

RISKS in normal and SLE women

	Normals	SLE
Maternal deaths	1/8000	1/8000
Cong. Abn.	2-3%	2-3%
Ab. < 10 wks	20%	9-35%
Late fetal deaths	3-5%	5-20%
Prematurity	10%	25-50%
< 34 wk	5%	?
IUGR	1-5%	12-30%

Normal pregnanciesL SLE; and Scleroderma?

WHAT WE KNOW : retrospective

Small case series and case reports

resulted in negative outcomes (Giordano M Arthritis Rheum 1985; Black CM Rheum Dis Clin North Am 1989; Maymon SR Obstet Gynecol Surv 1989; Slate WG Am J Obstet Gynecol 1968; Siamopoulou-Mavridou A Ann Rheum Dis 1988).

“Pregnancy in a patient with Scleroderma must be considered a serious and at least potential lethal situation” (Cook 1976)

Larger retrospective studies (Steen, 1999):214

women with SSc, 167 RA, 105 healthy controls:

- Increase in premature births and small full term infants.
- No difference in infertility (=never pregnant) after adjustment for contributing factors (never married, sexually inactive, choice not to have children)

With the mean age of onset of scleroderma symptoms in the early 40s, almost half of the women with this illness have the potential of becoming pregnant after the onset of their illness. Years ago, most women would have completed their pregnancies prior to this age, but more recently, women are frequently delaying pregnancy. Thus, there is an increased likelihood for a concurrent pregnancy in women who develop scleroderma early in their adult life.

WHAT WE KNOW: prospective

Steen, *Obstet Gynecol* 1999.

59 women, 91 pregnancies over 10 years.

Questionnaire based.

No increase in miscarriages, except in long standing diffuse scleroderma

Prematurity: 29% (all but one infants survived)

Raynaud improved

Esophageal reflux worsened

3 renal crisis, in early diffuse scleroderma

Large administrative database:

- Chakravarty et al. *Obstet Gynecol*, 2008 (not possible to identify single patients):
- SSc was associated with an increased risk of:
 - - hypertensive disorders including preeclampsia (OR 3.71),
 - - IUGR (OR 3.74, 95%CI 1.51-9.28),
 - - increased length of hospital stay.

**IMPRESS: the Italian
Multicentric study on
PREGNANCY in Systemic
Sclerosis**

**A MULTICENTRIC STUDY
OF > 100 PREGNANCIES**

Arthritis Rheum. 2011 Dec 28. [Epub ahead of print]

So we had studies from 1999, questionnaire based or from large administrative database, and the argument was somehow neglected in the pregnancy meetings. Italian pts asked us some more answers

WOMEN

- Data prospectively collected one year before pregnancy, during each trimester and after delivery were retrospectively analysed.
- 25 Italian centers prospectively followed 109 pregnancies in 99 women from 2000 to 2010
- Mean age at conception: 31.8 yrs
- Duration of disease at conception: 60 months (2-193)
- 102 ACR criteria, 54 limited (lSSc) and 48 diffuse (dSSc) cutaneous SSc;
- 6 early SSc.

	SSc	GOP	SLE
N.pregnancies	109	3939	147
Pregnancy loss (<10 wk)	6% (4%)	8% (5%)	15% (9%)
Prematurity (<34wk)	25% (10%)	12% (5%)	17% (2%)
Mean gest Age	36 wk	38 wk	38 wk
Mean maternal age	31.8 yrs	30.9 yrs	30 yrs
Cesarean sections	52% P<0,01	31%	50%

Prematurity is the first recognized cause of neonatal mortality and long-term neurological impairments in children.

	SSc (109 pregn)	GOP (3939 pregn)	SLE (147 pregn)
IUGR	6% P=0.001	1%	1%
Preeclampsia/ hypertension	2%	4%	7%
Renal crisis	1% after delivery	-	
Therapeutical abortions	4%	nd	1%
Very low birth weight < 1500 g	5% P=0.002	1%	Nd
SGA	11%	10%	9%

**Hazard Ratios for prematurity in SSc women
in IMPRESS study in the Cox Proportional Hazards Model.**

Risk Factor	Hazard ratio	95% CI	p
Anti Scl70	0.26	0.08-0.85	0.013
Folic acid	0.30	0.10-0.91	0.026
Corticosteroids	3.63	1.12-11.78	0.048

In multivariable analysis (including IUGR, very low birth weight, aSCL-70, corticosteroids, folic acid), only corticosteroids were associated with preterm deliveries, while folic acid was protective and so were aSCL-70 antibodies

- Diffuse vs Limited cutaneous:

**NO SIGNIFICANT
DIFFERENCE IN PREGNANCY
OUTCOMES**

SEVERITY OF DISEASE?

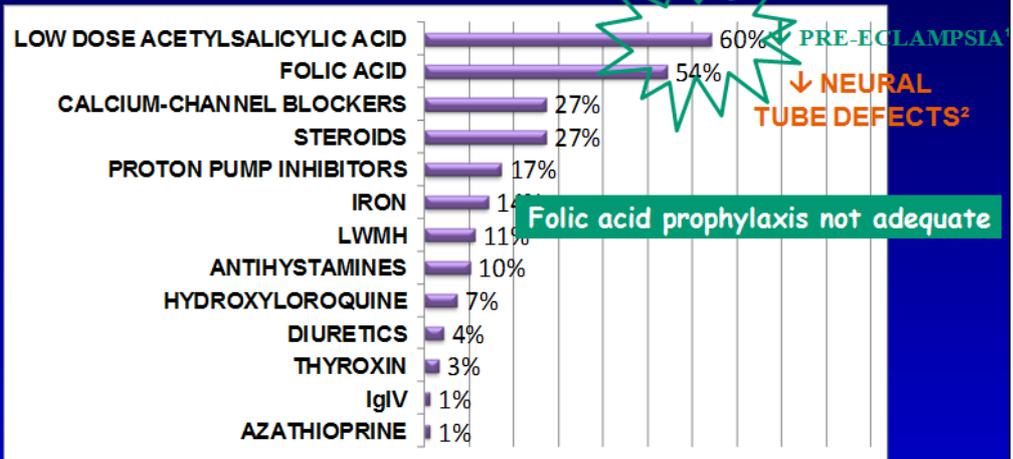
>3 Medsger disease severity scale

No patient had pulmonary hypertension (PAH) (mean PAP>25mmHg), severe renal or cardiac involvement at baseline

2 women had a severe gastrointestinal disease: 1 IUGR and preterm CS

3 women had severe lung fibrosis: no obstetrical complication.

THERAPIES



¹ *Bujold E et al. Acetylsalicylic acid for the prevention of preeclampsia and intra-uterine growth restriction in women with abnormal uterine artery Doppler: a systematic review and meta-analysis. J Obstet Gynaecol Can 2009; 31(9): 818-26.*

² *Wolff T et al. Folic acid supplementation for the prevention of neural tube defects: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2009; 150(9): 632-9.*

PREGNANCY INFLUENCE ON DISEASE

SKIN (mRSS): stable 69%; worsened 15% (from 7,7 to 15)

ULCERS: stable 74%, improved 22%

RAYNAUD: stable 63%, improved 32% (III Trim.)

Arthralgia/Arthritis: stable 88%

Esophageal reflux : stable 75%, worsened 19%

DYSPNEA: stable 88%; worsened 10%

SPIROMETRY: stable 79%

HEART: echocardiography stable 96%

The disease remained stable during pregnancy and in the subsequent year in most SSc patients (Table 3), but there were some noteworthy changes. In 15% (17 patients: 12 dcSSc, 4 lcSSc 4, 1 early) the mRSS was significantly worse after pregnancy, rising from a mean of 7.7 to 15. Raynaud's phenomenon temporarily improved (32%) from the second trimester and a similar improvement was observed for digital ulcers (22%); these benefits were lost after delivery. Dyspnea temporarily worsened during pregnancy in 10% of women (two with lung involvement), but none had any organic pulmonary progression. Assisted fecundation procedures were not related to any disease progression.

Disease evolution? After delivery: 4/99 women

Pt	Disease duration	Baseline organ damage	Ab	Complication	Time from delivery	Evolution
O.M.	4 months	lung	aSCL 70	Pulmonary hypertension	9 months	No response to therapy; waiting for lung Tx
C.S.	28 months	Ventricular arrhythmias	aSCL 70	Worsening of VA	1 months	ICD implant, but no discharge
D.F.	12 months	none	aSCL 70	Myocarditis and heart failure	6 months	CS+CTX, AZA. Improvement.
B.C.	60 months	none	aSCL 70	Renal crisis	1 months	High dose ACE I, Bosentan, transient dialysis.

3/23 (13%) aSCL70 + pts with early disease (<3 yrs) had some form of progression. RISK FACTORS??

In all, 13% (3/23) of aSCL-70 positive patients with disease lasting less than three years had some form of progression after delivery.

IMPRESS: CONCLUSIONS

- Total pregnancy loss low (6%)
 - Prematurity high (25%): CS risk factor, while Folic acid and aSCL70 protective
 - **Folic acid** (Czeizel: Possible association of folic acid supplementation during pregnancy with reduction of preterm birth: a population-based study. Eur J Obstet Gynecol Reprod Biol 2010)
 - Increase in IUGR and very low birth weight (<1500 g)
 - = **SIMILAR to SLE, APS, etc.**
-
- Mild improvement in Raynaud
 - Mild worsening of G.I. symptoms
 - Progression of the disease during or after pregnancy is rare but possible



avoid pregnancy in cases of severe organ damage and postpone it in cases of early SSc. Remember folic acid and low-dose ASA

Following the above listed recommendations these women too may experience a natural but extraordinary event: to have a child.

Pre-conceptual counselling

- Assessment of organ damage; PAH absolute contraindication
- length of disease (>3 yrs),
- Therapy (MTX, MMF); restrict use of CS
- Folic acid supplementation!
- antibodies: anti-topoisomerase and anti RNA Polymerase III more aggressive disease, but anti-centromere and rare Abs might be a risk for prematurity. aPL

During pregnancy

- High-risk obstetric care, including neonatologists
- Cautious use of proton pump inhibitors, anti H1 or Ca⁺ channel blockers; low dose aspirin; folic acid.
- Avoidance of corticosteroids as much as possible
- Monitoring of fetal growth, uterine and umbilical arteries flows
- Frequent blood pressure monitoring, aggressive treatment of any hypertension (preeclampsia or other)
- Close observation and treatment for premature labor (avoid beta-adrenergic agonists)

Labor and puerperium

- Epidural **anesthesia** is preferred
- Special **warming** of delivery room, intravenous fluids, patients themselves (e.g., extra blankets, thermal socks, gloves)
- Venous access before delivery
- Careful attention to the episiotomy and cesarean section incisions, which generally heal without difficulty
- Continued **monitoring postpartum, with early reinstatement of medication** and aggressive treatment of hypertension if it is present (don't assume it will resolve following delivery)

IMPRESS investigators



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IMPRESS 2: International Multicentric Prospective study on Pregnancy in Systemic Sclerosis

- Design: prospective, multi-center case-control study; at least 100 pregnant scleroderma women. Europe/USA
 - Three samples will be studied:
 - SSc pregnant women
 - SSc NON pregnant women matched for age, Abs, type of disease
 - Pregnant normal women
- Formal assessment also of the infants

After finishing IMPRESS 1, we now have a dream: IMPRESS 2, hoping useful for pts and their family and that women will be happy to be enrolled in this study

