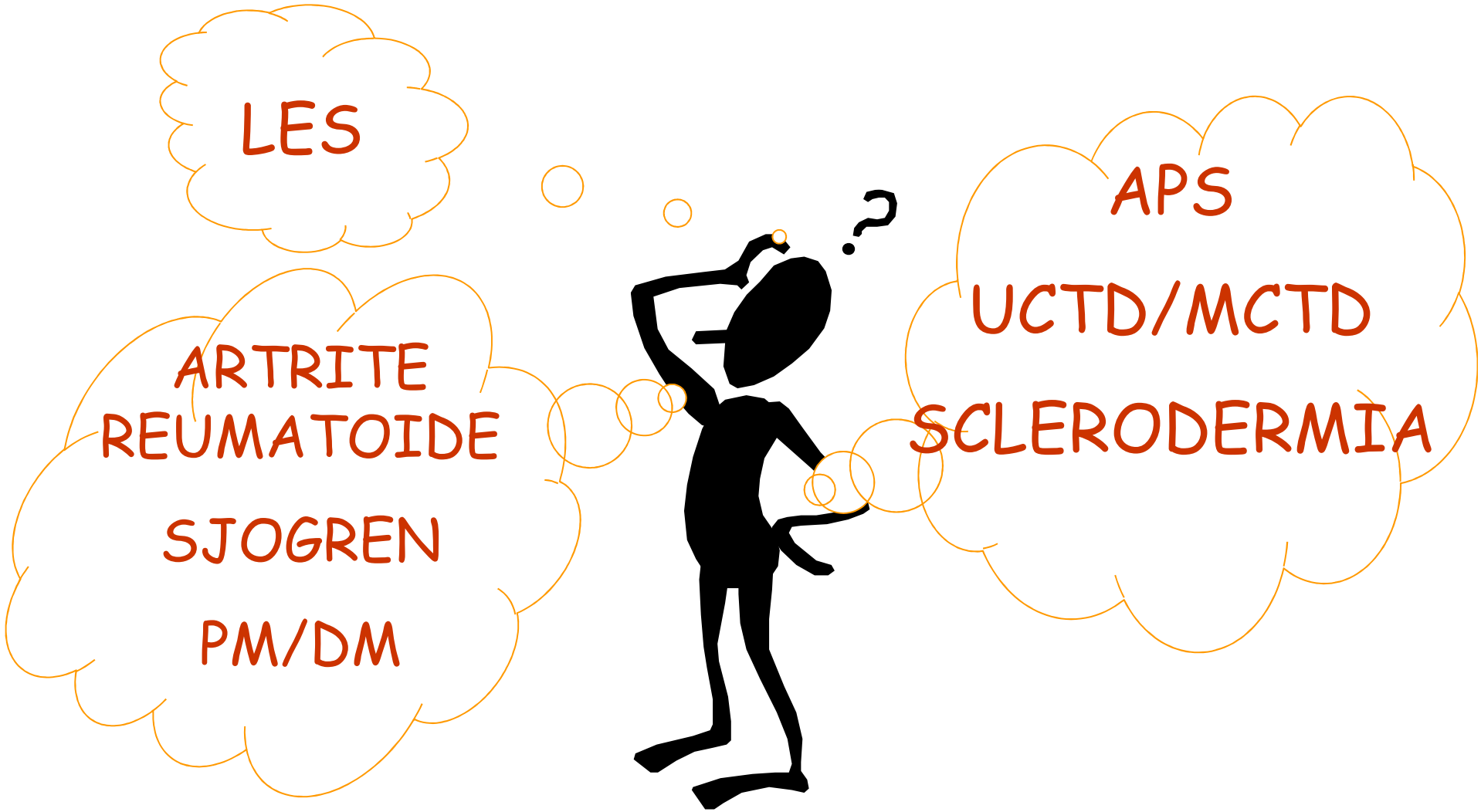
Ordine Medici Chirughi e Odontoiatri di Brescia
28 novembre 2017

LA MEDICINA DI GENERE IN REUMATOLOGIA: APPROCCIO MULTIDISCIPLINARE PER LA SALUTE DELLA DONNA

La salute della donna con malattia reumatica autoimmune: dalla pianificazione famigliare alla menopausa

Andrea Lojacono
Clinica Ostetrico Ginecologica
ASST- Spedali Civili Brescia

MALATTIE AUTOIMMUNI



EULAR Standing Committee for Clinical Affairs (ESCCA)
Task Force on SLE

EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome

L Andreoli,[1,2] G K Bertsias,[3] N Agmon-Levin,[4,5] S Brown,[6] R Cervera,[7] N Costedoat-Chalumeau,[8,9] A Doria,[10] R Fischer-Betz,[11] F Forger,[12] M F Moraes-Fontes,[13] M Khamashta,[14,15] J King,[16] A Lojacono,[1,17] F Marchiori,[18] P L Meroni,[19] M Mosca,[20] M Motta,[21] M Ostensen,[22] C Pamfil,[23] L Raio,[24] M Schneider,[11] E Svenungsson,[25] M Tektonidou,[26] S Yavuz,[27] D Boumpas,[28,29] A Tincani[1,2]

Annals of the Rheumatic Diseases 2017; 76:476–485.

PREGNANCY in SLE and APS

WHAT ARE THE LIMITATIONS OF THE LITERATURE?

WHAT ARE THE CHALLENGES IN THE MANAGEMENT?

- ✓ SLE patients may be affected by **different complications** and may have **different levels of disease activity** at the time of pregnancy.
- ✓ The **type of care** to pregnant SLE patients may be different across Countries (*multidisciplinary team of Rheumatologists & Obstetricians*).
- ✓ **Antiphospholipid antibodies** are not always considered as a risk factor in studies about SLE pregnancy.
- ✓ **Medications and treatment strategies** may be different from place to place (information about medications is often lacking in the studies!).
- ✓ **Planned** *vs.* **unplanned** pregnancies.

WHEN, WHERE and HOW:
what matters in SLE and/or APS pregnancy?

Methodology

EULAR REPORT

Ann Rheum Dis 2004;**63**:1172–1176. doi: 10.1136/ard.2004.023697

EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees

- **PANEL OF EXPERTS**
- **SELECTION OF RESEARCH QUESTIONS**
- **ANSWERS BY LITERATURE EVIDENCE RESEARCH and /or EXPERT OPINION**

Methodology: panel of experts

26 Members from 13 European Countries

- ***Rheumatologists/Internists*: 18**
- ***Gynecologists*: 2**
- ***Neonatologist*: 1**
- ***Rheumatology Nurse*: 1**
- ***Fellows*** (literature search-analysis)**: 2**
- ***Patient representative*: 2**

Methodology: selection of questions for the literature search (Delphi)

Overarching principles

✓Health professionals should **embrace** – rather than caution against – pregnancy in women with SLE or APS, after consideration of individual risks

✓Decisions regarding family planning are agreed upon by the patient herself, the family, and the health professionals

✓Discussions about family planning may take place at the first and reinforced during follow-up visits (comments: fertility decreases with age)

Andreoli L, Bertsias GK et al. EULAR Recommendations For Women's Health And The Management Of Family Planning, Assisted Reproduction, Pregnancy, And Menopause In Patients With SLE and/or APS. Ann Rheum Dis 2017;76:476–485.

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Methodology: selection of questions for the literature search (Delphi)

Major Themes

- ***Counselling / Contraception***

  (2 questions)

- ***Fertility and Assisted Reproduction Techniques***

  (3 questions)

- ***Monitoring and Treatment during pregnancy***

  (4 questions)

- ***Menopause*** *(1 question)*

- ***Malignancies and prevention*** *(2 questions)*

Andreoli L, Bertsias GK et al. EULAR Recommendations For Women's Health And The Management Of Family Planning, Assisted Reproduction, Pregnancy, And Menopause In Patients With SLE and/or APS. Ann Rheum Dis 2017;76:476–485.

The procedure – Evaluation of the literature

- **The PubMed and Cochrane Reviews databases were searched using an array of relevant terms (no additional filters)**
- **From an initial of 7,665 hits, a final set of ~550 published studies were evaluated**

LEVEL OF EVIDENCE		
	Diagnostic/Prognostic studies	**Intervention studies**
1	The available evidence is ***strong*** and includes consistent results from well-designed, well-conducted studies	At least one RCT or meta-analysis of RCTs
2	The available evidence is ***sufficient*** to determine effects, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies, inconsistency of findings across individual studies, limited generalizability of findings	Controlled (non-randomized) studies
3	The available evidence is ***limited or insufficient*** due to the limited number or size of studies, important flaws in study design or methods, inconsistency of findings across individual studies, gaps in the chain of evidence, lack of information on important outcomes.	Descriptive studies, such as comparative studies, correlation studies, or case control studies

GRADE OF RECOMMENDATION	
A	Based on Level 1 evidence without concerns for the validity of the evidence
B	Based on Level 1 evidence but with concerns about the validity of the evidence; or, extrapolated recommendations from Level 1 evidence; or, based on Level 2 evidence without concerns for the validity of the evidence
C	Based on Level 1 or 2 evidence but with concerns about the validity of the evidence; or, extrapolated recommendations from Level 2 evidence; or, based on Level 3 evidence without concerns for the validity of the evidence
D	**Expert opinion**; or, evidence from non-SLE/APS literature; or, based on Level 3 evidence but with concerns about the validity of the evidence

Andreoli L, Bertsias GK et al. EULAR Recommendations For Women's Health And The Management Of Family Planning, Assisted Reproduction, Pregnancy, And Menopause In Patients With SLE and/or APS. Ann Rheum Dis 2017;76:476–485.

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WOMEN's HEALTH: THE ITALIAN SURVEY

23 Italian Rheumatology Centers

398 women with rheumatic diseases (18-55 years)

1. University and Spedali Civili of Brescia, Brescia
2. Ospedale Papa Giovanni XXXIII, Bergamo
3. Ospedale of Bolzano, Bolzano
4. Azienda Provinciale Servizi Sanitari, Trento
5. Ospedale S.Croce e Carle, Cuneo
6. University and Azienda Ospedaliera of Padova, Padova
7. Istituto Ortopedico Gaetano Pini, Milano
8. Ospedale San Raffaele, Milano
9. Humanitas, Milano
10. University and Policlinico San Matteo, Pavia
11. Ospedale San Martino, Genova
12. Policlinico S.Orsola-Malpighi, Bologna
13. University of Ferrara, Ferrara
14. Arcispedale S.Maria Nuova, Reggio-Emilia
15. Ospedali Riuniti of Ancona, Ancona
16. University of Pisa, Pisa
17. Azienda Ospedaliera of Perugia, Perugia
18. Policlinico Tor Vergata, Roma
19. A.O. San Camillo, Roma
20. University Campus Biomedico, Roma
21. Spedali Riuniti of Foggia, Foggia
22. Ospedale San Carlo, Potenza
23. Policlinico V.Emanuele-Ferrarotto-Bambin Gesù, Catania

To investigate family planning, pregnancy, contraception, knowledge on drugs use during pregnancy, and children's follow-up in patients with a definite diagnosis of rheumatic disease

Poster ACR 2016 Washington
Abstract Number: 2435

Dall'Ara F et al., Counseling on Family Planning and Contraception, and Pregnancy Outcome in Women with Rheumatic Diseases: Analysis of 398 Patient-Reported Questionnaires from a Multicenter Italian Study

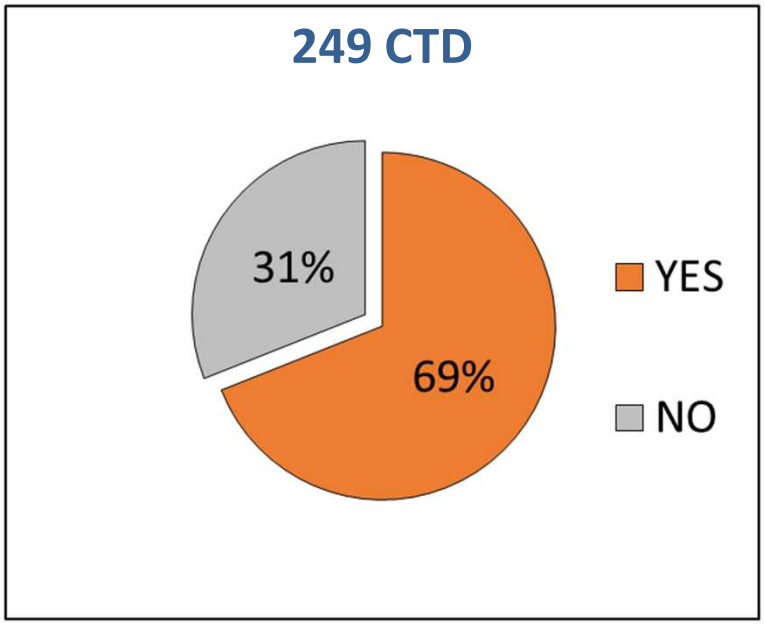
FAMILY PLANNING
IN RHEUMATIC DISEASES

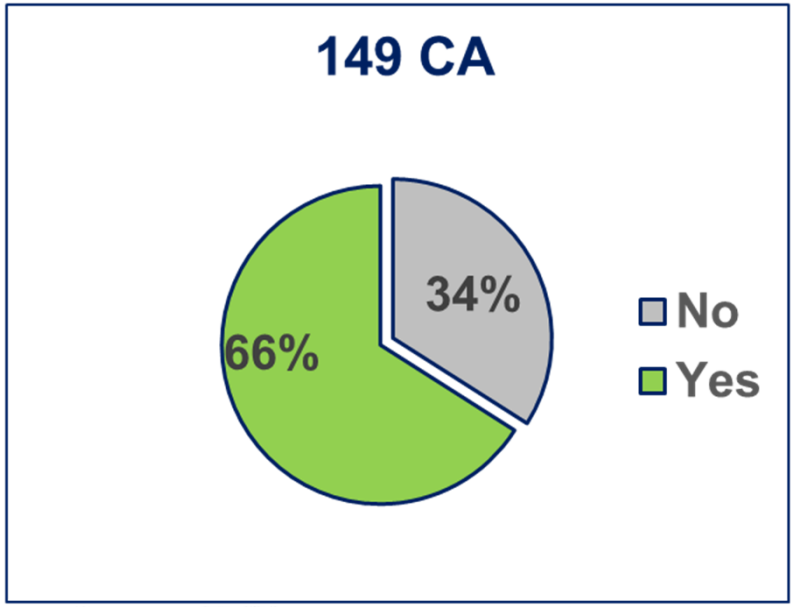
PREGNANCY

CONTRACEPTION

Counselling on family planning

Have you ever been asked on your desire to have children?





One third of patients has never been asked about their desire to have children!

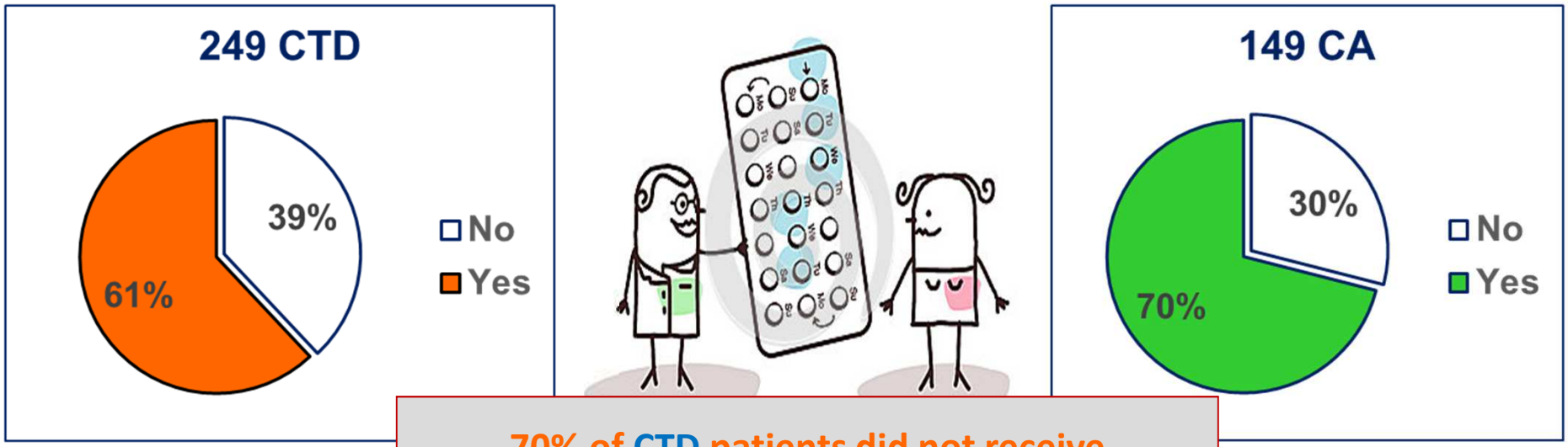
Poster ACR 2016 Washington, Abstract Number: 2435

Dall'Ara F et al., Counseling on Family Planning and Contraception, and Pregnancy Outcome in Women with Rheumatic Diseases: Analysis of 398 Patient-Reported Questionnaires from a Multicenter Italian Study

patients ≤ 45 years

Counselling on contraception

Did you receive a counselling on contraception?



From whom?

70% of CTD patients did not receive any counselling from Rheumatologist: this could be very dangerous for patients. It is mandatory to evaluate the possible effects of the oestrogen containing contraceptives on disease activity!

Poster ACR 2016 Washington, Abstract Number: 2435

Dall'Ara F et al., Counseling on Family Planning and Contraception, and Pregnancy Outcome in Women with Rheumatic Diseases: Analysis of 398 Patient-Reported Questionnaires from a Multicenter Italian Study

Why contraception in patients with rheumatic diseases?

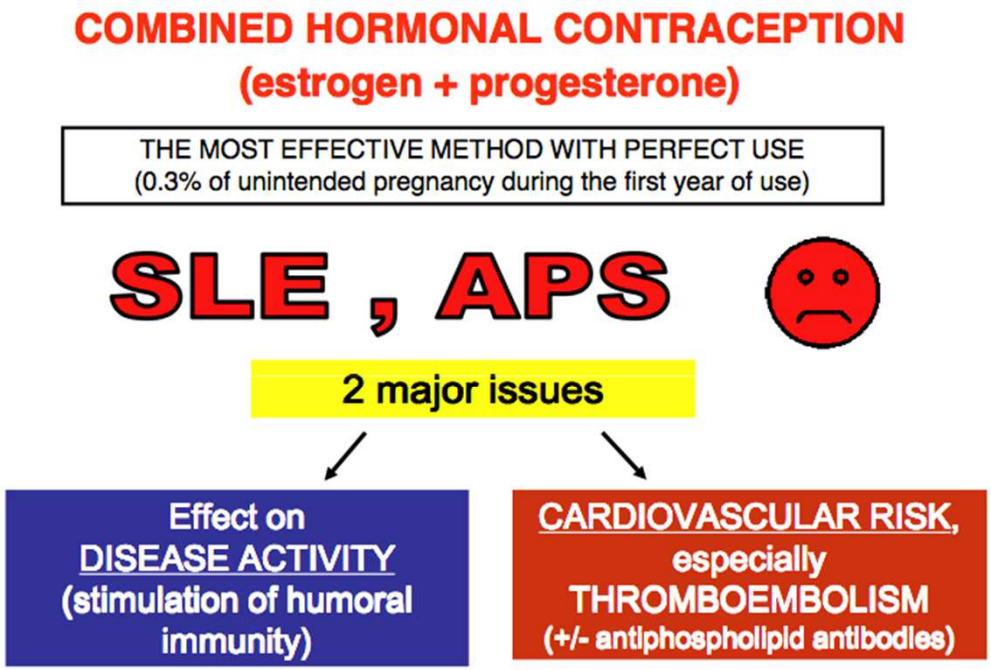
- In young women: family planning
- Avoid pregnancy during active disease
- Avoid pregnancy while on teratogenic medications
- Need for hormonal treatment for endometriosis, dysmenorrhea, hypermenorrhea

RHEUMATOLOGIST

Do we speak of contraception to our patients ??

Contraceptive Measures

- Women with SLE should be counselled about the use of effective contraceptive measures (oral contraceptives, subcutaneous implants, intra-uterine devices [IUD]) based on their disease activity and thrombotic risk (particularly aPL status).



Lisa R Sammaritano, Nature Clinical Practice Rheumatology 2007; 3: 273-81

Andreoli L, Bertsias GK et al. EULAR Recommendations For Women's Health And The Management Of Family Planning, Assisted Reproduction, Pregnancy, And Menopause In Patients With SLE and/or APS. Ann Rheum Dis 2017;76:476–485.

Which SLE patients may be candidate to combined hormonal contraception?

GENERAL FACTORS

- Normotensive
- Non-smoker
- No history of thrombosis, cerebrovascular disease or coronary artery disease
- No diabetes
- No estrogen-dependent neoplasia
- No congenital thrombophilia

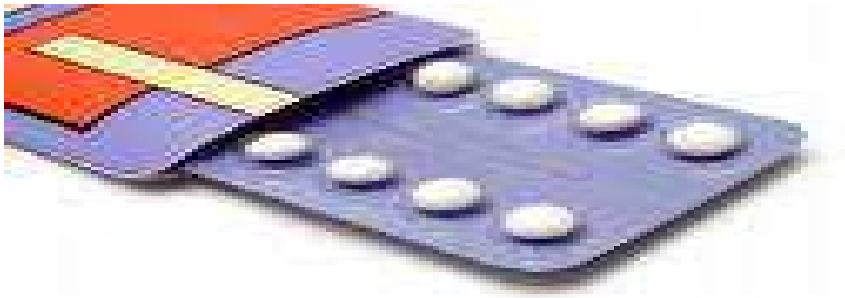
DISEASE-SPECIFIC FACTORS

- Disease remission (or low- active stable disease)
- Antiphospholipid antibodies negative
- No recent renal flare

PROBABLY NOT MANY PATIENTS!

Contraceptive Measures

- In patients with stable/inactive SLE and negative aPL, combined hormonal contraceptives can be considered **(1/A)**. In women with positive aPL with or without definite APS, hormonal contraception (with progesterone only) must be carefully weighed against the risk of thrombosis **(2/B)**.



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Contraceptive Measures

- IUD can be offered to all the patients with SLE and/or APS *free of any gynaecological contraindication* **(1/A)**.

What's new on Intrauterine Devices (IUDs)?

Nulliparity is no longer an absolute controindication for use.

World Health Organization (2004) Medical eligibility criteria for contraceptive use (Third edition)

Immunosuppressive therapy represent a relative controindication. It should be assessed on a case by case basis (patient's compliance, risk for sexually transmitted diseases, etc.). Studies report reassuring data on the theoretical increase in pelvic inflammatory disease, even in **high-risk populations**:

-No pelvic inflammation reported in trials in SLE women
(Julkunen HA 1993; Sànchez-Guerrero J 2005)

-No increased risk of pelvic inflammatory disease in women with history of sexually transmitted disease
(Campbell SJ, Am J Obstet Gynecol 2007; 197: 193.e1-6)

-No increased risk of pelvic inflammatory disease nor disease progression in HIV-infected women
(Stringer EM Am J Obstet Gynecol 2007; 197: 144.e1-8)

The **levonorgestrel-releasing IUD** may be indicated for those APS women who suffer from anticoagulation-related hypermenorrea (particularly suitable for Primary APS who do not usually take immunosuppressive drugs).

Andreoli L, Bertsias GK et al. EULAR Recommendations For Women's Health And The Management Of Family Planning, Assisted Reproduction, Pregnancy, And Menopause In Patients With SLE and/or APS. Ann Rheum Dis 2017;76:476–485.

TAKE HOME MESSAGES

Contraccettivi orali combinati (estroprogestinici)

UTILIZZABILI IN:

Artriti croniche (farmaci teratogeni)

Casi selezionati in LES
(malattia in remissione o stabilmente attiva a livello lieve-moderato)

SCONSIGLIABILI SE:

aPL positivi
(qualsiasi sia la malattia autoimmune di base)

LES attivo
LES con aPL

↓ Possibile impiego di

- **Contraccettivi con solo progestinico** (orali, sottocutanei, intramuscolari)
- **IUDs** (es. spirale medicata)

IUD (spirale)

La terapia immunosoppressiva **non è più considerata una controindicazione assoluta**.
Non esistono comunque dati su che grado di immunosoppressione sia da considerarsi maggiormente a rischio.

FAMILY PLANNING
IN RHEUMATIC DISEASES

PREGNANCY

CONTRACEPTION

Counseling ostetrico

REUMATOLOGO

?

DOTTORE,
POSSO INTRAPRENDERE
UNA GRAVIDANZA?

OSTETRICO

Incontro preconcezionale

anamnesi ostetrica

pregresse trombosi

assetto anticorpale

tipo di malattia e stato di attività

patologie concomitanti (ipertensione,nefropatie)

terapia farmacologica

Incontro preconcezionale

Effetto dei farmaci sul feto

Rischio di complicanze ostetriche

Programmare follow-up

RASSICURARE

INFORMARE

- CLINICO
- EMATOCHIMICO
- STRUMENTALE
- FARMACOLOGICO

PRECONCEPTION COUNSELING- RISK STRATIFICATION

MATERNAL and FETAL OUTCOMES

- ✓Disease activity
- ✓Treatment during pregnancy
- ✓Disease flare during pregnancy

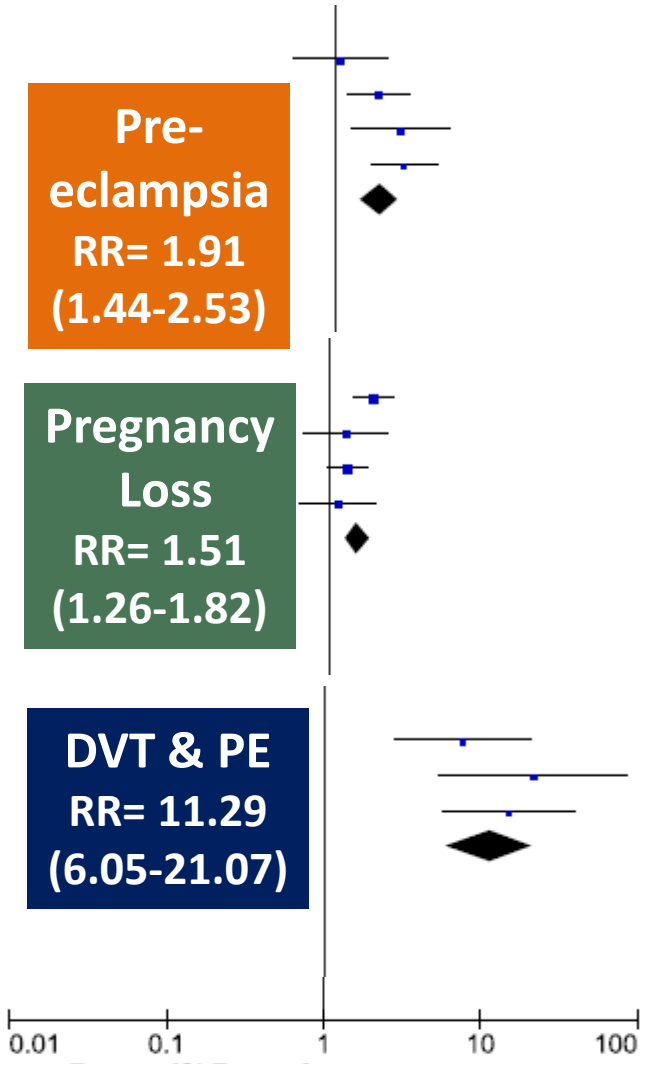
ABSTRACT NUMBER: 2522

High Risk of Flares during Pregnancy in Women with Rheumatoid Arthritis Who Discontinue Treatment with TNF Inhibitors at Conception

Rebecca Fischer-Betz[1], Oliver Sander[1], Christof Specker[2], Ralph Brinks[3] and Matthias Schneider[1],

Impact of SLE on maternal and fetal outcomes: a meta-analysis of studies 2001-2016

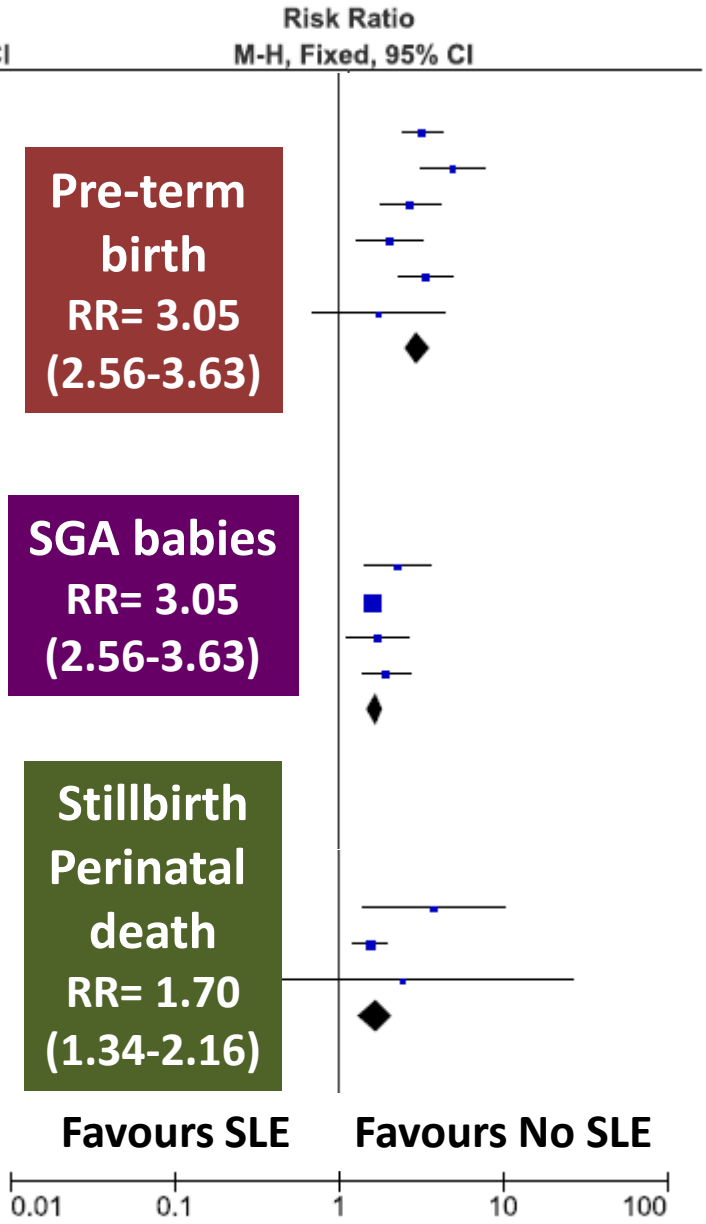
Study or Subgroup	SLE group Events	Total	No SLE group Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.2 Pre-eclampsia						
Barnabe2011	9	95	33	375	2.8%	1.08 [0.53, 2.17]
Barnado2014	45	577	29	694	5.5%	1.87 [1.19, 2.94]
Jakobsen2015	7	84	930	29059	1.1%	2.60 [1.28, 5.31]
Wallenius2014	14	95	13917	257327	2.1%	2.72 [1.68, 4.42]
Subtotal (95% CI)		**851**		**287455**	**11.5%**	**1.91 [1.44, 2.53]**
Total events	75		14909			
Heterogeneity: Chi² = 5.38, df = 3 (P = 0.15); I² = 44%						
Test for overall effect: Z = 4.48 (P < 0.00001)						
1.1.4 Spontaneous abortion						
Barnado2014	102	577	64	694	12.1%	1.92 [1.43, 2.57]
McGrory2013	10	60	50	382	2.8%	1.27 [0.68, 2.37]
Molokhia2007	62	352	90	667	13.0%	1.31 [0.97, 1.76]
Yuen2008	20	108	22	134	4.1%	1.13 [0.65, 1.95]
Subtotal (95% CI)		**1097**		**1877**	**32.0%**	**1.51 [1.26, 1.82]**
Total events	194		226			
Heterogeneity: Chi² = 4.86, df = 3 (P = 0.18); I² = 38%						
Test for overall effect: Z = 4.37 (P < 0.0001)						
1.1.6 Thromboembolic disease						
Arkema2016	4	133	51	12847	0.2%	7.58 [2.78, 20.66]
Nili2013	2	97	203	211355	0.0%	21.47 [5.41, 85.19]
Wallenius2014	4	95	722	257327	0.1%	15.01 [5.74, 39.27]
Subtotal (95% CI)		**325**		**481529**	**0.4%**	**11.29 [6.05, 21.07]**
Total events	10		976			
Heterogeneity: Chi² = 1.78, df = 2 (P = 0.41); I² = 0%						
Test for overall effect: Z = 7.61 (P < 0.00001)						



BundhunPK et al., J Autoimm 2017

Impact of SLE on maternal and fetal outcomes: a meta-analysis of studies 2001-2016

Study or Subgroup	SLE group Events	Total	No SLE group Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.2 Pre-term/pre-mature birth						
Arkema2016	42	198	835	12847	3.0%	3.26 [2.48, 4.30]
Barnabe2011	33	95	26	375	1.2%	5.01 [3.16, 7.95]
Barnado2014	66	577	29	694	3.1%	2.74 [1.79, 4.18]
Jakobsen2015	15	84	2528	29059	1.7%	2.05 [1.30, 3.25]
Wallenius2014	21	95	16723	257327	1.4%	3.40 [2.33, 4.96]
Yuen2008	10	108	7	134	0.7%	1.77 [0.70, 4.50]
Subtotal (95% CI)		**1157**		**300436**	**11.1%**	**3.05 [2.56, 3.63]**
Total events	187		20148			
Heterogeneity: Chi² = 9.39, df = 5 (P = 0.09); I² = 47%						
Test for overall effect: Z = 12.51 (P < 0.00001)						
1.2.3 Small for gestational age						
Barnabe2011	24	95	41	375	1.9%	2.31 [1.47, 3.63]
Chen2010	288	1010	882	5050	34.3%	1.63 [1.46, 1.83]
Nili2013	17	97	21194	211355	2.3%	1.75 [1.13, 2.69]
Wallenius2014	25	95	34592	257327	3.0%	1.96 [1.40, 2.74]
Subtotal (95% CI)		**1297**		**474107**	**41.5%**	**1.69 [1.53, 1.88]**
Total events	354		56709			
Heterogeneity: Chi² = 2.95, df = 3 (P = 0.40); I² = 0%						
Test for overall effect: Z = 10.08 (P < 0.00001)						
1.2.7 Stillborn/neonatal/perinatal death						
Barnado2014	16	577	5	694	0.5%	3.85 [1.42, 10.44]
Molokhia2007	90	352	109	667	8.8%	1.56 [1.22, 2.00]
Yuen2008	2	108	1	134	0.1%	2.48 [0.23, 27.00]
Subtotal (95% CI)		**1037**		**1495**	**9.4%**	**1.70 [1.34, 2.16]**
Total events	108		115			
Heterogeneity: Chi² = 3.11, df = 2 (P = 0.21); I² = 36%						
Test for overall effect: Z = 4.37 (P < 0.0001)						



BundhunPK et al., J Autoimm 2017

Sintomi gravidici parafisiologici

- lombalgie
- artralgie
- parestesie arti superiori
- facile affaticabilità
- aumento VES
- eritema palmare
- cloasma
- alopecia post-partum
- trombocitopenia
- dispnea
- proteinuria
- edemi

Preconception Counselling & Risk Stratification

In women with **SLE**, at the time of conception, risk factors for adverse maternal and fetal outcomes:

- ✓active/flaring SLE **(1/A)**, especially active nephritis **(1/A)**,
- ✓history of lupus nephritis **(2/B)**,
- ✓presence of antiphospholipid antibodies (aPL)/antiphospholipid syndrome (APS) **(1/A)**

Blood pressure monitoring **(2/B)**, use of safe medications to control disease activity (emphasis on introducing HCQ or continuing HCQ if already prescribed **(2/B)**) and limiting glucocorticoids exposure to minimum **(2/B)** are essential measures.

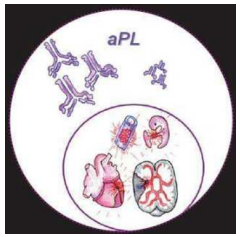
Andreoli L, Bertsias GK et al. EULAR Recommendations For Women's Health And The Management Of Family Planning, Assisted Reproduction, Pregnancy, And Menopause In Patients With SLE and/or APS. Ann Rheum Dis 2017;76:476–485.

PRECONCEPTION COUNSELING- RISK STRATIFICATION

The Rheumatologist's point of view

- Search for **autoantibodies** with potential negative impact on pregnancy and fetal outcomes

  anti-ENA → anti-Ro/SSA, anti-La/SSB antiphospholipid antibodies (3 tests)



- Need to control maternal disease activity during pregnancy: **what drugs can be used**?

MESSAGES TO GIVE TO THE PATIENT AND HER FAMILY:

✓ **MATERNAL DISEASE ACTIVITY IS DETRIMENTAL FOR THE BABY**

✓ **MOST DRUGS ARE HELPFUL – NOT HARMFUL - TO THE BABY**

Preconception Counselling & Risk Stratification

In women with **APS (primary or SLE-APS)**, risk factors include:

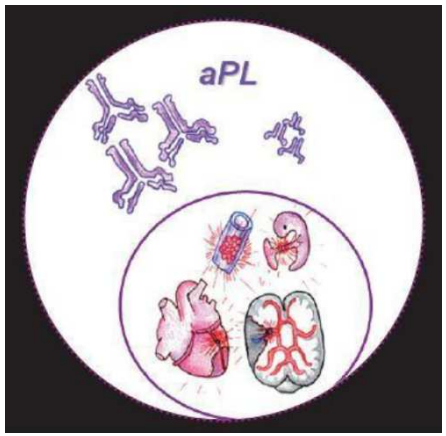
✓ high-risk aPL profile (lupus anticoagulant, multiple aPL, moderate to high titre aPL) **(1/A),**

✓co-existing SLE **(2/B),**

✓history of vascular/thrombotic APS **(2/B)**,

✓history of adverse pregnancy complications **(2/B)**.

Blood pressure monitoring **(3/C)** and use of appropriate medications with special emphasis on antiplatelet and/or anticoagulant therapy are of fundamental importance.



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CHECKLIST Preconception Counselling & Risk Stratification in SLE and/or APS

Disease-related risk factors

Parameters	Prognostic implications (increased risk)
SLE activity in the 6-12 months prior to conception	1) SLE flare during pregnancy; 2) hypertensive disorders; 3) fetal morbidity and mortality
Lupus Nephritis (history or active at conception)	1) Renal flare during pregnancy; 2) fetal loss and pre-term delivery
Serological activity (anti-dsDNA, C3, C4)	1) SLE flare during pregnancy; 2) pregnancy loss
Previous **adverse pregnancy outcome**	APS: pregnancy complications
History of **vascular thrombosis**	APS: pregnancy morbidity
SLE diagnosis	APS: pregnancy morbidity
aPL profile (high risk aPL profile)	1) Pregnancy complications (preeclampsia, IUGR, pre-term birth); 2) Maternal thrombosis
Anti-Ro/SSA and/or anti-La/SSB	Neonatal lupus (congenital heart block)
End-stage organ damage/comorbidities	

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CHECKLIST Preconception Counselling & Risk Stratification in SLE and/or APS

General risk factors

- MATERNAL AGE
- METABOLIC DISEASES or FAMILIARITY
  (arterial hypertension, diabetes mellitus)
- TOBACCO/ALCOHOL USE
- OBESITY
- THYROID DISEASE
- VACCINATION STATUS

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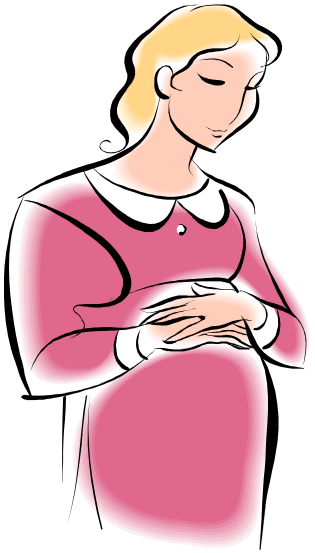
Predictive Biomarkers for maternal disease activity

In **pregnant women with SLE**, assessment of

- **disease activity (1/A)** – including renal function parameters (proteinuria, urine sediment, serum creatinine levels) **(2/B)** and
- **serological markers** (especially serum C3/C4, anti-dsDNA titres) **(2/B)** –

is recommended to monitor for obstetrical adverse outcomes and disease flares (during both pregnancy and the post-delivery period).



Andreoli L, Bertsias GK et al. EULAR Recommendations For Women's Health And The Management Of Family Planning, Assisted Reproduction, Pregnancy, And Menopause In Patients With SLE and/or APS. Ann Rheum Dis 2017;76:476–485.

Pregnancy Monitoring (Fetal Ultrasound)

- Women with SLE and/or APS should undergo supplementary fetal surveillance with **Doppler ultrasonography** and biometric parameters, particularly in the third trimester to screen for placental insufficiency and small for gestational age fetuses **(3/D)**.
- **Fetal echocardiography** is recommended in cases of suspected fetal dysrhythmia or myocarditis, especially in patients with positive anti-Ro/SSA and/or anti-La/SSB antibodies **(2/C)**.

Points to consider

oWomen with previous children with Congenital Heart Block (CHB) should be screened weekly between 16 and 28 weeks of gestation, then biweekly.

oDespite its unproven benefit, the current practice of intensive surveillance for CHB onsent in women with positive anti-Ro/SSA and anti-La/SSB and no previous child affected by CHB carries no risk and is well accepted by the mothers.

Andreoli L, Bertsias GK et al. EULAR Recommendations For Women's Health And The Management Of Family Planning, Assisted Reproduction, Pregnancy, And Menopause In Patients With SLE and/or APS. Ann Rheum Dis 2017;76:476–485.

Ultrasonographic fetal surveillance recommended for pregnant women with systemic lupus erythematosus and/or antiphospholipid syndrome

ROUTINE ultrasonographic screening

-First trimester (11-14 weeks of gestation)

-Second trimester (with Doppler, preferably at 20-24 weeks)

SUPPLEMENTARY fetal surveillance in the **THIRD TRIMESTER** at monthly intervals

-Doppler sonography of the umbilical artery, uterine arteries, ductus venosus and middle cerebral artery (particularly in fetuses that have been identified to suffer from ***early intrauterine growth restriction (IUGR)***, ie, prior to 34 weeks).

-In cases of ***late IUGR*** (diagnosed after 34 weeks), reduced abdominal circumference growth velocity and/or a reduced cerebroplacental ratio at Doppler investigation was shown to identify fetuses at higher risk of poor perinatal outcome (Doppler of the umbilical artery alone is insufficient).

Andreoli L, Bertsias GK et al. EULAR Recommendations For Women's Health And The Management Of Family Planning, Assisted Reproduction, Pregnancy, And Menopause In Patients With SLE and/or APS. Ann Rheum Dis 2017;76:476–485.

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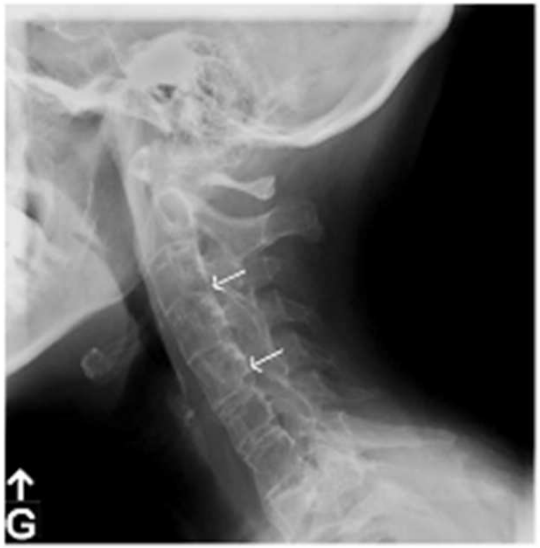
The obstetrician's point of view:

MODE of DELIVERY

✧ Problems related to joint deformities, e.g. limitation of hips extrarotation which may hamper vaginal delivery;

✧ Increased frequency of non-urgent, elective cesarean sections (up to 25% in SpA). Association with maternal chronic pain.

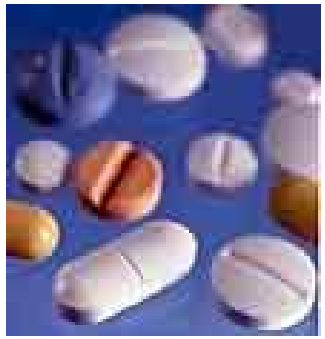


Epidural analgesia in parturients with ankylosing spondylitis: A role for ultrasound surveillance and ultrasound-guided placement

Himat Vaghadia, MD · Geneviève Germain, MD · Raymond Tang, MD

✧ problems related to spine calcification
→difficult epidural analgesia (calcification of the posterior longitudinal ligament)

Drugs for the Prevention and Management of SLE flares during pregnancy



- Hydroxychloroquine **(1/B)**, oral glucocorticoids, azathioprine, cyclosporine-A, and tacrolimus **(all 3/C)** can be used to prevent or manage SLE flares during pregnancy.
- Moderate-to-severe flares can be managed with additional strategies, including glucocorticoids intravenous pulse therapy, intravenous immunoglobulin and plasmapheresis **(all 3/C).**
- Mycophenolic acid, cyclophosphamide, leflunomide and methotrexate should be avoided.

Andreoli L, Bertsias GK et al. EULAR Recommendations For Women's Health And The Management Of Family Planning, Assisted Reproduction, Pregnancy, And Menopause In Patients With SLE and/or APS. Ann Rheum Dis 2017;76:476–485.

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ANTI-RHEUMATIC DRUGS DURING PREGNANCY AND LACTATION:

Overarching Principles

A: **Family planning** should be addressed in each patient of reproductive age and **adjustment of therapy** considered before a planned pregnancy.

B: Treatment of patients with rheumatic disease before/during pregnancy and lactation should aim to **prevent or suppress disease activity** in the mother and expose the fetus/child to no harm.

C: The **risk of drug therapy** for the child should be weighed against the risk that **untreated maternal disease** represents for the patient and the fetus or child.

D: The decision on drug therapy during pregnancy and lactation should be based on **agreement** between the internist/rheumatologist, gynaecologist/obstetrician and the patient, and including other health care providers when appropriate.

MESSAGES TO GIVE TO THE PATIENT AND HER FAMILY:

- ✓MATERNAL DISEASE ACTIVITY IS DETRIMENTAL FOR THE BABY
- ✓MOST DRUGS ARE HELPFUL – NOT HARMFUL- TO THE BABY

Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016 May;75(5):795-810.

HYDROXYCLOROQUINE

To be continued during pregnancy

….in the prevention of SLE flares…..

1. Parke A. Antimalarial drugs and pregnancy. Am J Med 1988; 85: 30-3.
2. Parke AL. Antimalarial drugs, systemic lupus erythematosus and pregnancy. J Rheumatol 1988; 15: 607-10.
3. Buchanan NM, Toubi E, Khamashta MA, Lima F, Kerslake S, Hughes GR. Hydroxychloroquine and lupus pregnancy: review of a series of 36 cases. Ann Rheum Dis.1996; 55: 486-8.
4. Clowse ME, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. Arthritis Rheum 2006; 54: 3640-7.
5. Bertsias G, Ioannidis JP, Boletis J, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis. 2008; 67: 195-205.

HYDROXYCLOROQUINE

To be continued or considered to be added for pregnancy

…in the prevention of CHB in patients with anti Ro/SS-A antibodies

1. Izmirly PM, Kim MY, Llanos C, Le PU, Guerra MM, Askanase AD, et al. Evaluation of the risk of anti-SSA/Ro–SSN/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine. Ann Rheum Dis 2010;69:1827–30.
2. Izmirly PM, Costedoat-Chalumeau N, Pisoni C, Khamashta MA, Kim MY, Saxena A, et al. Circulation 2012;126:76–82.

…in the prevention of pregnancy loss in patients with antiphospholipid antibodies

1. Mekinian A, Lazzaroni MG, Kuzenko A, et al. The efficacy of hydroxychloroquine for obstetrical outcome in anti- phospholipid syndrome: Data from a European multicenter retrospective study. Autoimmun Rev. 2015;14:498- 502
2. Sciascia S, Hunt BJ, Talavera-Garcia E, Lliso G, Khamashta MA Cuadrado MJ The impact of hydroxychloroquine treatment on pregnancy outcome in women with antiphospholipid antibodies. American Journal of Obstetrics and Gynecology 2015

ANTI-RHEUMATIC DRUGS DURING PREGNANCY AND LACTATION

REFERENCES

1-Ostensen M, Khamashta M, Lockshin M, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res. Ther.* 2006;8(3):209.

2-Ostensen M, Lockshin M, Doria A, et al. Update on safety during pregnancy of biological agents and some immunosuppressive anti-rheumatic drugs. *Rheumatology (Oxford)* 2008;47 Suppl 3:iii28-31.

2016: the turning point

3-Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016 May;75(5):795-810.

4-Flint J, Panchal S, Hurrell A, van de Venne M, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016 Sep;55(9):1693-7.

Anti-Rheumatic Drugs in Pregnancy

	EULAR POINTS TO CONSIDER	GdR
1	csDMARDs proven compatible with pregnancy are hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus and colchicine. They should be continued in pregnancy for maintenance of remission or treatment of a disease flare.	B
2	csDMARDs methotrexate, mycophenolate mofetil and cyclophosphamide are teratogenic and should be withdrawn before pregnancy.	B
3	Non-selective COX inhibitors (NSAIDs) and prednisone should be considered for use in pregnancy if needed to control active disease symptoms. NSAIDs should be restricted to the 1st and 2nd trimester	B
4	In severe, refractory maternal disease during pregnancy methylprednisolone pulses, intravenous immunoglobulin or even 2nd or 3rd trimester use of cyclophosphamide should be considered.	D
5	csDMARDs, tsDMARDs and anti-inflammatory drugs with insufficient documentation concerning use in pregnancy should be avoided until further evidence is available. This applies to leflunomide, mepacrine, tofacitinib, and selective COX II inhibitors.	B-D

Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016 May;75(5):795-810.

The conflict on Lactation in clinical practice

Statements on lactation have two main problems:

1- insufficient documentation
2 -propensity to discourage from breastfeeding patients who are in need of taking drugs.

Mothers may have the opposite view and would rather breastfeed than receive medications for active disease.

Non-ionised and lipophilic agents with a low molecular weight are the most likely to be transferred into breast milk.
Agents with high molecular weight are unlikely to cross extensively into breast milk.

Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016 May;75(5):795-810.

Anti-Rheumatic Drugs during Lactation

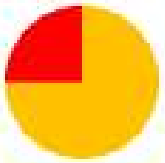
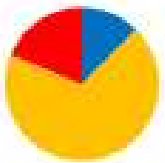
	EULAR POINTS TO CONSIDER	GdR
1	csDMARDs and anti-inflammatory drugs **compatible with breastfeeding** should be considered for continuation during lactation provided the child does not have conditions that contraindicate it. This applies to **hydroxychloroquine**, **chloroquine**, **sulfasalazine**, **azathioprine**, **ciclosporin**, tacrolimus, colchicine, **prednisone**, immunoglobulin, non-selective COX inhibitors and celecoxib.	D
2	csDMARDs, tsDMARDs and anti-inflammatory drugs with **no or limited data** on breastfeeding should be avoided in lactating women. This applies to **methotrexate**, **mycophenolate mofetil**, **cyclophosphamide**, **leflunomide**, tofacitinib and COX II-inhibitors other than celecoxib.	D

Anti-Rheumatic Drugs in Pregnancy

	EULAR POINTS TO CONSIDER	GdR
6	Among bDMARDs continuation of TNF inhibitors during the first part of pregnancy should be considered. Etanercept and Certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage.	B
7	bDMARDs Rituximab, Anakinra, Tocilizumab, Abatacept, Belimumab and Ustekinumab have limited documentation on safe use in pregnancy and should be replaced before conception by other medication. They should be used during pregnancy only when no other pregnancy compatible drug can effectively control maternal disease.	D

Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016 May;75(5):795-810.

TNFa inhibitors in pregnancy: the use in clinical practice

	Statement on compatibility of drug with pregnancy based on evidence	% agreement with statement	Expert opinion on use of drug
Infliximab	Current evidence indicates no increased rate of congenital malformations. Infliximab can be continued up to gestational week 20. If indicated, it can be used throughout pregnancy	100	
Adalimumab	Current evidence indicates no increased rate of congenital malformations. Adalimumab can be continued up to gestational week 20. If indicated, it can be used throughout pregnancy	100	
Golimumab	Current evidence does not indicate an increased rate of congenital malformations. Because of limited evidence, alternative medications should be considered for treatment throughout pregnancy	100	
Etanercept	Current evidence indicates no increased rate of congenital malformations. Etanercept can be continued up to gestational week 30-32. If indicated, it can be used throughout pregnancy	100	
Certolizumab	Current evidence indicates no increased rate of congenital malformations. Certolizumab can be continued throughout pregnancy	100	

I would recommend;
I would only recommend for moderate disease activity ;
I would only recommend for severe disease activity;
I would never recommend the drug

Skorpen CG, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy and during pregnancy and lactation. ARD 2016 2016 May;75(5):795-810

BELIMUMAB AND PREGNANCY

From clinical trials…

95 pregnancies reported in Belimumab trials up to March 2013:

-35 live births without congenital anomaly
-3 live births with congenital anomaly (corresponding to the national average of 3%)
-20 elective terminations
-23 spontaneous abortions
-2 stillbirths without congenital anomaly
-12 ongoing/unknown

Sandhu VK, Wallace DJ, Weisman MH. J Rheumatol 2015;42:4

…to Expert Opinion

	Pregnancy			Breast feeding		
Drug	Statement on compatibility of drug with pregnancy based on evidence	Percentage of agreement with statement	Expert opinion on use of drug in clinical practice (%)*	Statement on compatibility of drug with breast feeding based on evidence	Percentage of agreement with statement	Expert opinion on breast feeding and medication (%)†
Belimumab	Current evidence does not indicate an increased rate of congenital malformations; because of limited evidence, alternative medications should be considered for treatment throughout pregnancy	100		No data exist regarding belimumab in breast milk, therefore belimumab should be avoided in breast feeding	82	

*As an expert in the field.
I would recommend the drug in the same way as if the patient was not pregnant.
I would only recommend the drug if I feared at least moderate disease activity in its absence.
I would only recommend the drug if I feared at least severe disease activity in its absence.
I would never recommend the drug in pregnancy.

†As an expert in the field.
I would recommend the drug in the same way as if the patient did not breastfeed.
I would only recommend the drug if I feared at least moderate disease activity in its absence.
I would only recommend the drug if I feared at least severe disease activity in its absence.
I would never recommend the drug while the woman was breast feeding.

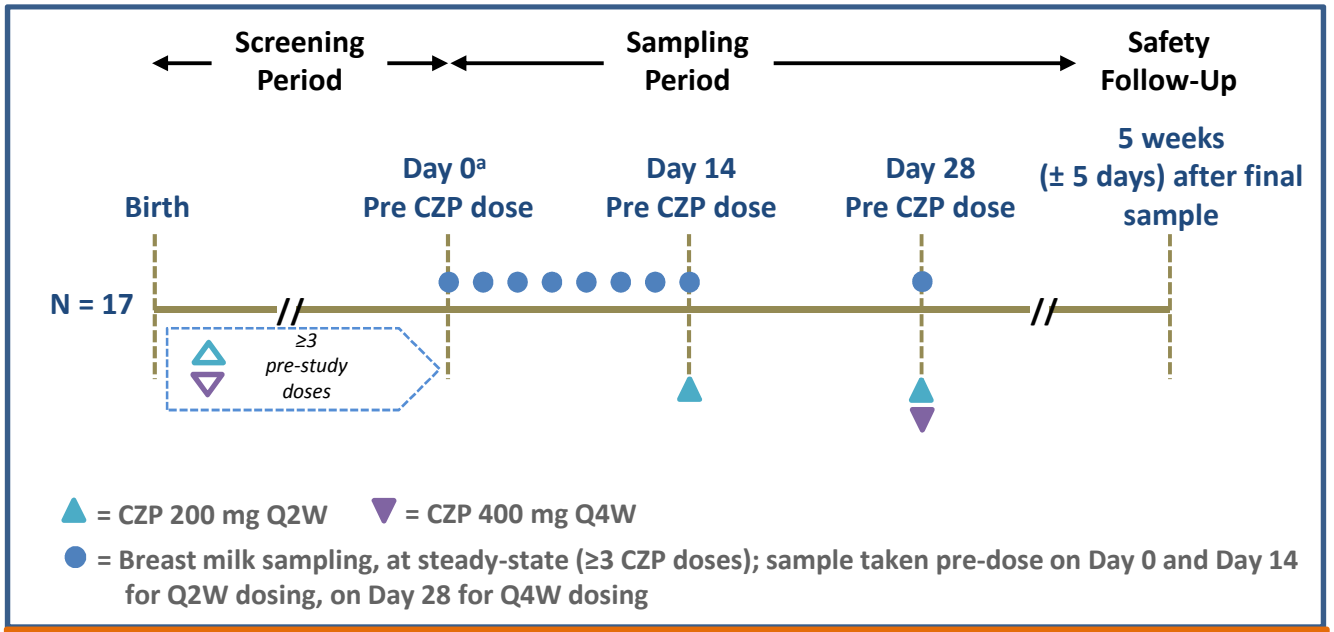
Götestam Skorpen C, et al. Ann Rheum Dis. 2016 May;75(5):795-810.

Anti-Rheumatic Drugs during Lactation

	EULAR POINTS TO CONSIDER	GdR
3	**Low transfer to breast milk** has been shown for Infliximab, Adalimumab, Etanercept, and Certolizumab. Continuation of **TNF-inhibitors** should be considered compatible with breastfeeding.	D
4	bDMARDs with **no data** on breastfeeding such as Rituximab, Anakinra, Belimumab, Ustekinumab, Tocilizumab and Abatacept should be avoided during lactation if other therapy is available to control the disease. Based on pharmacological properties of bDMARDs, lactation should not be discouraged when using these agents, if no other options are available.	D

Anti-Rheumatic Drugs during Lactation: the CRADLE Study

Design



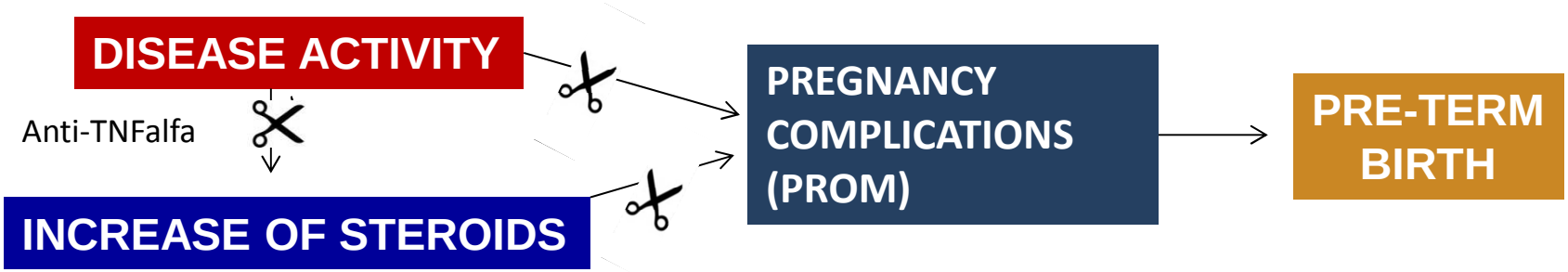
Conclusions

- CZP Average Daily Infant Dose (0–0.0104 mg/kg/day) is minimal.
- Highest concentration of CZP in breast milk (0.0758 µg/mL) is <1% of the expected plasma concentration of a therapeutic dose.
- Median CZP Relative Infant Dose (0.125%) is considered to be in safe range for breastfeeding (<10%).
- AEs in mothers exposed to CZP were consistent with known CZP safety profile; infants of mothers exposed to CZP had AE profile that could be anticipated in an untreated population of a similar age.

UCB Data on File (Clowse MEB et al. ACR 2016. Oral Presentation 2048).

The use of anti-TNFa during pregnancy

Nearly 50% of the women taking anti-TNFalfa agents have moderate to severe disease activity after stopping the drug at positive pregnancy test



Case-control study of children exposed in utero to anti-TNFalfa agents

1) No differences in growth parameters and developmental milestones

2) No excess nor particular pattern of congenital defects/malformations

3) No particular problems in children exposed during the **2nd-3rd trimester** **in comparison to those exposed to positive pregnancy test only**

Preliminary data on the long term follow-up of these children seem to be reassuring

Reggia R et al ACR poster 2015

Adjunct treatment during pregnancy

- **Hydroxychloroquine** is recommended pre-conceptionally and throughout pregnancy for patients with SLE **(2/B).**

- Women with SLE at risk of pre-eclampsia (especially those with lupus nephritis or positive aPL) should receive **low-dose aspirin** (LDA) **2/C).**

- In women with SLE-associated APS and Primary APS, **combination treatment with LDA and heparin** is recommended to decrease the risk of adverse pregnancy outcomes **(1/A).**

- Supplementation with **calcium**, **vitamin D**, and **folic acid** should be offered as in the general population **(-/D)**. Measuring blood vitamin D levels should be considered after pregnancy is confirmed **(-/D)**.

Andreoli L, Bertsias GK et al. EULAR Recommendations For Women's Health And The Management Of Family Planning, Assisted Reproduction, Pregnancy, And Menopause In Patients With SLE and/or APS. Ann Rheum Dis 2017;76:476–485.

Take Home Messages

COUNSELLING PRECONCEZIONALE

E

GESTIONE MULTIDISCIPLINARE DELLA GRAVIDANZA

- ✧ **Stratificazione del rischio**
- ✧ **Controllo dell'attività di malattia materna**
- ✧ **Farmaci utilizzabili in gravidanza e allattamento**
- ✧ **Possibili complicanze gravidiche**
- ✧ **Modalità di parto**
- ✧ **Lo stato di salute dei figli**

Risk Factors for Reduced Fertility

- There is no concrete evidence that the disease itself decreases fertility in women with SLE and/or APS **(2/B)**.
- Women who wish to plan a pregnancy should be counselled about fertility issues, especially the adverse outcomes associated with **increasing age** and the **use of alkylating agents** **(1/A)**.
- Treatment with alkylating agents should be balanced against the risk of ovarian dysfunction.

Andreoli L, Bertsias GK et al. EULAR Recommendations For Women's Health And The Management Of Family Planning, Assisted Reproduction, Pregnancy, And Menopause In Patients With SLE and/or APS. Ann Rheum Dis 2017;76:476–485.

PRECONCEPTION COUNSELING- RISK STRATIFICATION

INFERTILITY

Table 1 | Possible causes of subfertility in patients with RA

Cause	General consequences	Effects on reproductive function
Age >35 years	Reduced number of follicles, low ovarian reserves	Anovulatory cycles
High disease activity	Pain, stiffness, impaired physical function, fatigue	Reduced libido, reduced frequency of intercourse
Depression	Low self-esteem, negative body image	Reduced libido, reduced frequency of intercourse
NSAID use	LUF syndrome at high anti-inflammatory doses of cyclooxygenase inhibitors	Anovulatory cycles
Patient anxiety	Anxious to change therapy before or during pregnancy, fear of a disease flare during or after pregnancy, perceived difficulties with child caring, fear of heredity	Choice to limit family size

Abbreviations: LUF, luteinized unruptured follicle; RA, rheumatoid arthritis.

Østensen, M. *Nat. Rev. Rheumatol.* **10**, 518–519 (2014)

Nature REVIEWS RHEUMATOLOGY

Nat Rev Rheumatol. 2017 Aug;13(8):485-493. doi: 10.1038/nrrheum.2017.102. Epub 2017 Jul 6.

Sexual and reproductive health in rheumatic disease.

Østensen M[1,2].

⊕ Author information

Abstract

Family size is reduced among patients with rheumatic diseases. The causes for the low number of children are multifactorial and include impaired sexual function, decreased gonadal function, pregnancy loss, therapy and personal choices. Sexuality contributes to quality of life in patients with rheumatic disease, but is often ignored by health professionals. Both disease-related factors and psychological responses to chronic disease can impair sexual functioning. Toxic effects of anti-inflammatory and immunosuppressive drugs can induce transient or permanent gonadal failure in women and men. Furthermore, permanent infertility can be a consequence of treatment with cyclophosphamide, whereas transient infertility can be caused by NSAIDs in women and sulfasalazine in men. These adverse effects must be communicated to the patients, and measures to preserve fertility should be initiated before the start of gonadotoxic therapy. Management of patients of both genders should include regular family planning, effective treatment of high disease activity, sexual counselling, and, if necessary, infertility treatment.

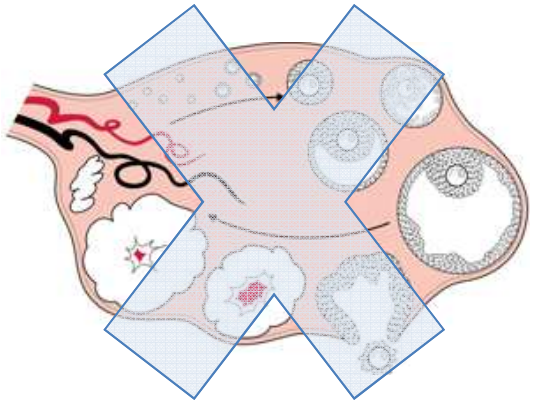
NSAIDs & FERTILITY

Arthritis Care & Research
Vol. 63, No. 9, September 2011, pp 1334–1338
DOI 10.1002/acr.20510

ORIGINAL ARTICLE

Luteinized Unruptured Follicle Syndrome Increased by Inactive Disease and Selective Cyclooxygenase 2 Inhibitors in Women With Inflammatory Arthropathies

MIHAELA C. MICU,[1] ROMEO MICU,[2] AND MONIKA OSTENSEN[3]



- ✓The use of NSAIDs increases the risk of LUF, especially in patients with inactive disease.
- ✓**COX-2 inhibitors with a long half-life** such as etoricoxib have a more potent effect in inhibiting the rupture of the follicle as compared to non-selective NSAIDs or with a short half-life.

CONTINOUS PERIOVULATORY EXPOSURE TO NSAIDs SHOULD BE AVOIDED WHEN PLANNING A PREGNANCY

Assisted Reproduction Techniques (ARTs)

- Assisted reproduction techniques, such as ovulation induction treatments and *in vitro* fertilization protocols, have comparable efficacy in women with SLE and/or APS as in the general population, and can be safely used in patients with stable/inactive disease **(3/C)**.
- Patients with positive aPL/APS should receive appropriate anticoagulation (at the dosage as would be recommended during pregnancy) and/or low dose aspirin **(3/D)**.

Points to consider

- Importance of prevention of Ovarian Hyperstimulation Syndrome
- "Appropriate anticoagulation": as it would be given during pregnancy

Andreoli L, Bertsias GK et al. EULAR Recommendations For Women's Health And The Management Of Family Planning, Assisted Reproduction, Pregnancy, And Menopause In Patients With SLE and/or APS. Ann Rheum Dis 2017;76:476–485.

Preservation of Fertility

Fertility preservation methods, especially **GnRH analogues**, should be considered for all menstruating women with SLE who are going to receive alkylating agents **(2/B).**

Points to consider

- Low dose CYC regimens (Eurolupus)
- GnRH analogues may help to prevent premature ovarian failure but there are no data on subsequent pregnancies.
- Share with the patients the uncertainties regarding the use of GnRH analogues: it is a drug likely to help preventing premature ovarian failure but it carries side effects (mostly menopause-like symptoms, fully reversible).

Andreoli L, Bertsias GK et al. EULAR Recommendations For Women's Health And The Management Of Family Planning, Assisted Reproduction, Pregnancy, And Menopause In Patients With SLE and/or APS. Ann Rheum Dis 2017;76:476–485.

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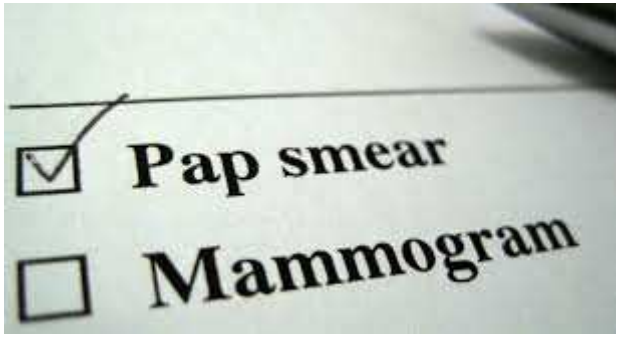
Menopause

- In women with SLE with stable/inactive disease and negative aPL, **Hormone Replacement Therapy (HRT)** can be used for the management of **severe** vasomotor menopausal manifestations **(1/A)**.

- The use of HRT in patients with positive aPL should be carefully weighed against the risk of thrombosis and cardiovascular disease **(-/D)**.

Screening for Malignancies

- Women with SLE and/or APS should undergo screening for malignancies similar to the general population **(-/D)**.

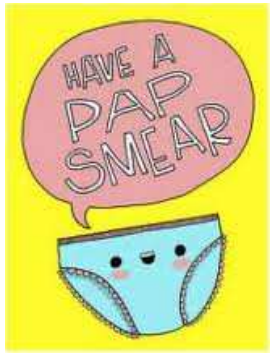


- Women with SLE, especially those exposed to immunosuppressive drugs, are at higher risk of **cervical pre-malignant lesions** and should be monitored with vigilance **(2/B)**.

Points to consider

Suggested timing for PAP cervical smear:

- heavily immunosuppressed patients: once a year
- low risk patients: may follow the local screening program.



HPV immunization

HPV immunization can be considered in women with SLE and/or APS and **stable/inactive disease** (3/D).

Points to consider

oDiscuss possible harms of HPV immunization. Increased risk of thrombosis and syncope in the general population.
oEULAR recommendations on vaccinations: caution in aPL positive women
oTiming for immunization as in the general population

Slade BA, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA. 2009;302(7):750-7.

van Assen S et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2011;70(3):414-22.

Ostetricia e Ginecologia
Ambulatorio Autoimmunità in gravidanza
Lupus Clinic

Andrea Lojacono, Francesca Ramazzotto,
Cristina Zanardini, Sonia Zatti

Tel : 0303996664
Mail : cup.ostetrico@asst-spedalicivili.it