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Review article

Pregnancy Outcomes in Women with Systemic Sclerosis: A Systematic Review and Meta-Analysis

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Abstract
Systemic sclerosis (SSc) is a rare chronic autoimmune disease of the body's connective tissue. It affects women who are of childbearing age. Although there has been only one prior systematic review and meta-analysis (in 2020) addressing this issue, many additional controlled studies have recently appeared. The present analysis followed the PRISMA 2020 Guidelines for a systematic review and meta-analysis. A comprehensive literature search was conducted on all databases from the start date through 15 June 2026 without regard to language. Eligible studies were comparative observational studies that provided raw event counts regarding pregnant women with SSc compared to women without SSc. Pooled risk ratios (RR) along with 95% confidence intervals (CI) were generated using a random-effects Mantel-Haenszel method (DerSimonian-Laird). Outcomes that were reported by fewer than 3 of the included studies were summarized narratively. Heterogeneity among studies was estimated using the I^2 statistic. Thirteen controlled studies (one case-control study and twelve cohort studies; nine countries; years 1999 – 2026) qualified for inclusion. Of those thirteen, eight studies contributed to the quantitative synthesis. Pregnancies in women with SSc had significantly greater risks of developing preeclampsia (RR = 4.84 [3.05 – 7.67]; I^2 = 0%) and giving birth before term (RR = 3.39 [2.59 – 4.44]; I^2 = 39.5%) when compared to women without SSc. There was also a significantly increased risk of preterm premature rupture of membranes (RR = 3.32 [1.17 – 9.41]; I^2 = 83%), intrauterine/ fetal growth restriction (RR = 3.25 [1.65 – 6.39]; I^2 = 0%), C-sections (RR = 1.91 [1.49 – 2.46]; I^2 = 69%), and low birth-weight babies (RR = 1.48 [1.08 – 2.04]; I^2 = 33%). Studies that could not be included in the quantitative analysis due to an insufficient number of events reported similar results concerning direction. There appears to be a significant association between pregnancy in women with SSc and an elevated risk for hypertension, preterm birth, and issues related to growth and development in newborns. This finding provides further support for providing education on preconception counseling.
Keywords. Systemic Sclerosis, Pregnancy Outcomes, Meta-Analysis

Introduction

Systemic Sclerosis (SSc), is a chronic autoimmune condition, characterized by chronic progressive fibrosis in the skin and internal organs along with immune dysfunction and small vessel vasculopathy [1]. According to estimates, the prevalence of systemic sclerosis worldwide is 17.6/100,000 people. The yearly incidence of systemic sclerosis is approximately 1.4 /100,000 persons/year. Systemic sclerosis affects predominantly females with sex ratios of approximately 4-9:1 (female to male), and it peaks in the 40s and 50s [2]. As many women remain in their childbearing years at the time of diagnosis of systemic sclerosis, the number of pregnant women seeking care has increased; consequently, reproductive health planning has evolved into an essential component of managing this disease [3].

Pregnancy in women with systemic sclerosis is considered to be associated with an elevated risk. There are two major biologic pathways involved in both the vascular pathology of systemic sclerosis and in the vascular changes that support placenta formation and adaptation to pregnancy. Therefore, there exists a significant basis from a biological standpoint for increased maternal and fetal risks during pregnancy due to the vascular pathology of systemic sclerosis [3]. These risks include gestational hypertension, pre-eclampsia, premature birth, intra-uterine growth retardation (IUGR), low birth weight, and fetal loss; additionally, a higher rate of caesarean section deliveries has been reported [4]. In addition, some studies have indicated that disease-specific complications, including scleroderma renal crisis, can occur during pregnancy or after delivery and, although rare, pose considerable risks to maternal health [4,5]. Patients who also experience pulmonary symptoms, including those with pulmonary arterial hypertension, increase the maternal risk of these complications [6]. The majority of existing knowledge about pregnancy in Systemic Sclerosis (SSc) comes from individual center-based case reports or small series.

A prior systematic review and meta-analysis concerning this subject area has been performed by Blagojevic et al. in 2020. In the study, 16 other relevant studies were included in a pooled analysis. That pooled analysis demonstrated greater risks for the pregnant mother of developing pregnancy-induced hypertension, preterm birth, and intrauterine growth restriction [7]. Several additional cohort and population-based studies since that time have been published. As such, the methodology used to define outcomes, select comparators, and perform analyses at each level is changing. Thus, as new studies continue to emerge, it is appropriate to update this information with an updated synthesis. Therefore, the purpose of the current systematic review and meta-analysis was to develop an up-to-date and complete summary of the risk of adverse maternal and fetal outcomes during pregnancies in women with systemic sclerosis when compared to those who do not have systemic sclerosis. Therefore, the most recently available and appropriately controlled evidence will be incorporated into this updated analysis using explicit criteria for determining whether results can be pooled across different studies and/or levels of bias among studies.

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Methods

Search Strategy

This systematic review's conduct and reporting were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) Statement [8]. Four major databases — PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) — were systematically searched from inception to 15th June 2026 without restrictions as to publication year or language, using an extensive combination of free-text terms and Medical Subject Headings (MeSH), which used the Boolean operator AND to combine two concept blocks: Block 1 — all aspects of systemic sclerosis and its variations; and Block 2 — pregnancy, obstetrics, and fetal/neonatal outcomes. A general confirmatory web search and backward/forward citation chasing of the single prior meta-analysis [7] complemented the electronic search. The full search strategy for each database can be found in (Table S1).

Eligibility Criteria

Studies were selected for evaluation if they represented a form of comparative observational research (either prospective or retrospective cohort or case-control), contained a group of pregnant women with systemic sclerosis (as defined using either the ACR/EULAR 2013 Classification Criteria or equivalent), and included a control group representing a defined "non-SSc" comparator (healthy controls or a general/background obstetric population). Studies were also allowed to include pregnancies that occurred after or during the time of disease onset. Each study examined at least one of the relevant pregnancy outcomes of interest and provided the investigator with raw event and total counts from which the events could be extracted. Randomized Controlled Trials do not exist within this field of research.

Primary outcomes evaluated included miscarriage/pregnancy loss and hypertensive disorders of pregnancy (gestational hypertension/pre-eclampsia). Secondary outcomes evaluated included preterm birth, intrauterine growth restriction/ fetal growth restriction, low birth weight, small-for-gestational-age, caesarean delivery, live births, gestational diabetes, stillbirths, scleroderma renal crises, and worsening of maternal disease status peripartum/postpartum. Exclusion criteria included E1: If the population was not individuals diagnosed with systemic sclerosis; E2: if there were no reported pregnancy outcomes or if the study utilized a reverse direction/design (i.e., mechanistic), including microchimerism studies; E3: if no comparison arm existed; E4: if the study was classified as ineligible due to being a review, letter/editorial, case report/case series less than five patients, or conference abstract without access to the full text; E5: if the study population consisted of duplicated data/overlapping datasets; in those cases the investigators retained the larger/more comprehensive report; and E6: if only fertility/hormonal outcomes were reported. Investigators judged whether a study could be pooled based upon four specific criteria: extractable data; presence of a valid comparison arm; presence of outcomes common among all studies included in the analysis; and identical definitions/scales used when reporting these outcomes. Studies that met inclusion criteria but did not meet all criteria for pooling were summarised through narrative means.

Study Selection and Data Extraction

The original list of references from PubMed was screened using a two-step process by two independent reviewers based upon predefined inclusion/exclusion criteria. During the first step (abstract/title screening), an abstract/report was removed for exclusion if both reviewers agreed that it had no relevance to the systematic review being completed. If either or both reviewers disagreed/expressed doubt as to whether the report met the inclusion/exclusion criteria, then the abstract/report was moved forward to a full-text screening. During the second step (full-text screening), two independent reviewers evaluated the potentially relevant literature identified during the title and abstract screening. An article/study was considered included in the meta-analysis only when both reviewers agreed that it fulfilled all of the inclusion criteria; however, if either reviewer felt that there was sufficient doubt about meeting these criteria, they began a discussion and/or initiated contact with a third reviewer. All data extraction was performed by two independent reviewers utilizing a previously developed Excel sheet (Microsoft) designed specifically for this purpose. Data fields that were used for analysis included but were not limited to: study name/year, country of origin, study design, duration of study, number of pregnancies in SSc vs. control groups, type of comparison group, SSc skin disease type (diffuse/limited), maternal age, and pregnancy outcomes as reported in each individual study.

Risk of Bias Assessment

The risk of bias in this review was assessed using the Newcastle-Ottawa Scale (NOS) [9], which is a validated tool to assess the quality of observational studies, including cohort and case-control designs. Studies are assessed at the item level within the NOS across the selection, comparability, and exposure/outcome domains. Three reviewers contributed to the quality assessments. Two reviewers independently reviewed all of the included studies, and the third reviewer resolved any disagreements between them.

Statistical Analysis

The analyses used for this systematic review were performed in R (meta package version 4.4.2) [10]. All analyses were completed using a random-effects model. For those outcomes measured as dichotomies, the RR with CI was chosen as the primary measure of effect. Risk Ratios (RR) were then calculated using the Mantel-Haenszel method, which is a fixed-effect model. However, since we chose to use a random-effects model to pool our results, we did so by estimating the

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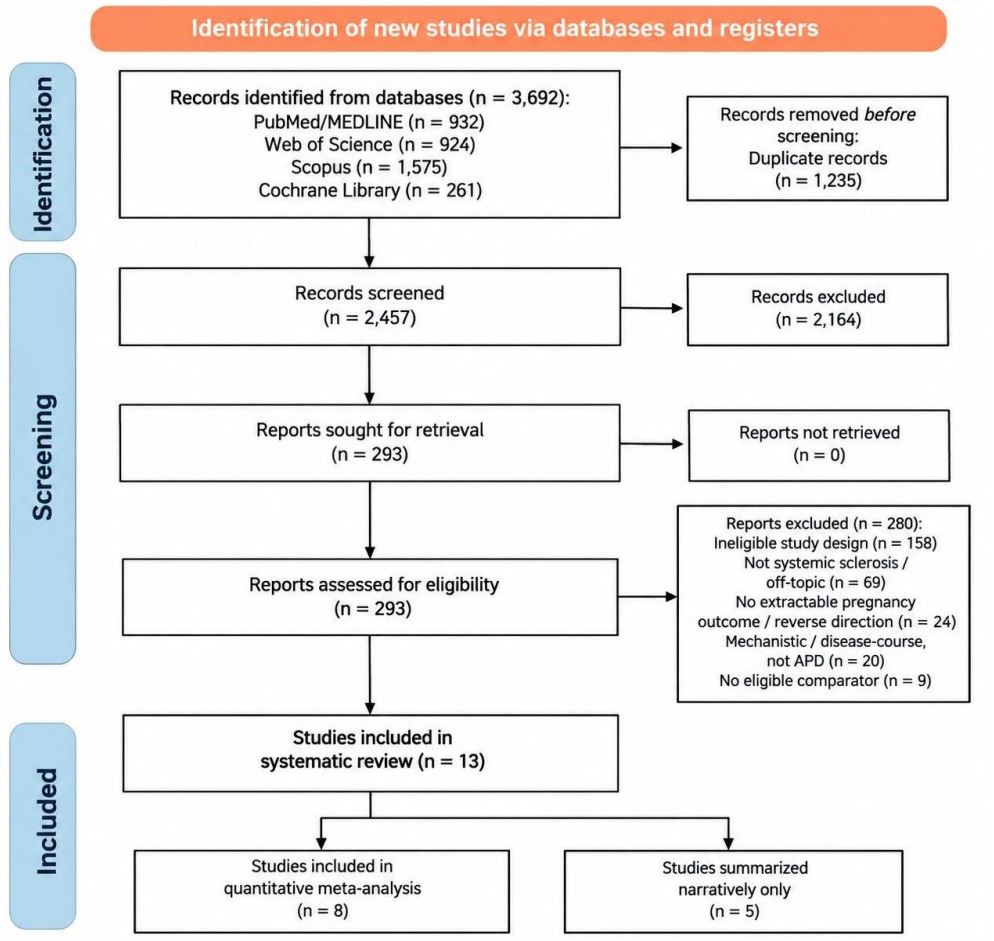
DerSimonian-Laird method [11] for the between-study variance. When pooling outcomes, there had to be at least 3 studies reporting the same definitions and scales. When fewer than three studies reported the same definitions and scales, we were unable to create a pooled estimate. Therefore, these outcomes were summarized using narrative summaries rather than being pooled. We also assessed statistical heterogeneity among the included studies using both Cochran's Q-test and the I squared statistic.

Results

Study Selection

There were 1,235 duplicate citations found that were removed, and therefore 2,457 citations remained that were screened using title/abstract. Of these, 2,164 citations were removed based on established inclusion/exclusion criteria. Following this process, 293 citations were selected for full-text review, with 280 of those citations being removed due to established eligibility criteria. In summary, 13 controlled studies were selected for a systematic review, with eight studies contributing data towards the quantitative pooled analysis of at least one outcome measure and five studies reporting only narrative summaries, as they provided non-pooled estimates (women-, hospitalization-, or pregnancies before diagnosis-level denominators or only adjusted effect size). The literature search strategy employed in the development of this manuscript can be located in (Table S1). The process used to select studies within this manuscript, along with specific rationale for selecting each citation for full-text evaluation, is illustrated in (Figure 1) of the PRISMA flow diagram.

Figure 1. PRISMA flow diagram of study identification, screening, and inclusion



Baseline Characteristics: Thirteen studies evaluated this question, published between 1999 and 2026. Twelve studies used cohort designs, while one used a case-control design (Ismail et al. [12]). The cohort studies ranged from a small single-center clinical series to large population-based registries and administrative databases. The time frame of the studies varied as well. The longest study period started in 1987, and the shortest ended in 2021. The nine countries where the studies took place included: Four studies were done in the USA; Two studies were done in Italy; One study was done in Brazil; One study was done in Egypt; One study was done in Australia; One study was done in Spain; One study was done in France; One study was done in the UK; and One study was done in Sweden. The number of women who became pregnant with systemic sclerosis (SSc), or the number of pregnancies that occurred among women with SSc, in each study ranged from twenty to many thousands. On the other hand, the number of comparison arms ranged from twenty matched controls to over 2.4 million births in the population-based comparisons. There was some variation in what type of data was analyzed by each of the studies. Most of the studies analyzed their data at the pregnancy/delivery level. However, Triggianese et al.

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[13] and Ismail et al. [12] analyzed their data at the woman-level. Additionally, Kawano et al. [14] analyzed their data at the hospitalisation level. The comparative groups included healthy control populations (Steen [15], Francisco [16], Ismail [12], and Barilaro [17]), as well as a defined general background obstetric population (Taraborelli [18], Triggianese [13], Chen [19], Kolstad [20], Kawano [14], Hwang [21], Murarasu [22], Singh [23], and Che [24]). SSc was identified using either formal classification criteria (ACR 1980 or ACR/EULAR 2013) for the clinical cohorts and administrative diagnostic codes (ICD 9/ICD-10 or SNOMED) for the population-based and database studies, with subtypes of SSc, presence of autoantibodies, extent of internal organ involvement, and treatment generally unreported. Both limited and diffuse forms of SSc were documented as types in the clinical cohort(s) that also provided a description of subtype. The primary baseline features of each of the 13 studies reviewed are presented in (Table 1).

Table 1. Baseline characteristics of the 13 included studies.

Study (year)	Country	Design	Study period	SSc N (unit)	Comparator N	Comparator type	SSc criteria; subtype	Outcomes reported
Steen 1999 [15]	USA	Prospective cohort	1987–1996	91 pregnancies (59 women)	158 pregnancies	Historical healthy controls	LeRoy; lc 44%/dc 56%	Miscarriage, preterm, neonatal death, LBW
Francisco 2005 [16]	Brazil	Cohort (case-control design)	2004	96 pregnancies (26 women)	94 (26 women)	Healthy, matched	ACR 1980; lc 77%/dc 23%	Miscarriage, LBW
Taraborelli 2012 [18]	Italy	Multicentre prospective cohort	2000–2011	109 pregnancies (99 women)	3,939 deliveries	General obstetric	ACR 1980; lc 53%/dc 47%	Miscarriage, preterm, PPROM, caesarean, PE, IUGR, SGA, LBW, fetal death
Ismail 2013 [12]	Egypt	Case–control (20 vs 20)	2006–2012	20 women	20 women	Age-matched low-risk	ACR; lc 40%/dc 60%	Miscarriage, preterm, IUGR, SGA, PE, caesarean, IUFD
Chen 2015 [19]	Australia	Population-based linked cohort	2001–2011	53 births (42 women)	991,292 births	General obstetric	ICD-10-AM M34	Preterm, SGA, HTN (composite), GDM, caesarean, perinatal death
Triggianese 2017 [13]	Italy	Retrospective cohort (women-level)	2005–2015	77 women	50 women	Age-matched general	ACR/EULAR 2013; lc 60%/dc 40%	Recurrent loss, preterm, IUGR, infertility, fetal death
Kolstad 2019 [20]	USA	Population-based cohort	2007–2011	88 births	2,481,516 births	General obstetric	ICD-9 710.1	Preterm (+phenotypes), PPROM, pre-eclampsia
Barilaro 2022 [17]	Spain	Single-centre retrospective	2008–2019	33 pregnancies (21 women)	40 (healthy)	Healthy controls	ACR/EULAR 2013; lc 43%/dc 10%/ss 48%	Miscarriage, fetal/neonatal death, IUGR, SGA, preterm, PE, caesarean
Kawano 2023 [14]	USA	Administrative cross-sectional (NIS)	2000–2017	3,740 hospitalisations	374,035	General obstetric	ICD-9/10 M34	Fetal death, caesarean, preterm, HTN (composite), IUGR
Hwang 2024 [21]	USA	Retrospective EHR cohort (PS-matched)	2013–2022	54 pregnancies	54 matched	Matched non-IMID	SNOMED EHR	Preterm, LBW, SGA, caesarean
Murarasu 2026 [22]	France	Prospective multicentre cohort (GR2)	2014–2020	53 pregnancies (52 women)	530 matched	General (ENP 2016)	ACR/EULAR; lc/dc	PE, FGR, preterm, SGA, LBW, caesarean, live birth
Singh 2026 [23]	UK	Population-based cohort	NR	SSc subgroup	Non-autoimmune	General (non-autoimmune)	Administrative	Preterm, GDM, hyperemesis (forest: caesarean, SGA, PE, stillbirth)
Che 2026 [24]	Sweden	Population-based register cohort	1998–2021	94 pregnancies	1,440 matched	General (matched)	ICD-10 M34	PE, preterm, caesarean, GDM, gest. HTN, stillbirth, PPROM, SGA

Abbreviations: ACR, American College of Rheumatology; dc, diffuse cutaneous; EULAR, European Alliance of Associations for Rheumatology; GDM, gestational diabetes mellitus; HTN, hypertension; ICD, International Classification of Diseases; IMID, immune-mediated inflammatory disease; IUGR, intrauterine growth restriction; IUFD, intrauterine fetal death; lc, limited cutaneous; LBW, low birth weight; NIS, National Inpatient Sample; NR, not reported; PE, pre-eclampsia; PPROM, preterm premature rupture of membranes; PS, propensity-score; SGA, small-for-gestational-age; ss, sine scleroderma; SSc, systemic sclerosis.

Risk of Bias Assessment

The risk of bias of all the included studies has been evaluated by utilizing the Newcastle–Ottawa Scale (NOS), using the cohort version for the 12 cohort studies and the case–control version for Ismail et al. [12]. In total, nine studies (69%) were deemed to be of high methodological quality (≥ 7 stars), and four studies (31%) were found to be of fair quality (4 – 6 stars); there were no studies that were determined to be of low quality. Many common issues included exposure assessment via

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administrative diagnostic codes; the utilization of non-concurrent historical controls (Steen et al. [15]); an analysis level based upon hospitalizations instead of pregnancies (Kawano et al. [14]); and very small single-center sample sizes with a zero-event cell. The item-level summary of the risk-of-bias assessments can be viewed in Table S2.

Table S2. Item-level risk-of-bias assessment (Newcastle–Ottawa Scale)

Risk of bias was assessed with the Newcastle – Ottawa Scale (NOS), using the cohort version for the 12 cohort studies and the case – control version for Ismail et al. A star (★) indicates that the criterion was met and a dash (–) that it was not. The maximum score is 9 stars (Selection 4, Comparability 2, Outcome/Exposure 3).

Cohort studies

Study	Selection (S1 S2 S3 S4)	Comparability (Ca Cb)	Outcome (O1 O2 O3)	Total (/9)	Quality
Steen et al. 1999	★ – ★ ★	★ –	★ ★ ★	7	Good
Francisco et al. 2005	★ ★ – –	★ –	★ ★ ★	6	Fair
Taraborelli et al. 2012	★ ★ ★ ★	★ ★	★ ★ ★	9	Good
Chen et al. 2015	★ ★ – ★	★ ★	★ ★ ★	8	Good
Triggianese et al. 2017	★ ★ ★ –	★ –	★ ★ –	6	Fair
Kolstad et al. 2019	★ ★ – ★	★ ★	★ ★ ★	8	Good
Barilaro et al. 2022	★ ★ ★ ★	★ –	★ ★ ★	8	Good
Kawano et al. 2023	★ ★ – ★	★ ★	★ – –	6	Fair
Hwang et al. 2024	★ ★ ★ ★	★ ★	★ ★ ★	9	Good
Singh et al. 2026	★ ★ ★ ★	★ ★	★ ★ ★	9	Good
Murarasu et al. 2026	★ ★ ★ ★	★ ★	★ ★ ★	9	Good
Che et al. 2026	★ ★ ★ ★	★ ★	★ ★ ★	9	Good

Case–control study

Study	Selection (S1 S2 S3 S4)	Comparability (Ca Cb)	Exposure (E1 E2 E3)	Total (/9)	Quality
Ismail et al. 2013	★ – ★ –	★ –	★ ★ –	5	Fair

Cohort domains — Selection: S1 representativeness of the exposed (SSc) cohort, S2 selection of the non-exposed cohort (same community/period), S3 ascertainment of exposure (medical record/register or clinician diagnosis, not administrative-code-only or pre-pregnancy timing), S4 outcome not present at start. Comparability: Ca controls for maternal age, Cb controls for additional confounders. Outcome: O1 assessment of outcome, O2 follow-up long enough, O3 adequacy of follow-up. Case–control Exposure: E1 ascertainment of exposure, E2 same method for cases and controls, E3 non-response rate. Quality thresholds: Good ≥ 7, Fair 4–6, Poor ≤ 3. These judgements are preliminary and should be confirmed against the full texts before submission. Principal reasons for lost stars: Steen — historical (non-concurrent) healthy controls; Francisco — 86/96 pregnancies predated diagnosis (exposure timing); Triggianese — women-level (not pregnancy-level) denominators; Kawano — unit of analysis is hospitalizations, no follow-up to outcome; Chen/Kolstad — exposure via administrative ICD codes; Barilaro — single-centre, limited adjustment; Ismail — small single-centre, sparse reporting of case representativeness and control definition.

Outcomes

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There were six outcomes that met the predetermined minimum number of studies that had to report raw event data on a similar scale. These were therefore pooled: pre-eclampsia, caesarean delivery, preterm birth, preterm premature rupture of membranes (PPROM), intrauterine growth restriction/fetal growth restriction (IUGR/FGR), and small for gestational age (SGA). For those studies that used RR, a value >1 would indicate an increased risk of the studied pregnancy outcome when compared to normal pregnancies. The cumulative findings are demonstrated in (Table 2), and the individual forest plots for each of the six pooled outcomes are illustrated in (Figures 2–7). Additionally, a leave-one-out sensitivity analysis for caesarean delivery has also been provided within the (Figure S1). Due to limited data availability, outcomes which have been reported in two or fewer studies, or reported as adjusted/non pregnancy level estimates, have not been pooled and will therefore be summarized below and in Table S3.

Maternal outcomes

Pre-eclampsia

The results from five studies indicate an extremely high risk of developing pre-eclampsia in women who are pregnant with SSc (compared to the number of preeclamptic events among those without) (Relative Risk= 4.84; 95% Confidence Interval= [3.05-7.67]; I^2 = 0%) (Table 2; Figure 2). In addition, all included studies were homogeneous; therefore, the overall association is statistically significant and does not demonstrate variability in the association of preeclampsia with SSc pregnancy as determined by the individual studies**.**

Caesarean delivery

Caesarean delivery was found to be higher in women with SSc pregnancies across the five studies (RR= 1.91; 95% CI = [1.49 – 2.46]; I^2 = 69.4%) (Table 2; Figure 3). As the RR for this outcome was significant, it appears that Caesarean deliveries were significantly associated with SSc pregnancies. However, due to the large amount of heterogeneity present within the data set, there may have been variability in how each author defined the variables used to determine if a patient underwent a Caesarean delivery or vaginally delivered their baby.

Non-pooled maternal outcomes

There were limited reports of gestational hypertension, with some conflicting findings. However, neither study had enough data to be pooled: Che et al. [24] demonstrated that women with SSc were at greater risk of developing hypertension than controls (RR=1.8 [CI: 0.6 – 6.0]), while Taraborelli et al. [18] did not find a significant difference (2/98 vs. 123/3,939). Similarly, there were only a small number of studies reporting on gestational diabetes, which also showed variable estimates (Che et al. [24], RR =1.8 [CI: 0.6 – 6.1]; Chen et al. [19], RR=0.92 [CI: 0.30 – 2.83]), while Singh et al. [23] used an adjusted estimate from their UK-based general population cohort and found a positive association (adjusted RR=1.87 [CI: 1.02 – 3.42]). When studies reported composite hypertensive disorders, they generally found these conditions to have an elevated prevalence (e.g., Kawano et al. [14]: adjusted OR=1.97 [CI: 1.61 – 2.41] at the level of hospitalization; Kolstad et al. [20]: severe pre-eclampsia adjusted RR=6.1 [CI: 2.7 – 13.5]) but since these composite forms of hypertension were either only described as composites or reported using only adjusted estimates, we did not pool them for analysis with pure pre-eclampsia**.**

Fetal and neonatal outcomes

Preterm birth: Preterm births were the most frequently recorded of all the outcomes that were examined in this review. There were also an increased number of preterm births in SSc pregnancies than in non-SSc pregnancies. This is shown by pooling the results from the eight included studies, which demonstrated that there were 3.39 times as many preterm births in SSc pregnancies compared to non-SSc pregnancies (95% CI 2.59–4.44) (Table 2; Figure 4). The level of heterogeneity for the eight studies included in this meta-analysis was 39.5%. Also, after performing leave-one-out sensitivity analyses to assess the stability of the findings, it was found that removing each study individually still resulted in a highly statistically significant association.

Preterm premature rupture of membranes (PPROM)

Preterm premature rupture of membranes (PPROM) occurred at higher rates in SSc pregnancies when compared to those without SSc. This finding is based on the three studies that provided data on PPROM. Pooled estimates of the RR indicated that PPROM occurred at 3.32 times the rate in SSc pregnancies than in non-SSc pregnancies (95% CI 1.17–9.41) (Table 2; Figure 5). Although the confidence interval was quite large due to variability in rates of events and definitions of events used by researchers who contributed to these studies, the overall pooled estimate was statistically significant. However, since the degree of heterogeneity was very high (I^2 = 82.6%), interpretation of the pooled RR should be viewed with caution because there are multiple possible reasons why heterogeneity may have been so high, including differences in event rates or how events were defined across individual studies.

Intrauterine growth restriction / fetal growth restriction (IUGR/FGR)

There were also more cases of intrauterine growth restriction/fetal growth restriction (IUGR/FGR) in SSc pregnancies when compared to non-SSc pregnancies. These findings were determined through pooling the data from the three studies that evaluated IUGR/FGR. The RR indicated that IUGR/FGR occurred at 3.25 times the rate in SSc pregnancies than in non-SSc pregnancies (95% CI 1.65–6.39) (Table 2; Figure 6). There appeared to be no observed heterogeneity among the studies evaluating IUGR/FGR.

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Small-for-gestational-age (SGA) Small for gestational age (SGA)
infants were more commonly seen in SSc pregnancies than in non-SSc pregnancies. This conclusion was reached through pooling the data from the five studies that evaluated SGA status. The RR indicated that SGA infants occurred at 1.48 times the rate in SSc pregnancies than in non-SSc pregnancies (95% CI 1.08–2.04) (Table 2; Figure 7). The amount of heterogeneity was relatively small to moderate (I^2 = 33.0%).

Non-pooled fetal and neonatal outcomes
Low birth weight has been reported using different and inconsistent cutoffs that did not allow for pooling: Taraborelli et al. [18] reported very low birth weight less than 1500g (OR=4.88, 95%CI=1.66-13.24) while Murarasu et al. [22] defined low birth weight as less than 2500g (crude OR=6.1, 95%CI=2.7-13.7) both suggesting increased risks, however Steen et al. [15] noted that there were no term low-birth-weight events within the SSc cohort (0/91vs3/158). A miscarriage, which is one of several predefined primary outcomes, was also reported with different time frames for gestation (<10weeks, <20weeks or first trimester) and therefore could only be summarized on a narrative basis to avoid pooling the data: Barilaro et al. [17] (5/33 vs. 0/40; p=0.016) and Ismail et al. [12] (4/20 vs. 1/20; p<0.05) demonstrated higher rates in the SSc group, however Steen et al. [15] found no statistically significant differences (RR=1.14; 95%CI=0.71-1.82). Stillbirth/fetal death and neonatal deaths were too frequently zero-event cell results to estimate these endpoints reliably (for example, neonatal death had two zeros in both Barilaro [17] and Che [24] studies); Kawano et al. [14] noted an increased adjusted odds ratio of fetal death at the hospitalization level (adjusted OR=4.00; 95%CI=2.55-6.27). In total, there were five studies that provided only non-poolable estimates. Singh et al. [23], using their adjusted UK population cohort, demonstrated both an increase in risk of preterm birth (RR 2.34; 95% CI 1.67-3.27) and protection against Hyperemesis Gravidarum (RR 0.25; 95% CI 0.08-0.78). Kawano et al. [14] also used data from their national inpatient sample to demonstrate an increase in adjusted odds of having a premature baby (odds ratio 2.65; 95% CI 2.23 – 3.14), delivering by Caesarian section (OR 1.66; 95% CI 1.44 – 1.92) and intrauterine growth restriction (IUGR) (OR 2.45; 95% CI 1.74 – 3.45) when hospitalized. Hwang et al. [21], using propensity matching as part of their study design, could find no statistically significant association for the following conditions when studying a smaller sub-group of women who had Systemic Sclerosis (SSc) (n=54): preterm birth, low birth weight, Small for Gestational Age (SGA), and Caesarean delivery. The remaining two studies, Triggianese et al. [13] and Francisco et al. [16], which studied women individually, found no statistically significant difference between groups regarding the outcome measures of each study. Details of these estimates can be seen in Table S3.

Figure S1. Leave-one-out sensitivity analysis — cesarean delivery
Figure S1.
Leave-one-out sensitivity analysis for cesarean delivery. Each row shows the pooled random-effects relative risk after omitting one study. The association remained statistically significant throughout (range of pooled RR 1.75–2.02), confirming that no single study drove the overall estimate (RR 1.91; 95% CI 1.49–2.46; I^2 = 69.4%).

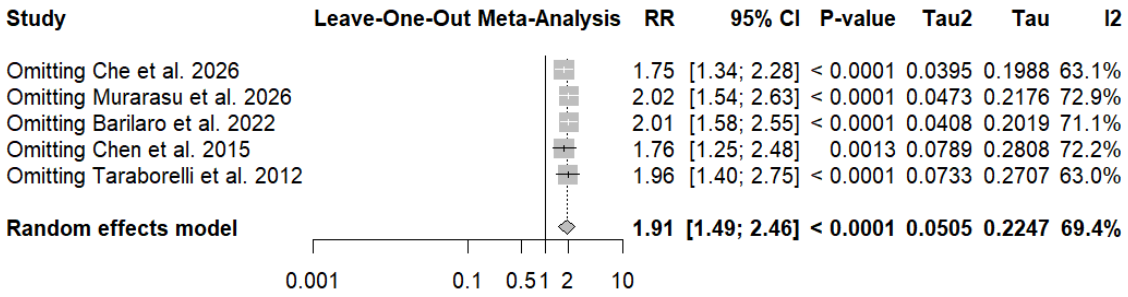

Figure 2. Forest plot of pooled relative risk of pre-eclampsia in SSc versus unaffected pregnancies.

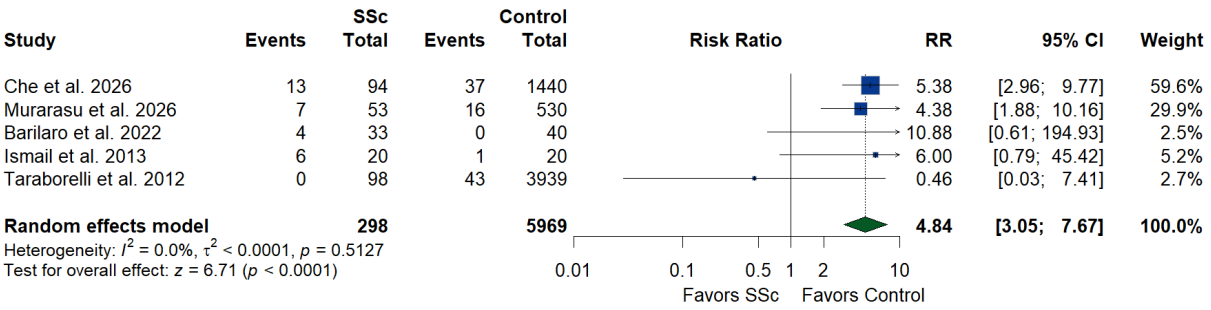

Figure 3. Forest plot of pooled relative risk of caesarean delivery

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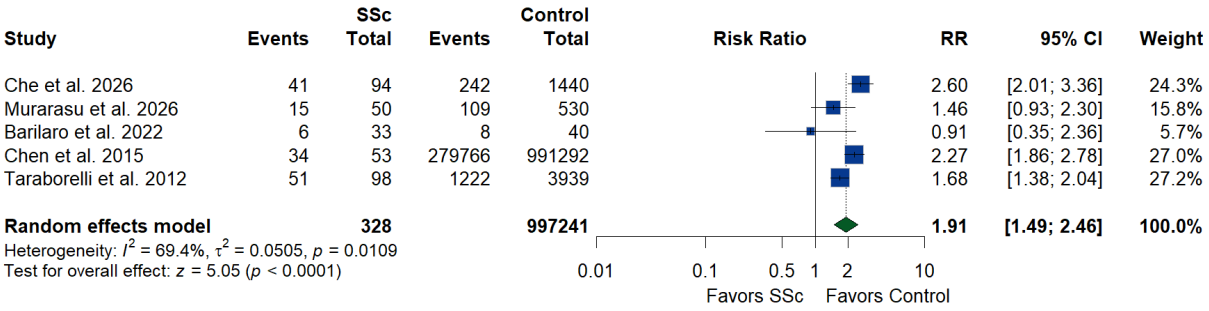

Figure 4. Forest plot of pooled relative risk of preterm birth

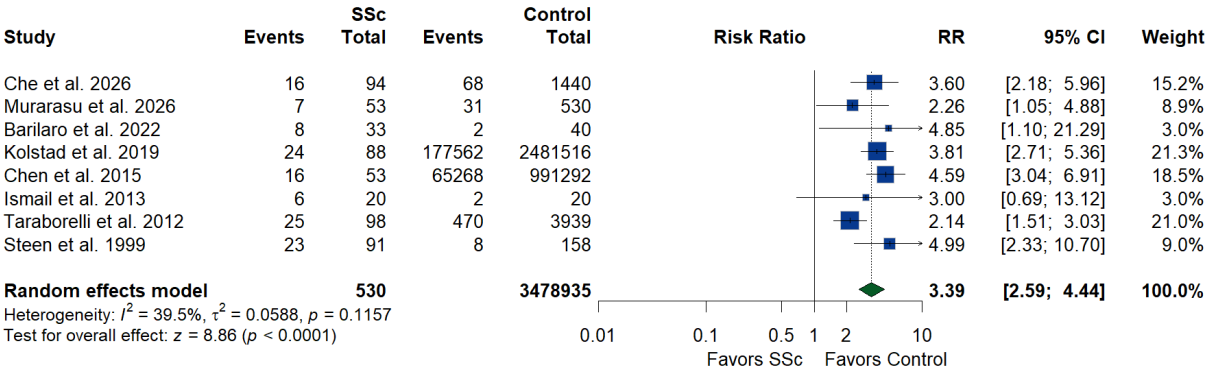

Figure 5. Forest plot of pooled relative risk of PPROM

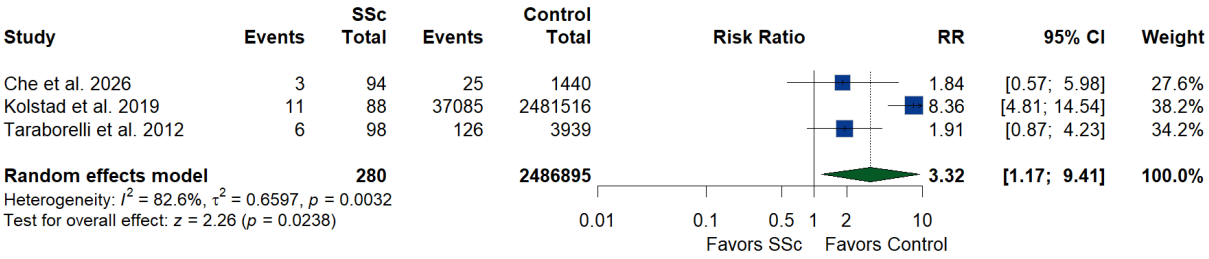

Figure 6. Forest plot of pooled relative risk of IUGR/FGR

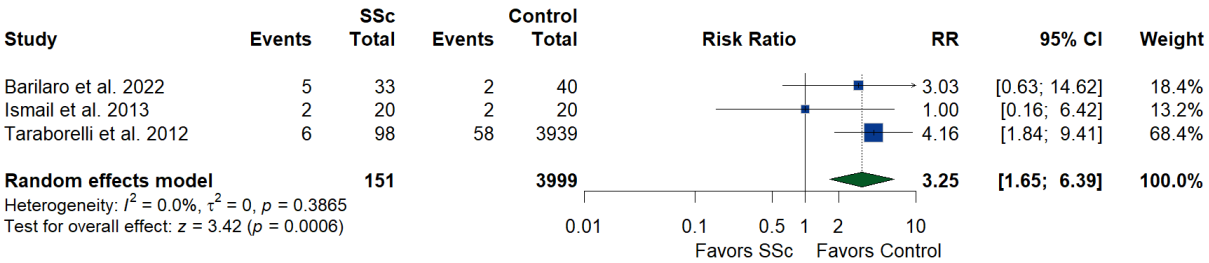

Figure 7. Forest plot of pooled relative risk of SGA

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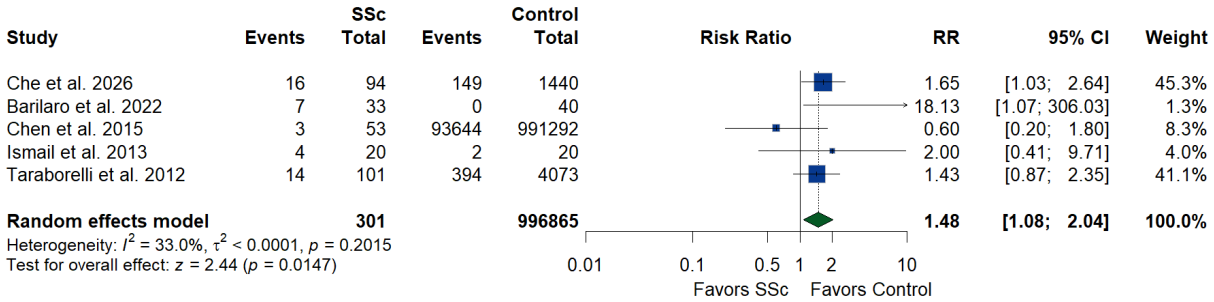

Table S3. Outcomes reported but not meta-analyzed (raw/crude data)

The following outcomes were reported by fewer than three studies on a consistent scale, or were reported with heterogeneous outcome definitions (e.g., differing gestational-age thresholds for miscarriage or birthweight cut-offs), and were therefore summarized narratively rather than pooled.

Outcome	Study	SSc (n/N)	Comparator (n/N)	Effect/significance	Reason not pooled
Miscarriage	Barilaro 2022 (<10 wk)	5/33	0/40	p = 0.016	Heterogeneous gestational-age definitions
	Steen 1999 (<20 wk)	13/91	21/158	RR 1.14 (0.71–1.82)	
	Ismail 2013 (1st trimester)	4/20	1/20	p < 0.05	
	Francisco 2005	13/96	9/94	p = 0.46 (pre-diagnosis)	
Gestational hypertension	Taraborelli 2012	2/98	123/3,939	crude RR 0.65 (NS)	< 3 studies; inconsistent
	Che 2026	3/94	25/1,440	crude RR 1.8 (0.6–6.0)	
Gestational diabetes	Che 2026	4/94	33/1,440	crude RR 1.8	< 3 raw datasets; mixed crude/adjusted
	Chen 2015	—	—	adjusted RR 0.92 (NS)	
	Singh 2026	—	—	Adjusted RR 1.87 (1.02–3.42)	
Stillbirth / fetal death	Barilaro 2022	6/33	0/40	—	Zero cells; differing denominators
	Che 2026	0/94	4/1,440	—	
	Ismail 2013	2/20	0/20	—	
	Triggianese 2017	2/77	0/50	women-level	
Low birthweight	Taraborelli 2012 (VLBW <1500 g)	5/101	43/4,073	OR 4.88	Inconsistent birthweight cut-offs
	Steen 1999 (term <2500 g)	0/91	3/158	—	
	Murarasu 2026 (<2500 g)	11/52	23/530	crude OR 6.1	
	Francisco 2005 (<2490 g)	8/96	6/94	p = 0.54	
Neonatal death	Barilaro 2022	0/33	0/40	—	Very rare; zero cells
	Che 2026	0/94	0/1,440	—	
	Steen 1999	1/91	4/158	RR 0.58	

NS = not statistically significant; RR = risk ratio; OR = odds ratio; VLBW = very low birthweight; — = not reported as extractable raw counts.

Discussion

The systematic review and meta-analysis of 13 controlled studies using the raw event data from eight of the studies demonstrated that pregnancies in patients who have systemic sclerosis (SSc) are at a significantly greater risk of having

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poor pregnancy outcomes compared to pregnancies in SSc-free mothers. The Mantel-Haenszel random-effects model found a pooled relative risk of 4.84 for pre-eclampsia in the pregnant mother with SSc (CI 95%, 3.05-7.67; I^2 = 0%) when compared to non-SSc mothers. The risk of premature birth was approximately 3.4 fold increased in SSc mothers (RR, 3.39; CI 95%, 2.59-4.44; I^2 = 39.5%), as well as an increase in the risk of PPROM (RR, 3.32; CI 95%, 1.17-9.41; I^2 = 82.6%), IUGR-FGR (RR, 3.25; CI 95%, 1.65-6.39; I^2=0%), C-section delivery (RR, 1.91; CI 95%, 1.49-2.46; I^2 = 69.4%), and SGA babies (RR, 1.48; CI 95%, 1.08-2.04; I^2 = 33%). Therefore, all of this information confirms that SSc is a condition that should be considered to have a high risk of both hypertensive and placental-mediated complications during pregnancy. We found our study's conclusions were largely consistent with, and extended upon, a prior study of its kind. Blagojevic et al. [7], completed the first meta-analysis regarding the association between SSc and adverse outcomes during pregnancy. They completed a meta-analysis using data from sixteen studies and concluded there was an increase in odd ratios (OR) for preterm birth (OR=2.4, 95% CI=1.14–4.86); intrauterine growth restriction (IUGR) (OR=3.2, 95% CI=2.21–4.53); low birth weight (LBW) (OR=3.8, 95% CI=2.16 6.56); gestational hypertension (GH) (OR=2.8, 95% CI=2.28–3.39); and caesarean delivery (CD) (OR=2.3, 95% CI=1.37–3.80).

This current analysis is an update to their findings using more recent studies based on registry and cohort designs. In addition, this analysis restricts pooling to raw event data expressed as relative risk, which resulted in more precise estimates of effect for pre-eclampsia compared to the prior meta-analysis. We also noted the magnitude of risk associated with SSc during pregnancy is similar to what has been described in other connective tissue diseases such as SLE. For example, Liu et al. [25] indicated that active disease, hypertension, and renal involvement are predictors of preterm birth and pre-eclampsia in pregnancies complicated by SLE.

Similarly, the Society for Maternal-Fetal Medicine [26] stated that autoimmune rheumatic disease significantly contributes to both maternal and fetal morbidity in pregnant patients. These findings support the notion that systemic vasculopathy and immune dysregulation, rather than any one disease name, contribute to the increased risk of adverse obstetric events. The biological feasibility for such findings can be understood through the vascular mechanisms of SSc; specifically, through the early loss of function and/or increased activity of endothelium in SSc (as has been described in Refs. [27] & [28]) and subsequent chronic endothelial dysfunction generated through continued oxidative stress, autoantibody formation, and reduced vascular repair (which may represent the central or initiating event within the spectrum of SSc vasculopathies) [29]. Pregnancy involves a significant amount of remodeling of the spiral arteries supplying blood to the uterus by extravillous trophoblast cells; during this process the spiral arteries transition from being high-resistance vessels with limited capacity for flow to low-resistance vessels with greater capacity for flow to support placenta perfusion [30]. Therefore, a maternal vascular bed that is damaged through an existing level of endothelial damage and/ or abnormal vessel constriction would create a substrate conducive to failure of placentation. The mechanism behind this model explains how the results were achieved. The mechanism behind preeclampsia, which we identified as having the largest and most homogeneous effect (RR = 4.84; I^2 = 0%), is a two-stage placenta-based disorder that begins when the spiral artery of the placenta fails to remodel correctly, leading to placental ischemia and an anti-angiogenic state in the mother that produces the syndrome of maternal hypertension [31].

Not only are poor remodeling of the spiral artery and the associated lesion of acute atherosclerosis linked to both preeclampsia and other placenta-mediated pregnancy complications such as fetal growth restriction, placental abruption, and spontaneous preterm premature rupture of membranes [32], but also the elevated risks for IUGR-FGR and PPROM in our data offer a unified explanation for these outcomes. While SGA was significantly increased, caesarean delivery had substantially more heterogeneity (I^2 = 69.4%) than SGA, and PPROM had (I^2 = 82.6%). Therefore, the modest increase in SGA and the high levels of heterogeneity seen with caesarean delivery and PPROM were primarily due to variability in definitions used within studies, obstetrical thresholds for intervening in labor, and case mix across studies rather than one single biological effect on pregnancies; Local practices, in addition to clinicians' caution when managing high-risk pregnancies, have significant effects on rates of caesarean delivery.

In addition to placental-related risks, SSc presents unique pregnancy-associated risks as a result of the characteristics of the disease itself. The single biggest maternal complication from SSc is scleroderma renal crisis (SRC), which is thought to occur at a higher rate in the very early stages of diffuse cutaneous systemic sclerosis and in those patients who have anti-RNA polymerase III autoantibodies; it also necessitates the use of ACE inhibitors during pregnancy, although this class of medication has traditionally been avoided during pregnancy [4, 33]. Both interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) pose an increased risk to pregnant mothers, and if either condition is severe enough to make pregnancy undesirable, then the decision would be made to forego pregnancy [4]. Thus, all current recommendations suggest that timing of conception should coincide with periods of relative stability of disease and that all patients with rapidly progressing diffuse disease should avoid or delay pregnancy, where possible, through formalized preconception counseling and individualized risk assessment and stratification by their healthcare provider before conception [34]. The continued increased risk of developing pre-eclampsia found in our study will likely have important implications regarding how pregnant patients are managed. Aspirin 150mg a day is a well-established, inexpensive method of preventing pre-eclampsia: In the ASPRE Trial, use of aspirin 150 mg per day from 11-14 weeks of gestational age resulted in a reduction in the incidence of pre-term pre-eclampsia of approximately 62% when compared to the placebo group (Odds Ratio=0.38, Confidence Interval = 0.20-0.74) [35], and the U.S.

Preventive Services Task Force [36] recommends low-dose aspirin be started after 12 weeks' gestation in those at high risk of developing pre-eclampsia. Thus, based on the substantial degree of increased risk seen in our population of women with

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Systemic Sclerosis (SSc), all these women should be eligible for low-dose aspirin for prevention of pre-eclampsia. Additionally, while continuing disease-modifying therapy during pregnancy is ideal, it is also necessary to continue therapy using medications that are compatible with pregnancy. The 2024 Update of the European League Against Rheumatism (EULAR) Recommendations confirms compatibility with pregnancy of certain systemic therapies such as Hydroxychloroquine, Azathioprine, Cyclosporine and Tacrolimus; whereas Methotrexate and Mycophenolate must be stopped before conception and the use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Glucocorticoids must be restricted [37]. Therefore, the coordinated, multidisciplinary approach to the health care needs of women who plan to become pregnant with SSc must begin before they conceive to improve their outcomes [33]. It should be noted that the increased risk of premature delivery associated with systemic sclerosis (SSc) can contribute substantially to the global health burden of premature births.

Premature delivery is the primary cause of infant deaths in children under 5 years old, and it is estimated that approximately 13.4 million infants were premature at birth globally in 2020, which equates to about one out of every 10 live births [38]. There have been relatively small declines in age-standardized rates of premature delivery during the last few decades, but there are still considerable numbers of premature deliveries occurring around the world, and they tend to occur in different parts of the globe [39]. Additionally, premature delivery is a major factor influencing both early and late life morbidity in addition to being a significant contributor to neonatal mortality [40] – as such, a more than three-fold increase in premature delivery among women with SSc could represent a preventable component of perinatal morbidity within this patient group and supports further investigation into antenatal surveillance and timely interventions.

Strengths and limitations

Strengths of this review include that we consistently utilized raw event counts and relative risk measures (avoiding the combined measure of inverse variance weighted and adjusted estimates) and broke down composite outcome measures into their constituent parts in order to preserve clinical interpretation. Our risk of bias assessment utilizing the Newcastle-Ottawa scale was performed at an item level, and our leave-one-out sensitivity analysis provided evidence that the estimate of caesarean delivery is robust. However, there are several important limitations to this review. For example, the number of studies included in certain outcomes was low (i.e., only 3 studies were included in the meta-analysis for PPROM and IUGR-FGR), which limits the precision of these estimates and produces large confidence intervals. In addition, many of the studies included in the meta-analyses were retrospective in design and relied upon either administrative coding or comparisons based upon historical or population levels, which could lead to classification error and confounding. Lastly, differences in how various authors defined concepts (e.g. growth restriction, gestational hypertension), along with the preliminary nature of the risk-of-bias assessments, contribute to significant heterogeneity among the studies analyzed.

Conclusion

In conclusion, our updated systematic review and meta-analysis confirmed that pregnancies in women suffering from systemic sclerosis have significantly increased risks for complications such as pre-eclampsia, preterm birth, premature rupture of membranes (PPROM), intrauterine growth retardation (fetal growth restriction), caesarean section, and small-for-gestational-age (SGA) babies. Our new data are consistent with previous data [7] and support an underlying biological mechanism due to the vascular damage resulting from the endothelial and microvascular dysfunction seen in patients with SSc and possible effects on placental development. The study also suggests a potential model of care for women with SSc including: counseling before conception regarding their condition, planning pregnancy when disease activity is at a minimum, use of low-dose aspirin during pregnancy for prevention, and coordination of prenatal care by multiple specialists. Further larger cohort studies with clearly defined outcomes will be required to validate the estimated risks associated with SSc pregnancies, as well as to assess specific preventable measures for those pregnant with SSc.

Conflicts of Interest

The authors declare no conflicts of interest.

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