Συστηματικός Ερυθηματώδης Λύκος στην κύηση και αντιφωσφολιπιδικό σύνδρομο: νεότερα δεδομένα στη διαχείριση και θεραπευτική προσέγγιση μέσα από κλινικά περιστατικά

10/5/2026

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Case 1
Biologics in SLE pregnancies

SLE diagnosis 2013 (14yo)

- Arthritis
- ACLE
- SCLE
- Hair loss
- Raynaud's
- Serology:
  - ANA 1:640
  - Anti-dsDNA +
  - Anti-Smith+
  - Anti-RNP+
  - Low C3/C4

-> HQ 400mg/d

-> steroids

2018 (19yo)
No wish for pregnancy
Severe ACLE ->
Methotrexate
Mild improvement

5/2020 (22yo)
Persistent rash and serological activity ->
Belimumab
Improvement

12/2021 (23yo) pregnancy
HQ 400mg/d
Stop **Belimumab**

SLE diagnosis 2013 (14yo)

-> HQ 400mg/d

-> steroids

12/2021 (23yo) uncomplicated pregnancy

- HQ 400mg/d
- Delivery at 40w of gestation
- Healthy infant, 3.650gr

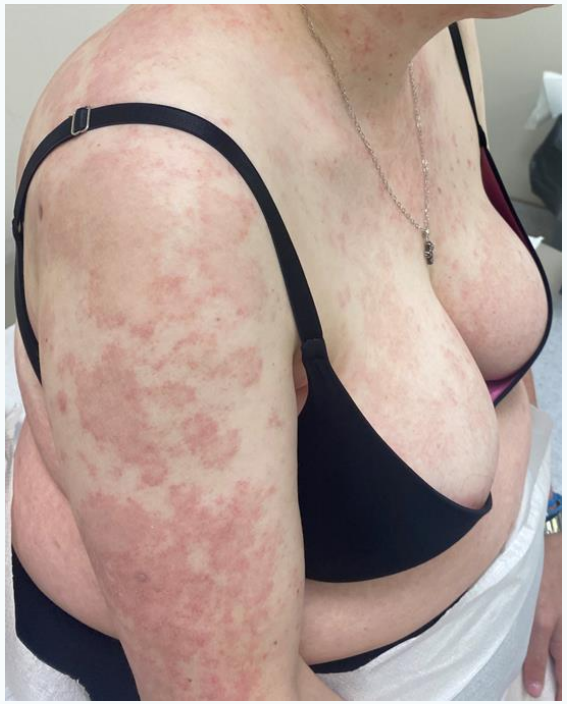
SLE diagnosis 2013 (14yo)

-> HQ 400mg/d

-> steroids

6/2024 (24yo) under HQ 4O0mg/d

- Severe skin flare (face and trunk)
- CLASI=22
- **Anifrolumab**



SLE diagnosis 2013 (14yo)

-> HQ 400mg/d

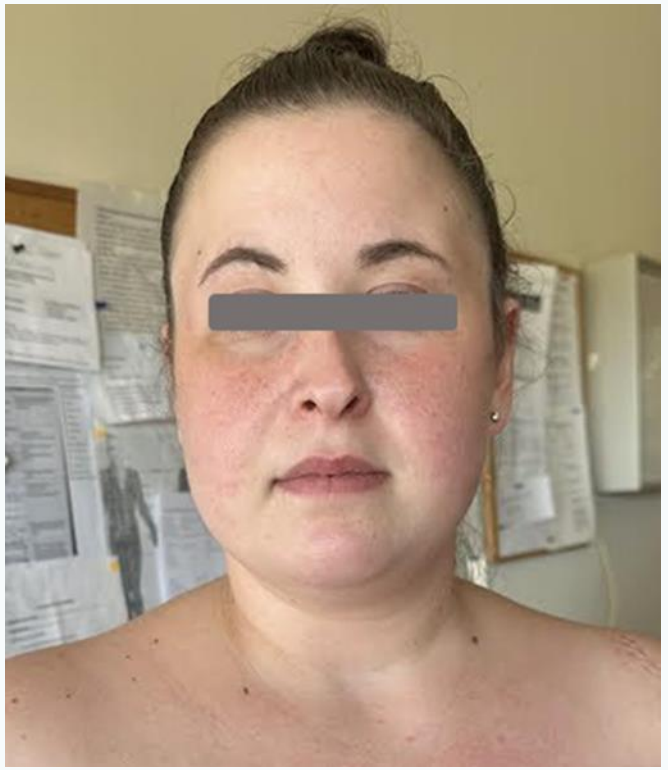
-> steroids

6/2024 (24yo) under HQ 4O0mg/d

- Severe skin flare (face and trunk)
- CLASI=22
- **Anifrolumab**

Anifrolumab 6/2024 - 6/2025

- Good response
- Dc due to regulatory issues



SLE diagnosis 2013 (14yo)

-> HQ 400mg/d

-> steroids

6/2025
Dc of Anifrolumab
HQ 400mg/d

11/2025 (26yo)
Skin flare
Unplanned pregnancy
9w gestation
normal C3/C4, **anti-dsDNA+++**

Risk stratification for pregnancy complications

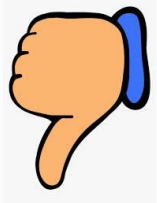
SLE diagnosis (2013)

- **1st trimester**
- **Active skin disease**
- Normal C3/C4
- **High titers anti-dsDNA**
- ApLs negative
- Anti-SSA, anti-SSB negative
- **Need of steroids PDN>30mg/d**

Past treatments

- **Belimumab**: Good response
- **Anifrolumab**: Great

- Young patient (26yo)
- Hx of an uncomplicated pregnancy
- No Hx of lupus nephritis
- apLs negative
- Anti-SSA, anti-SSB negative
- Under pregnancy compatible medication



- Overweight (BMI 35)
- Active lupus from skin
- Serological activity (high ds-DNA)

SLE diagnosis (2013)

Unplanned pregnancy

-> HQ 400mg/d

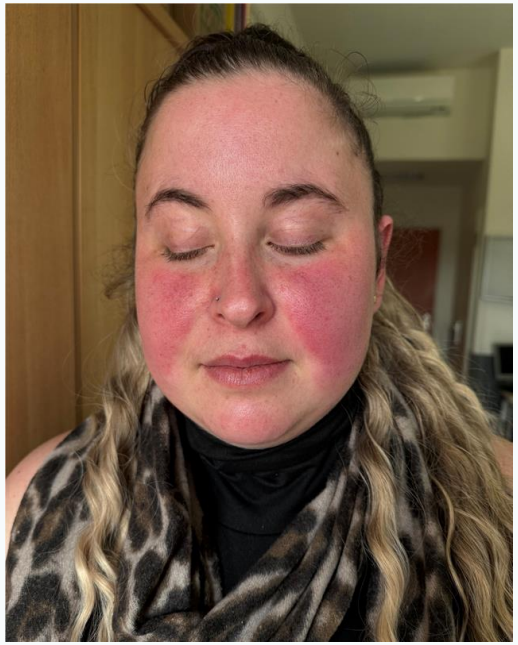
- ❑ **Pulses MP 500mg + 500mg IV**
- ❑ **AZA 200mg/d**
- ❑ **Aspirin 100mg/d**

1/2026

17w gestation

No improvement

->Belimumab



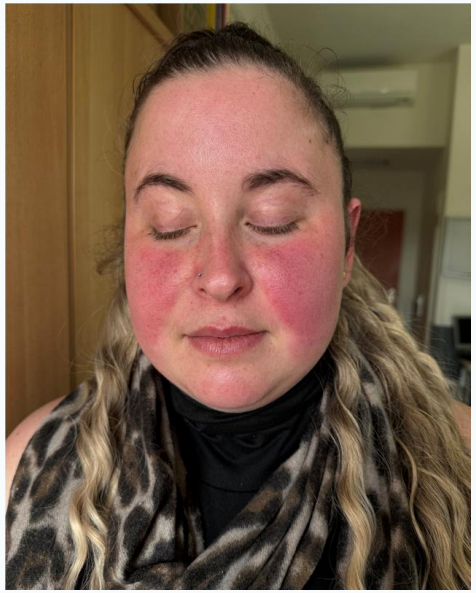
SLE diagnosis (2013)

2nd trimester

- Active skin disease
- Normal C3/C4
- **High titers anti-dsDNA**

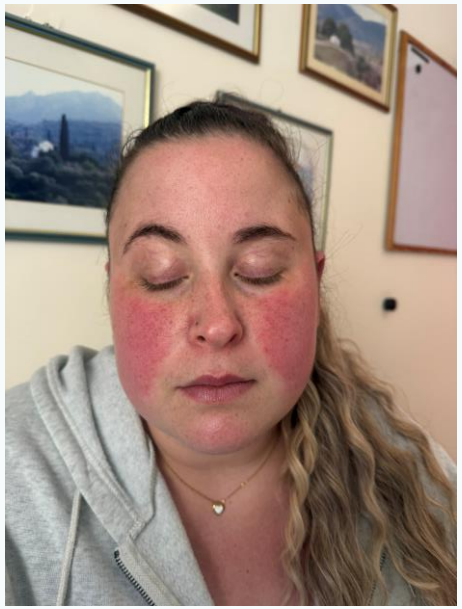
1/2026
17w gestation

- **PDN 15mg/d**
- **Belimumab**



2/2026
22w gestation
Gradual improvement

- **PDN 10mg/d**



SLE diagnosis (2013)

- **3rd trimester**
- Normal C3/C4
- **Normal titers anti-dsDNA**

5/2026 (32w)

- **32w gestation**
- **HQ 400mg, AZA 200mg**
- **Belimumab**
- **PDN 5mg/d**
- **Aspirin 100mg**

Clinical improvement

Expected date of delivery 6/2026….

The core dilemma

Two risks coexist; neither option is risk-free.

Maternal disease risk

Active SLE is associated with flare progression, glucocorticoid exposure, hypertension/preeclampsia, preterm birth and fetal growth restriction

Medication uncertainty

Biologics often have limited pregnancy datasets, confounding by disease severity, sparse 2nd/3rd trimester exposure data, and neonatal immune considerations.

Decision is not “safe vs unsafe”
It is: which plan gives this mother–fetus the best chance of a good outcome

EULAR women’s health recommendations 2017; ACR reproductive health guideline 2020; Winterfeld et al. Front Drug Saf Regul 2025.

Belimumab and pregnancy

British Society for Rheumatology

--Limited evidence-> **not teratogenic**; however, there remains insufficient evidence to be confident that it is compatible with pregnancy

--Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (2C)

--May be considered **to manage severe maternal disease in pregnancy** if no other pregnancy-compatible drugs are suitable (2C)

--If exposure in the **3rd trimester**, -> avoid all live vaccines in the infant vaccination schedule **until 6 months of age** (2C)

--BEL is compatible with breastmilk exposure (2C)

eular | EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

- May be used **if needed** to effectively **control maternal disease** (4C)
- **Compatible with breastfeeding**

Belimumab in pregnancy: the conversation-worthy facts

Mechanism	Human data	Neonatal issue
Human monoclonal anti-BLyS/BAFF **Placental IgG transfer increases as pregnancy progresses, highest in 3rd trimester.**	Across **319 pregnancies** with known outcomes in clinical trials, BPR and postmarketing reports: **no consistent birth-defect pattern; data limited by small numbers, confounding, incomplete information.**	Animal data show reversible B-cell/Ig changes; labeling advises monitoring infants exposed in utero for B-cell reduction and immune dysfunction and considering risks/benefits of live vaccines.

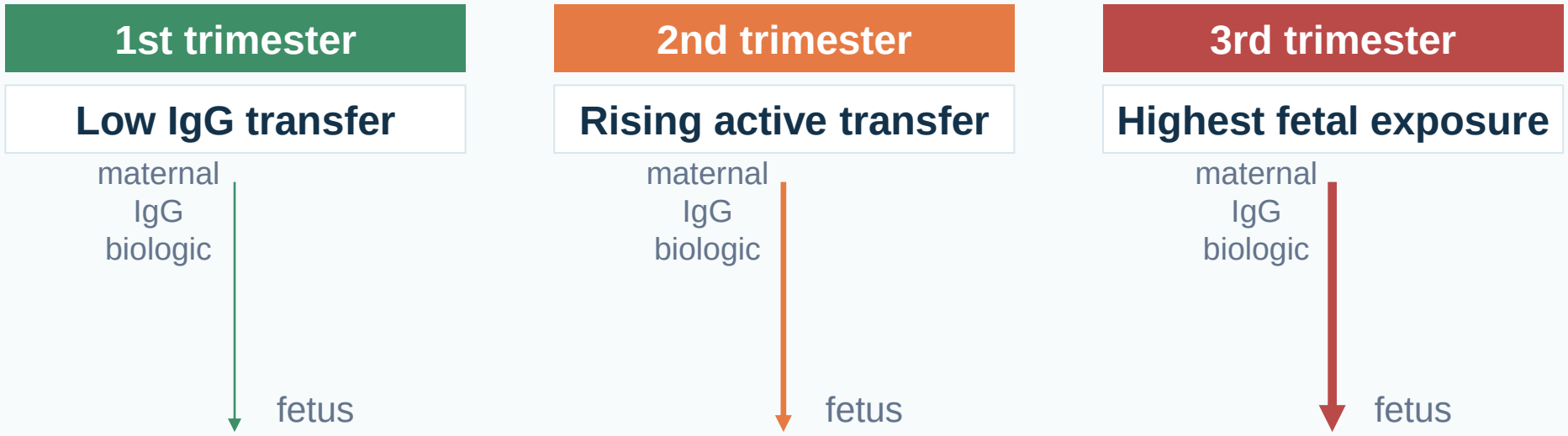
PUBLISHED DESCRIPTIVE DATA

5.6% Clinical trials birth defects	21.7% BPR prospective birth defects	1.1% Postmarketing birth defects	31.8% Clinical trials pregnancy loss	31.4% Postmarketing pregnancy loss

Petri et al. Ann Rheum Dis 2023; Juliao et al. Birth Defects Res 2023; FDA BENLYSTA label 2025
BPR: belimumab pregnancy registry

Placental transfer changes the neonatal conversation

Timing matters — especially for IgG1 biologics and B-cell-directed therapy.



Counseling points for belimumab/rituximab exposure later in pregnancy

- Neonatal CBC/lymphocyte subsets if clinically indicated
- Pediatrician/neonatologist aware before delivery
- Discuss live vaccines individually; rotavirus is time-sensitive
- Track infections through infancy when exposed late

FDA BENLYSTA label 2025; ACR vaccination guideline 2022/2023; Klink et al. rituximab placental transfer/neonatal B cells

Risk stratification before discussing biologics

Disease activity	current flare severity, organs involved, serology trend
Obstetric risk	preeclampsia, fetal growth, placental insufficiency
Autoantibodies	aPL/APS, anti-Ro/SSA and anti-La/SSB
Medication context	HCQ adherence, steroid dose, compatible immunosuppressants tried

Team huddle: rheumatology + maternal–fetal medicine + dermatology ± nephrology ± neonatology/pediatrics

EULAR 2017 recommends risk stratification including disease activity, antibodies, morbidity, hypertension, renal/serologic monitoring; ACR 2020 emphasizes OB/GYN collaboration.

Evidence landscape for biologics in SLE pregnancy

Biologic	Pregnancy data	SLE role	Pregnancy position	Infant issue
Rituximab	Observational data	Off-label rescue for severe organ/life-threatening SLE	May be used when severe maternal disease warrants	Transient neonatal B-cell depletion; delay rotavirus if exposed late
Anifrolumab	Very sparse	Approved extrarenal SLE	EULAR 2025: severe refractory disease if no alternative	Unknown; registry encouraged
Dapirolizumab pegol	Current phase I pregnancy trial	Phase III SLE trials, promising efficacy	No in vivo data	Limited infant transfer

ACR 2020; EULAR 2025 update summarized by RheumNow; FDA BENLYSTA label; ACR vaccination guideline 2022/2023

Case 2
Cardiac neonatal lupus

SLE diagnosis 2012 (22yo)

- Arthritis
- ACLE
- Raynaud's
- Lymphopenia
- Serology:
  - ANA 1:320
  - Anti-dsDNA +
  - **Anti-SSA+**
  - Direct coombs+
  - Low C3/C4
- **APS (LA+), Stroke (2017)**

2012

- **Cytopenias, fever**

HQ, AZA, steroids

2017 (27yo)

- Ischemic stroke -> thrombolysis

LA+ -> **acenocoumarol**

2023 (33yo)

- SLE in remission

Pregnancy

HQ, AZA, salospir 100mg, LWMH therapeutic dosage

SLE diagnosis 2012 (22yo)

- Anti-dsDNA +
- **Anti-SSA++**
- Direct coombs+
- Low C3/C4

- **APS (LA+), Stroke (2017)**

2023 (33yo)

- SLE in remission

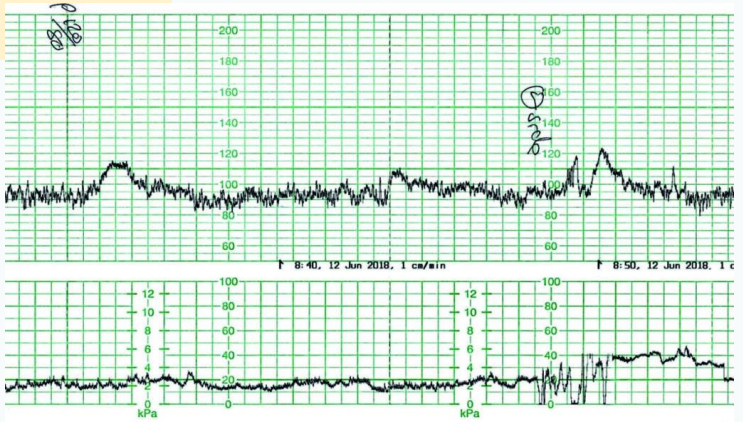
Pregnancy

HQ, AZA, salospir 100mg, LWMH therapeutic dosage

Hospitalization in the Obstetrics unit

21w of gestation

- **Fetal bradycardia 55bpm**
- **3rd degree CHB**



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- ACLE
- Raynaud's
- Lymphopenia
- Serology:
  - ANA 1:320
  - Anti-dsDNA +
  - Anti-SSA+
  - Direct coombs+
  - Low C3/C4
- APS (LA+), Stroke (2017)

Hospitalization in the Obstetrics unit

- **Dexamethasone 8mg/d**
- **IVIG**
- **Maternal beta-agonist**

24w of gestation

- **Fetal death due to severe bradycardia**

Fetal necrotomy

- ***Cardiac fibroelastosis***
- ***Hydrops***
- ***Severe heart failure***

Karyotype, WES: normal

Neonatal Lupus: Cardiac Involvement — Epidemiology & Clinical Data

~2%
Risk of CHB in anti-Ro(+) mothers (1st pregnancy)

15–20%
Recurrence risk after affected sibling

~20%
Mortality in untreated 3° CHB

~65%
Of CHB neonates require permanent pacemaker

Spectrum of Cardiac Involvement

- 1st degree AV block: usually transient
- 2nd degree AV block: may progress to 3° in utero
- 3rd degree (complete) AV block: permanent, irreversible — requires pacemaker; onset typically 18–24 weeks gestation
- Endocardial fibroelastosis (EFE): fibrotic thickening of endocardium → dilated cardiomyopathy; poor prognosis

Management of CHB by Degree: Therapeutic Options & Evidence

Intervention	1° AV Block (PR prolongation)	2° AV Block	3° AV Block	Cardiomyopathy
Hydroxychloroquine (Prevention)	✔ Recommended (primary prevention)	✔ Continue; ↓ anti-Ro titers	Continue; no reversal of established block	No evidence for reversal
Dexamethasone	Not indicated	Consider	No reversal of complete block; may ↓ EFE (controversial)	Dexamethasone may slow EFE progression (PRIDE data)
IVIG	Not indicated	Tried; did NOT prevent progression to 3°	No benefit on established 3° CHB; not recommended	No data
β-sympatho-mimetics (salbutamol IV)	Not indicated	Not indicated	Temporizing: ↑ fetal HR in severe bradycardia / hydrops	Bridge to delivery or pacing only
Pacemaker (postnatal)	Not indicated	Rarely needed; monitor	✔ SOC; If neonatal HR <55 bpm or symptomatic	✔ Required if associated CHB; +/- transplant for severe EFE

The FcRn Pathway: Mechanism of Placental Antibody Transfer

FcRn Blockade Strategy

- FcRn (neonatal Fc receptor) is the key transporter of maternal IgG across the placenta
- **Blocking FcRn reduces maternal IgG levels AND inhibits transplacental transfer of pathogenic antibodies**

Why FcRn Blockade for CHB?

- Anti-Ro titer correlates with CHB severity → reducing maternal IgG reduces fetal risk
- IVIG (conventional approach) partially lowers IgG — FcRn blockers are significantly more potent
- Treatment window: ideally before 16–18 weeks, prior to peak placental transfer

Nipocalimab (FcRn Blocker) in Neonatal Lupus: The UNITY Trial

- Phase 2 RCT • Status: ACTIVELY ENROLLING (2026)

Trial Design

- **Population: Pregnant women anti-Ro/SSA(+) with prior child with CHB or neonatal cutaneous lupus**
- Timing: Administration from gestational **week 14–17**, until week 35
- **Primary endpoint: Live birth without CHB (2° or 3°) or EFE**

Preclinical & Early Evidence

- Nipocalimab reduces IgG by 50–80% in healthy volunteers and pregnant patients in other indications
- Proof-of-concept: patient with EFE risk treated with nipocalimab → anti-Ro significantly reduced, neonatal IgG low

Current Status & Key Message

- No published efficacy data yet
- **Represents a paradigm shift: targeting the mechanism of Ab transfer rather than downstream inflammation**

Case 3
Pregnancy in SLE/APS patient

SLE diagnosis (2019)

- Arthritis
- Fever
- **Myocarditis**
- ITP
- Serology:
  - ANA 1:640
  - Low C3/C4

Thrombotic and microvascular APS (triple positive)

- DVT, PE

-> HQ 400mg/d, GCs

->MMF 2gr/d

2022

Acenocoumarol, MMF2gr, HQ 400mg/d

- **Adrenal hemorrhage – insufficiency**
- Replacement treatment (hydrocortisone)

2023

Wish for pregnancy

HQ 400mg, AZA 200mg, LWMH therapeutic dosage

2025, 2026

SLE in remission for 2 years

LWMH therapeutic dosage + aspirin 160mg/d

- 1 biochemical pregnancy
- 1 early miscarriage (7w gestation)

Antiphospholipid Syndrome (APS) in Pregnancy: The High-Risk Phenotype

APS & Adverse Pregnancy Outcomes

Antiphospholipid syndrome (APS)
is associated with significant placental-mediated adverse pregnancy outcomes (APOs):

- Fetal death (≥10 weeks' gestation)
- Pre-eclampsia with severe features
- Placental insufficiency → preterm delivery

Success rates 70–75% with SOC
-Lupus anticoagulant (LA) positivity confers especially high risk — APO rates of 37–44% despite SOC.

THE RATIONALE OF IMPACT TRIAL

TNF-α plays a key role in complement-mediated placental injury in APS.

Certolizumab pegol (CZP) — a PEGylated anti-TNF-α Fab' fragment:

- Minimal/no placental transfer (no Fc region)
- Safety established in pregnancy (CRIB study)
- Anti-inflammatory + potential anti-thrombotic effects
- No fetal Fc receptor-mediated transport

Standard therapy (LMWH + LDA) alone is insufficient for high-risk LA+ patients.

PROMISSE study: APO rate 44% in APS+LA patients on standard therapy (N=61)

The IMPACT Trial: Certolizumab Pegol in LA-Positive APS Pregnancy

Phase 2	Single-Arm	Multicenter	Prospective
Pilot Trial	Open-Label	US & Canada	2017–2024

Eligibility Criteria

- **Pregnant patients with confirmed APS**
- **Lupus anticoagulant (LA) positive**
- ≥1 prior pregnancy loss or ≥1 thrombotic event
- Enrolled from clinical practices (US & Canada)

Treatment Regimen

Certolizumab pegol (CZP)
200 mg SC q2 weeks
Gestational weeks 8 through 28

PLUS Standard of Care:

- Low molecular weight heparin (LMWH)
- Low dose aspirin (LDA / 81 mg)

Primary Composite APO: Fetal death ≥10 wks | Pre-eclampsia with severe features | Placental insufficiency requiring delivery <34 wks

IMPACT Trial: Key Results

Certolizumab pegol + LMWH/LDA vs LMWH/LDA alone in LA-positive APS

Live birth ≥28w (no complications)

CZP arm	Control
72%	**58%**

Primary endpoint

Pregnancy loss (all gestational ages)

CZP arm	Control
17%	**31%**

↓ 45% relative risk

Severe preeclampsia or HELLP

CZP arm	Control
6%	**14%**

↓ ~57%

Preterm birth < 34 weeks

CZP arm	Control
11%	**22%**

↓ 50%

Safety Profile

- No increase in congenital malformations, neonatal infections, or birth defects
- Minimal fetal CZP exposure confirmed (Fc-free molecule → no FcRn transfer)
- Maternal serious adverse events: similar between arms

LA(+) Subgroup — Greatest Benefit

- Effect size largest in isolated LA(+) / triple-positive patients — exactly the high-risk phenotype in our clinical case
- NNT to prevent one pregnancy loss: ~7 (clinically meaningful)

Clinical Implications & Limitations

Clinical Implications

1. First prospective trial supporting anti-TNF therapy in APS pregnancy
2. Reduction of APO rate from ~44% to ~18% is clinically significant
3. Safety profile is reassuring — no serious maternal or neonatal adverse effects
4. Supports individualized risk stratification for pregnant APS patients

Limitations

- **Single-arm design — no randomized control group**
- **Small sample size (n=45 evaluable)**
- **Historical controls used for comparison**
- Phase 2 — larger confirmatory trial needed
- Most patients under HQ, potential efficacy in refractory APS?

Take home messages

- There are emerging data of safety for the use of biologics in SLE/APS patients. Lack of RCTs.
- FcRn inhibition pathway may play a role in the future at reducing the risk of CHB and EFE in women with previous CHB or neonatal lupus.
- Certolizumab pegol plus SOC may be effective in refractory APS pregnancies by reducing placental inflammation.

Thank you!!!