Pregnancy in systemic sclerosis (SSc): results of systematic review and meta-analysis

Jelena Blagojevic[1], Khitam Abdullah AlOdhaibi[2], Aly M Aly[3], Silvia Bellando–Randone[1], Gemma Lepri[1], Cosimo Bruni[1], Alberto Moggi-Pignone[4], Serena Guiducci[1], Federico Mecacci[5], Marco Matucci-Cerinic[1], Daniel E Furst[6]

[1]Department of Experimental and Clinical Medicine, University of Florence, and Department of Geriatric Medicine, Division of Rheumatology and Scleroderma Unit AOUC, Florence Italy

[2]Department of Family Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

[3] Faculty of Medicine, Alexandria University, Alexandria, Egypt

[4]Department of Experimental and Clinical Medicine, University of Florence, and Department of Emergency, Division of Medicine IV AOUC, Florence, Italy

[5]Department of Maternal-Neonatal Care, DAIMI, Careggi University Hospital, Florence, Italy

[6]Los Angeles, USA UCLA (emeritus); University of Washington, Seattle, Washington; University of Florence, Florence, Italy

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Corresponding author:

Jelena Blagojevic

Address: Department of Experimental and Clinical Medicine, University of Florence, and Department of Geriatric Medicine, Division of Rheumatology and Scleroderma Unit AOUC, Florence, Italy, Villa Monna Tessa, viale Pieraccini 18, 50139 Florence, Italy

Tel +393496615873

Fax + 39055431420

Mail: jelena308@hotmail.com

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J Blagojevic[1], MD, PhD, K A AlOdhaibi[2], MD, A M Aly[3], MBBch, S Bellando-Randone[1], MD, PhD, G Lepri[1], MD, Alberto Moggi-Pignone[4], MD, PhD, S Guiducci[1], MD; PhD, F Mecacci[5], MD, PhD, M Matucci-Cerinic[1], MD, PhD, Daniel E Furst[6], MD

ABSTRACT

OBJECTIVES: Through a systemic literature research (SLR) and meta-analysis, to determine maternal and foetal outcomes in SSc pregnancies, to analyse the effect of pregnancy on disease activity and to explore predictors of foetal and maternal outcomes.

METHODS: A SLR was performed for articles on SSc and pregnancy published between 1950 and 1st February 2018. Reviewers double extracted articles to obtain agreement on>95% of pre-defined critical outcomes.

RESULTS: 461 publications were identified, 16 were included in the meta-analysis.

The metanalysis showed that SSc pregnancies were at higher risk of miscarriages (OR 1.6,CI95% 1.22-2.22), foetuses with intrauterine growth retardation (IUGR) (OR 3.2,CI95% 2.21-4.53), preterm births (OR 2.4,CI95% 1.14-4.86) and newborns with low birth weight (OR 3.8,CI95% 2.16-6.56).

SSc patients had 2.8 times higher chance of developing gestational hypertension (OR 2.8,CI95% 2.28-3.39) and 2.3 times higher chance of having Caesarean delivery compared to controls (OR 2.3,CI95% 1.37-3.8).

The definitions of disease worsening/new visceral organ involvement were too inexact to have any confidence in the results although there were said to be worsening or new disease manifestations during pregnancy in 44/307(14.3%) cases and during the 6-months post-partum in 32/306(10.5%) cases. The data did not permit definition of predictors of disease progression and of maternal and foetal outcomes.

CONCLUSIONS: SSc pregnancies have increased frequency of miscarriages, IUGR, pre-term deliveries and newborns with low birth weight compared to healthy controls. SSc women were more prone to develop gestational hypertension and to undergo Caesarean section. Disease manifestations seem to remain stable or improve in most patients.

INTRODUCTION

Systemic sclerosis (SSc) is a complex autoimmune disease characterized by small vessel vasculopathy, immune system activation and fibrosis (1), leading to skin and internal organ involvement. SSc has a strong female predominance (2) and women can be affected in their childbearing age, potentially leading to adverse pregnancy outcomes. Therefore, the ability to carry a pregnancy to a safe conclusion may be important to the quality of life and well-being of SSc patients (3).

Several studies, mainly retrospective and/or questionnaire-based, on foetal and maternal outcomes in SSc patients have been reported. Earlier manuscripts, published before 1990, showed high rates of pregnancy-related maternal mortality and morbidity and an increased frequency of miscarriages and fetal loss (4-6). More recently, a better outcome has been described with mostly successful pregnancies, but an increased risk of premature births (7-11), intrauterine growth restriction (IUGR) (10,12) and low-birth weight (7,8,10) have also been reported.

Data on maternal adverse outcomes are limited. Ismail at al reported an increased prevalence of pre-eclampsia in a small observational study of 20 pregnant SSc patients and 20 age-matched healthy controls (13). This finding was not confirmed in an Italian multicentre study including 109 SSc pregnancies (10).

No significant changes in maternal SSc disease activity have been described during pregnancy (7,14,15). Still, SSc is considered a condition at increased risk of pregnancy complications and maternal and fetal morbidity. In particular, patients with early diffuse cutaneous SSc (< 4 years of disease duration) (7), anti-topoisomerase I or anti-RNA polymerase III positive (16,17) and use of corticosteroids (10) seem to be at higher risk for obstetric complications. To date no clear predictors of adverse fetal and maternal outcome have been identified.

The aim of this study was to assess maternal and fetal outcomes in SSc pregnancies, to analyse the effect of pregnancy on SSc disease activity and to explore whether there are predictors of fetal and maternal outcomes. The study was conducted with a PRISMA-driven systematic review and meta-analysis of the published literature.

MATERIALS AND METHODS

A systematic literature search (SLR), according to the PRISMA recommendations (18) was performed in four different data bases: PubMed, Cochran, EMBASE and Web of Science for articles published in peer-reviewed journals between 1950 and 1st February 2018 in English and Italian. All articles reporting on SSc and pregnancy were examined. The keyword search terms included: systemic sclerosis OR scleroderma, AND pregnancy.

A written protocol for data search and extraction was prepared (supplementary data file 1). Studies were eligible if they met the following inclusion criteria: pregnancies occurred after disease onset, the article included solely SSc patients or the SSc patients and their outcomes were able to be separated from patients with other conditions and there was at least one clinical outcome of interest. Studies could be randomised clinical trials, retrospective or observational studies, registries, case series with and without controls and case reports with ≥ 10 pregnancies. The exclusion criteria were: non-human studies, articles including only patients with overlap syndrome by ACR/EULAR classification criteria and case reports including < 10 pregnancies.

Full-text articles were included as were abstracts if they contained enough clinical data required for the SLR. The bibliographies of the articles were also evaluated for additional references. Reviews were listed and examined for articles in the bibliography that were not surfaced during the SLR; the reviews per se were not extracted.

Ethics approval was not required since the study did not include human and/or animal subjects.

A dedicated research librarian (BM) performed the systematic literature search. Two reviewers (KA and JB) screened all articles for inclusion/exclusion criteria and agreement was obtained on all of them. The same two reviewers (KA and JB) double extracted articles, with a third reviewer (DF) resolving differences, to: (1) obtain agreement on> 95% of pre-defined critical outcomes and >90% of the other variables; (2) maintain quality assurance; (3) screen and extract data.

The studies that met inclusion criteria and were not excluded were extracted in an electronic data-base for descriptive variables, SSc disease activity, relevant clinical outcomes, and for effect of pregnancy on maternal and fetal outcomes. Data on pregnancies in controls were also extracted, where available.

Summary of included outcomes (see supplementary Table 1S for details):

1) Fetal outcomes: miscarriage (generally fetal loss < 20 weeks), stillbirth/perinatal death, (generally fetal loss ≥ 20 weeks or < 4 weeks of life), IUGR (estimated fetal weight <10th percentile), premature delivery (birth occurring before < 37th week of pregnancy), low birth weight (< 2,500 grams at birth), small for gestational age (weight <10th percentile for age) and congenital malformations. We included only spontaneous abortions among miscarriages, where this information was available.
2) Maternal outcomes: maternal death, eclampsia or preeclampsia and their components. The rate of Caesarean deliveries was also assessed. In addition, rates of gestational hypertension and diabetes were recorded.

Since none of the selected articles specifically reported SSc activity indexes, disease activity was determined by assessing the proportion of pregnancies in which disease/single organ manifestations worsened/improved/remained stable during pregnancy and within 6 months post-partum, as reported in the included studies. The occurrence of new organ manifestations was considered as worsening. The number of studies in which the disease/organ manifestations

worsened/improved/remained stable during and after pregnancy were also listed to allow the reader to understand the strength of the data analysed. Definitions of disease activity and organ involvement, where available, are reported in supplementary data file 2.

Analysis

For the continuous variables descriptive analysis included means and standard deviations; for the categorical variables, proportions and percentages have been reported. Quality and risk of bias assessment was performed by JB using the Newcastle-Ottawa Scale (NOS) (19).

Since not all the studies reported all the maternal and fetal outcomes, separate meta-analyses were performed for each outcome. Publication bias was assessed by visual inspection of funnel plots.

In addition, other potential sources of bias (recall bias for studies based on questionnaire, not uniform classification of SSc and definition of maternal and fetal outcomes across the studies) were considered (reported in supplementary data file 2) and causes of publication bias were investigated.

The heterogeneity across the studies was assessed by Woolf's test (there was significant heterogeneity for the p values < 0.005). The Random effects (DerSimonian-Laird) meta-analysis model was used to estimate the pooled effect for results with significant heterogeneity. Fixed effects (Mantel-Haenszel) meta-analysis model was applied if there was no heterogeneity across the studies analysed. Each meta-analysis provides a pooled odds ratio and its 95% confidence interval.

Data were analysed by R Studio version 1.2.1.

RESULTS

461 publications were identified. Sixteen studies meeting the inclusion criteria were included in the data SLR and meta-analysis (supplementary figure 1S).

The summary of the characteristics of 16 included studies is shown in supplementary Table 2S. Seven articles had no controls and one article was only in summary form, so these articles were not quantifiable by the NOS criteria. In the other eight, one was of high quality, four were medium quality articles and 3 were of low quality (supplementary Table 3S).

Funnel plots describing publication bias are shown in supplementary figures 2S-10S (it was not possible to assess the publication bias for articles reporting maternal death and eclampsia because so few studies were available). The year of publication did not impact the publication bias. A total of 1,403 pregnancies in the SSc group and 12,196,221 pregnancies in the healthy controls group were analysed. Clinical characteristics of SSc pregnant patients are shown in supplementary Table 4S. Disease duration was just over seven years. All of them had skin involvement before pregnancy (where reported) and 47.5% had diffuse cutaneous disease. Reports of visceral involvement were uncommon.

Disease treatment during pregnancy could not be reliably ascertained because there were so few patients in whom it was described (30/461 patients) and even there the definitions were variable and inexact.

Description of maternal and fetal outcomes in SSc patients across single studies is shown in supplementary Table 5S.

The results of the meta-analyses of the studies reporting different fetal outcomes are shown in the figures 1, 2, 3 and 4 and supplementary figures 11S, 12S and 13S. There was no significant heterogeneity across the studies, except among the studies on premature deliveries.

SSc pregnancies ended in miscarriages 1.6 times more often than control pregnancies (odds ratio (OR) 1.6, CI 95% 1.22-2.22) (Figure 1). Fetuses of SSc women had 3.2 times higher chance of having IUGR (OR 3.2, CI 95% 2.21-4.53) than controls (Figure 2). Newborns of SSc mothers had a 2.4 times higher risk of being premature deliveries (OR 2.4, CI 95% 1.14-4.86) (Figure 3) and a 3.8 times higher chance of having low birth weight (OR 3.8, CI 95% 2.16-6.56) (Figure 4).

The results of the meta-analyses of the studies reporting different maternal outcomes are shown in the figures 5, 14S, 15S and 16S. There was no increased risk of pre-eclampsia in pregnant SSc women compared to controls (Figure 5). SSc patients had a 2.8 times higher chance of developing gestational hypertension (OR 2.8, CI 95% 2.28-3.39) (Figure 14S) but not diabetes (Figure 15S), and a 2.3 times higher chance of having Caesarean delivery compared to controls (OR 2.3, CI 95% 1.37-3.8) (Figure 16S).

There were too few articles reporting on maternal death and eclampsia in SSc patients to perform meta-analyses on those outcomes.

Disease activity remained stable or improved in most SSc patients. One or more disease manifestations worsened or appeared during pregnancy in 44/307 (14.3%) cases. In 32/306 (10.5%) pregnancies, SSc manifestations worsened or appeared during the 6-months post-partum period. In two reported cases, this worsening led to maternal death, due to scleroderma renal crisis (1) and aspiration pneumonia complicated by respiratory and multiorgan failure (1). Data on worsening and improvement of SSc and its single organ manifestations, extrapolated from the studies included in the meta-analysis are summarised in table 1 (for more details see supplementary tables 6S and 7S).

It is important to note that, except for overall disease activity, data on visceral involvement during and after pregnancy were documented in less than 50% of the studies (Tables 6S and 7S)

and the definitions were variable and inexact, so it is not possible to confidently ascribe specific visceral changes that might have occurred.

DISCUSSION

This is the first systematic PRISMA-based review and meta-analysis that specifically addresses maternal and fetal outcomes and impact of pregnancy on disease activity in SSc pregnancies that occurred after the disease onset.

There are a number of review articles on pregnancies in autoimmune connective tissue diseases, but few of them specifically addressed SSc pregnancies (3,12,14,15,17,20-26). None were systematic literature reviews, several were done more than 20 years ago when diagnostic criteria were not as uniform (14, 20-23) and the number of studies available for review were even fewer than today.

To allow some context, we compared maternal and fetal outcomes in SSc pregnancies versus healthy women/general obstetric populations by quantitative analysis of published data. We also examined, for the first time, disease activity in the 6-months post-partum period.

Our systematic literature review and meta-analysis indicate that SSc pregnancies have an increased prevalence of miscarriages, IUGR, preterm births and newborns with low birth weight, but not small for gestational age, compared to pregnancies in healthy controls.

Sobanski et all's review reported that the rates of miscarriages were not increased in SSc pregnancies (17). However, they included studies on pregnancies which occurred both before and after disease onset and no meta-analysis was performed. Moreover, other maternal and foetal outcome were not analysed in detail.

Betelli et al recently published a review focused on maternal and fetal outcomes in SSc pregnancies, occurring after the disease onset (3). They concluded that the risk of miscarriages in SSc women

which were followed as high-risk pregnancies was comparable to the healthy population (3). However, this review was not based on a systematic literature research, no meta-analysis was performed, and no conclusion was made for SSc women not followed as high-risk pregnancies.

On the other hand, an older review by Scarpinato, which included only case reports and one case series published from 1932 to 1984, reported 23% of near-term fetal death in SSc pregnancies (22). Their data is probably skewed by the nature of the data, case reports and series. On the contrary, the rate of late fetal loss was low in our meta-analysis (4.4%).

Regarding other fetal outcomes, premature births and IUGR were also more frequent in SSc pregnancies according to Betelli's review (3). A possible reason for these adverse fetal outcomes could be the impairment of placental vascularisation as part of SSc related vasculopathy (27).

Scarpinato reported high maternal mortality (15% of 82 women with SSc included in their review) (22). The main cause of the maternal death was accelerated hypertension (most likely scleroderma renal crisis, although not specified). However, the author noted that case reports were likely biased towards more severe outcomes because pregnancies with normal outcomes were probably reported less frequently compared to those leading to maternal or fetal loss. In our literature review, SRC was often not mentioned, but, when mentioned, was documented in only 1-3% of pregnancies. This is not greatly different from the literature in a recent, meta-analysis of the non-pregnant SSc population (4%) (28). This comparison must be viewed in the context of the lack of mention of SRC in our literature review, thus making it possible that the 1 – 3% represents underreporting.

The data regarding maternal mortality were too scarce to perform a meta-analysis. There were 3 studies (all published before 2000) that reported maternal death in 4 patients (1.3%) (4,7,29). The causes of the deaths were: scleroderma renal crisis (1), aspiration pneumonia complicated by

respiratory and multiorgan failure (1), viral pneumonia (1) and bronchopneumonia complicated by congestive heart failure (1).

Our meta-analysis indicates that SSc women had a greater chance of developing gestational hypertension. However, they were not at increased risk of pre-eclampsia, different from expected. This is different from expected as pregnancy-induced hypertension, pre-eclampsia and SSc are all related thru endothelial dysfunction so one would expect that hypertension and pre-eclampsia would be corelated (1,30). The reasons that SSc pregnancies seem to be at higher risk of gestational hypertension but not of pre-eclampsia, have to be investigated.

Our results show that Caesarean sections were more frequent in SSc pregnancies compared to controls. One of the reasons for this increase might be the fact that SSc patients are considered at risk of disease-related musculoskeletal alterations of the pelvic region and thus were referred to Caesarean deliveries more frequently.

We attempted to evaluate the effect of pregnancy on SSc disease activity, based mainly on the descriptions available in single articles and reported as patients' or authors' judgement of disease activity. None of the studies used standardized disease activity indexes and the descriptions were variable and often very inexact. The analysis of available data indicates that overall disease activity, however defined, appeared to remain stable or improved during pregnancy in most cases. Peripheral vascular manifestations such as Raynaud's phenomenon, digital ulcers, skin and articular involvement appeared to remain stable or improved during pregnancy, as already suggested by previous reviews on this topic (17,25).

The same limitations applicable regarding disease activity during pregnancy also applied to the 6-months period post-partum. Within those limitations, inherent in the data, overall disease activity, peripheral vascular and skin manifestations appeared to remain stable or improved in the majority of the cases.

Unfortunately, we could not perform an analysis of the impact of pregnancy on other SSc manifestations, such as interstitial lung disease, scleroderma renal crisis, heart involvement or pulmonary arterial hypertension, due to the small number of cases described in the articles.

Betelli et al reported, in their recent review, that "overall disease activity" was generally stable during pregnancy (3). According to these authors, cardio-pulmonary involvement, including PAH, also remained stable, but this statement was based only on data of the IMPRESS study (Italian multicentre retrospective study on 109 SSc pregnancies followed from 2000 to 2011) (3).

It has been reported that patients with early diffuse SSc and severe organ involvement are at higher risk of developing adverse maternal and fetal outcomes (8,16,17). In our pooled analysis of the literature, half of the patients had diffuse cutaneous subset, the mean disease duration was 7 years and ILD was present in 17% patients before pregnancy. Only 0.8% of patients had PAH and 1.3% had a history of SRC before becoming pregnant, thus making it likely that these data represent underreporting.

One of the objectives of this study was to investigate predictors of maternal and fetal outcomes. To make predictions there needed to be full descriptions of disease manifestations during pregnancy as well complete descriptions of outcomes post-partum. In addition, the medications used during and after pregnancy needed to be complete. Unfortunately, none or very few of these data were available in the available literature. The data of the IMPRESS study showed that corticosteroid use was associated with preterm deliveries, whereas folic acid supplementation and anti–Scl-70 antibodies were protective (10), but we could not examine these factors in the literature as they will rarely reported. Therefore, we were not able to construct a predictive model.

Our study has significant strengths. It was a thorough systematic literature review and meta-analysis, the first for pregnancies in SSc and documented using PRISMA principles. Data were double

extracted throughout, minimizing errors. Methods were transparent, and our interpretations were conservative, allowing the reader clarity and, hopefully, allowing our conclusions to be credible.

On the other hand, our study has some limitations. All the articles were retrospective and most included a very small number of subjects, although this shortcoming will be difficult to overcome because pregnancies appear to be infrequent in SSc (personal observation). The meta-analyses were very limited and in some cases were based only on few studies.

The studies were carried out over nearly 50 years and the definition of SSc changed, so it was not clear that the patient populations were comparable. However, the 1980 and 2013 SSc definitions are sufficiently similar (31,32), so that it is not likely to be a major problem. Also, there was no uniform definition of maternal and fetal outcomes, although there seemed to be general agreement (eg; miscarriage defined as foetal loss before 20 weeks). There was probably a tendency to report pregnancies with worse outcomes, especially in the older case series; therefore, more contemporary studies are need. We compared SSc pregnancies to normal controls; it would be instructive to compare SSc pregnancies to other connective tissue disease. Unfortunately, these data were simply not available within the extracted SSc studies. Finally, there were incomplete data available on patient characteristics and treatments as well as measures of disease activity, so we could not credibly define the prevalence of worsening or internal organ involvement nor construct a predictive model.

In conclusion, pregnancy seems to be safe for the mother in SSc, although there seems to be an increased risk of miscarriages, IUGR, premature deliveries, newborns with low-birth weight, and gestational hypertension.

As far as could be determined with incomplete and variable data, SSc appeared to remain stable or improved in the majority of patients. About 10-15% of the patients had “worsening” or “new disease

manifestations" during and within 6 months of completing pregnancy. We could not assess the effect of SSc on major organ involvement nor could predictors of negative maternal and fetal outcomes be assessed because data were lacking.

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Legends

Figure 1 Comparison of miscarriages in SSc patients and control subjects

SSc = systemic sclerosis; N = number; OR = odds ratio; ref = reference

Figure 2 Comparison of intrauterine growth retardation in SSc patients and control subjects

SSc = systemic sclerosis; IUGR (intrauterine growth retardation); N = number; OR = odds ratio; ref = reference

Figure 3 Comparison of premature deliveries in SSc patients and control subjects

SSc = systemic sclerosis; N = number; OR = odds ratio; ref = reference

Figure 4 Comparison of newborns with low birth weight in SSc patients and control subjects

SSc = systemic sclerosis; N = number; OR = odds ratio; ref = reference

Figure 5 Comparison of preeclampsia in SSc patients and control subjects

SSc = systemic sclerosis; N = number; OR = odds ratio; ref = reference

Legends of the supplementary figures

Figure 1S Prisma flow diagram

Figure 2S Funnel plot of publication bias for miscarriages

Figure 3S Funnel plot of publication bias for stillbirths/perinatal deaths

Figure 4S Funnel plot of publication bias for IUGR

Figure 5S Funnel plot of publication bias for premature deliveries

Figure 6S Funnel plot of publication bias for low birth weight

Figure 7S Funnel plot of publication bias for small for gestational age

Figure 8S Funnel plot of publication bias for congenital malformations

Figure 9S Funnel plot of publication bias for preeclampsia

Figure 10S Funnel plot of publication bias for Caesarean deliveries

Figure 11S Comparison of stillbirths/perinatal deaths in SSc patients and control subjects

SSc = systemic sclerosis; N = number; OR = odds ratio; ref = reference

Figure 12S Comparison of newborns small for gestational age in SSc patients and control subjects

SSc = systemic sclerosis; N = number; OR = odds ratio; ref = reference

Figure 13S Comparison of congenital malformations in SSc patients and control subjects

SSc = systemic sclerosis; N = number; OR = odds ratio; ref = reference

Figure 14S Comparison of gestational hypertension in SSc patients and control subjects

SSc = systemic sclerosis; N = number; OR = odds ratio; ref = reference

Figure 15S Comparison of gestational diabetes in SSc patients and control subjects

SSc = systemic sclerosis; N = number; OR = odds ratio; ref = reference

Figure 16S Comparison of Caesarean deliveries in SSc patients and control subjects

SSc = systemic sclerosis; N = number; OR = odds ratio; ref = reference

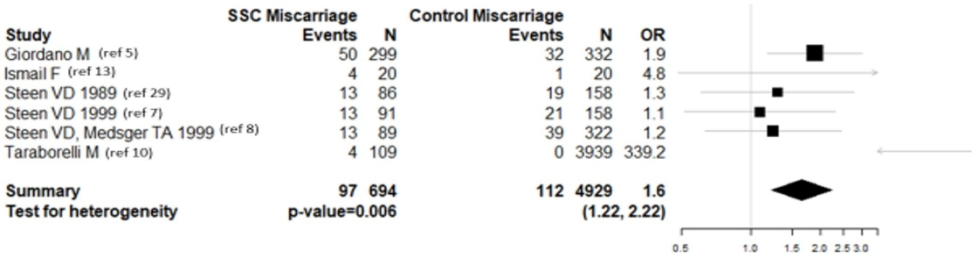

Figure 1. Comparison of miscarriages in SSc patients and control subjects
SSc = systemic sclerosis; N = number; OR = odds ratio; ref = reference

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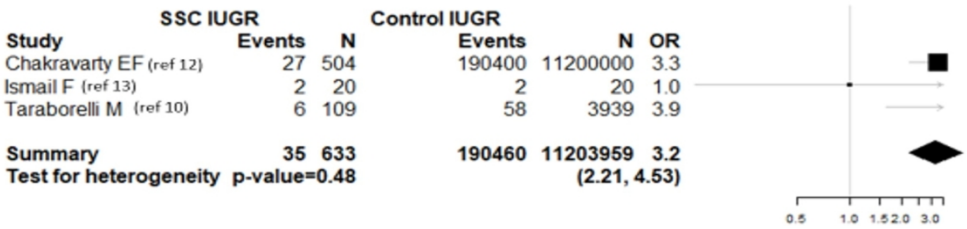

Figure 2. Comparison of intrauterine growth retardation in SSc patients and control subjects
SSc = systemic sclerosis; IUGR (intrauterine growth retardation); N = number; OR = odds ratio; ref = reference

447x110mm (119 x 119 DPI)

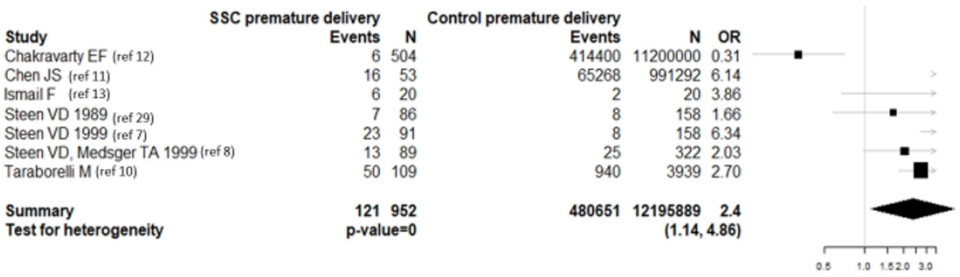

Figure 3. Comparison of premature deliveries in SSc patients and control subjects
SSc = systemic sclerosis; N = number; OR = odds ratio; ref = reference

549x175mm (119 x 119 DPI)

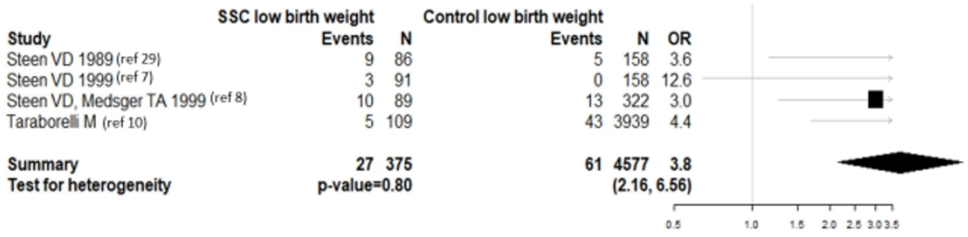

Figure 4. Comparison of newborns with low birth weight in SSc patients and control subjects
SSc = systemic sclerosis; N = number; OR = odds ratio; ref = reference

621x180mm (119 x 119 DPI)

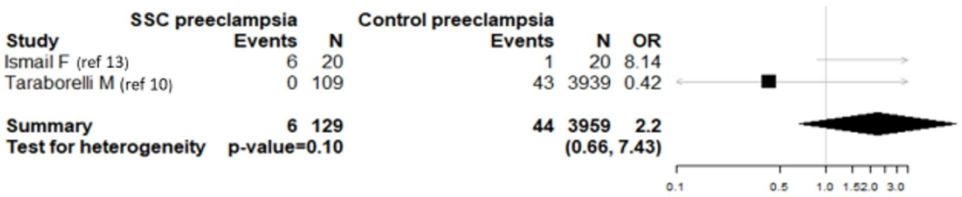

Figure 5. Comparison of preeclampsia in SSc patients and control subjects
SSc = systemic sclerosis; N = number; OR = odds ratio; ref = reference

410x96mm (119 x 119 DPI)

Table 1. Pregnancy and SSc activity: worsening and improvement

	SSc worsening		SSc improvement	
	Pregnancy	Postpartum (within 6 months after delivery)	Pregnancy	Postpartum (within 6 months after delivery)
Overall disease activity	44/307 (14.3%)	32/306 (10.5%)	41/221 (18.6%)	6/20 (30%)
Peripheral vascular (Raynaud's and/or digital ulcers)	2/12 (16.6%)	18/111 (16.2%)	77/220 (35%)	22/109 (20.2%)
Skin	3/103 (2.9%)	30/220 (13.6%)	4/20 (20%)	na
Gastro-intestinal	17/111 (15.3%)	na	na	13/111 (11.7%)
Arthritis	7/111 (6.3%)	5/91 (5.5%)	na	13/111 (11.7%)
ILD	2/118 (1.7%)	na	0/86 (0%)	na
PAH	1/20 (5%)	na	na	na
SRC	6/197 (3%)	3/286 (1%)	na	0/86 (0%)
Heart	3/177 (1.7%)	2/109 (1.8%)	0/86 (0%)	na

Percentages are relative to the number of pregnancies for which data are available in single studies

ILD = intestitial lung lung disease

PAH = pulmonary arterial hypertension

SRC = scleroderma renal crisis

na= not available