Monitoring of Systemic Lupus Erythematosus Pregnancies: A Systematic Literature Review

Emily G. McDonald, Lyne Bissonette, Stephanie Ensworth, Natalie Dayan, Ann E. Clarke, Stephanie Keeling, Sasha Bernatsky, and Evelyne Vinet

ABSTRACT. ***Objective.*** Few data exist to guide the frequency and type of monitoring in systemic lupus erythematosus (SLE) pregnancies. A systematic literature review was performed to address this gap in the literature.

Methods. A systematic review of original articles (1975–2015) was performed using Medline, Embase, and Cochrane Library. We included search terms for SLE, pregnancy, and monitoring. We also hand-searched reference lists, review articles, and grey literature for additional relevant articles.

Results. The search yielded a total of 1106 articles. After removing 117 duplicates, 929 articles that were evidently unrelated to our topic based on title and/or abstract, and 7 that were in a language other than English or French, 53 articles were included for full-text review. Following a more in-depth review, 15 were excluded: 6 did not use any measure of SLE activity and 6 did not specifically address SLE monitoring in pregnancy; 1 case series, 1 review, and 1 metaanalysis were removed. Among the 38 included studies, presence of active disease, antiphospholipid (aPL) antibodies positivity, and abnormal uterine and umbilical artery Doppler studies predicted poor pregnancy outcomes. No studies evaluated an evidence-based approach to the frequency of monitoring.

Conclusion. Few existing studies address monitoring for optimal care during SLE pregnancies. The available data imply roles for aPL antibodies measurement (prior to pregnancy and/or during the first trimester), uterine and umbilical artery Doppler studies in the second trimester, and following disease activity. Optimal frequency of monitoring is not addressed in the existing literature. (First Release July 15 2018; J Rheumatol 2018;45:1477–90; doi:10.3899/jrheum.171023)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
MONITORING
PREGNANCY
ADVERSE PREGNANCY OUTCOMES

Systemic lupus erythematosus (SLE) predominantly affects women during their reproductive years, occurring in about 1/1000 women aged between 15 and 45 years[1]. SLE is associated with substantial maternal and fetal morbidity during pregnancy. Compared with the non-SLE population, SLE has been shown to be associated with an increased risk of preterm birth, cesarean delivery, preeclampsia, low birth weight, intrauterine growth restriction (IUGR), congenital heart block (CHB), and intrauterine and neonatal death[2,3,4,5]. Preterm birth is the most common adverse pregnancy outcome in women with SLE, with incidence ranging from 15% to 50% (as opposed to 10% in unaffected women), with increased risk in women with lupus nephritis or high disease activity. In the general population, preterm birth is the leading cause of neonatal death and the second most common cause of death (after pneumonia) in children younger than 5 years[6].

SLE has a waxing and waning course and it has been shown that if women conceive during a period of disease quiescence, this will minimize the risk of flare in pregnancy, but will not eliminate it, with rates of flare still ranging between 20% and 40% of pregnancies that are conceived during a period of remission[7,8,9,10]. In addition to a greater frequency of pregnancy complications, the SLE disease course itself can be negatively affected by pregnancy, with a

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greater number of women developing an SLE flare in the peripartum period[11,12,13].

SLE pregnancies are considered high risk, being associated with higher maternal and fetal morbidity. Although the majority of SLE pregnancies end with live births, active disease and major organ involvement can affect the outcomes in both mother and fetus. In addition, major fetal issues such as IUGR and neonatal SLE syndromes make monitoring imperative in SLE pregnancies[14].

Finally, some symptoms of SLE can be silent, such as renal flare or thrombocytopenia, emphasizing the need for closer monitoring in pregnancy; these silent flares can still increase the chance of obstetrical complications[15].

Quality indicators pertaining to reproductive health in SLE have been developed but are limited only to the recommendation that anti-SSA/SSB and antiphospholipid (aPL) antibodies be documented in the chart, prior to conception[16]. Optimal quality indicators remain undefined, and topics to be addressed include not only laboratory monitoring but also newer imaging modalities for monitoring high-risk pregnancies, such as umbilical and uterine artery Doppler studies. These are believed to be useful in monitoring pregnancies at high risk of placental insufficiency, which include SLE pregnancies[17]. Because the issue of how best to follow disease activity, and how often to monitor for disease flares, has not been systematically addressed in the literature, current practice is heterogeneous and not necessarily evidence-based[18].

To address this important knowledge gap, a Canadian SLE working group was established, funded by the Canadian Institutes of Health Research and endorsed by the Canadian Rheumatology Association. One of the aims of this group was to determine what investigations are needed to optimally monitor pregnancy in SLE, in the Canadian context (which includes universal healthcare access).

MATERIALS AND METHODS

The systematic literature review was performed according to the Preferred Reporting Items for Systematic review and Meta-analysis Protocols (PRISMA-P) 2015 statement[19] (Table 1).

The review was conducted through 3 search engines: Embase, Medline, and Cochrane. The search was performed on publications between 1975 and 2015, without any language restrictions. We used Medical Subject Heading and free text terms adapted for each database to identify original articles. We included search terms for SLE, pregnancy, and monitoring variables. All terms within each set were combined using the Boolean operator "OR" and then the 3 sets were combined using "AND." This was supplemented by hand-searching reference lists, review articles, and grey literature for relevant articles not identified by the electronic searches, as well as including relevant articles published after completion of our review. Exclusion criteria then included any abstract in a language other than French or English, case reports, case series, and review articles.

Study selection. First, titles from the initial search were reviewed by 3 individuals (EGM, LB, and EV) to initially include any potential studies related to the study question, and to exclude any duplicates. Second, titles and abstracts were reviewed to identify relevant studies that met our inclusion criteria and to exclude case reports and studies unrelated to the systematic review. Third, 2 reviewers (EGM and LB) independently reviewed each full-text article for inclusion in the final set of articles, with a third reviewer (EV) settling discrepancies. Two reviewers (EGM and EV) summarized evidence on monitoring of SLE in pregnancy. None of the reviewers were blinded to the authors or journal titles.

Data extraction and quality assessment. Relevant data pertaining to monitoring were extracted from each article as well as general information such as country of the study, type of study, year of publication, and first author. Monitoring was divided into 4 categories: serological tests [which included anti-DNA, antiextractable nuclear antibody, IgG and IgM anticardiolipin antibodies (aCL), lupus anticoagulant (LAC), and complement levels]; measures of SLE activity using a validated scoring system [examples include the SLE Disease Activity Index (SLEDAI) and European Consensus Lupus Activity Measure scores; studies that did not use any type of scoring system to measure disease activity were not included]; obstetrical Doppler ultrasound monitoring (either uterine or umbilical artery Doppler studies); and other (monitoring variables not falling into one of the above categories). When applicable, we recorded whether the frequency of monitoring was addressed, as well as any associations with negative maternal or obstetrical outcomes. Maternal outcomes were classified as the development of preeclampsia, or worsening of SLE disease activity, including lupus nephritis. Obstetrical outcomes were classified as IUGR, spontaneous abortion (prior to 20 weeks of gestational age), small for gestational age (SGA) or low birth weight (SGA and low birth weight were defined within individual studies), preterm delivery (prior to 37 weeks gestational age), complete CHB, or intrauterine fetal demise. Relevant data were extracted, synthesized, and presented in tabular format.

Risk of bias in individual studies: the Newcastle-Ottawa scale. Final studies included in the systematic review were evaluated for quality of evidence and risk of bias using the Newcastle-Ottawa scale, which uses a star system whereby a study is judged on 3 measures: the selection of the study groups, the comparability of the groups, and how the exposure for case-control (or outcome of interest for cohort studies) was ascertained.

RESULTS

Study characteristics. A general description of the characteristics of each study is presented in Table 2[2,9,13,15,20-53] including first author, year of publication, study population, and study type, as well as monitoring variables studied. A description of the search process, including the reasons for excluded studies, is shown in Figure 1. In total, 1106 titles were evaluated from the initial search strategy, of which 117 were removed because they were duplicates, and 7 were removed because they were in a language other than French or English. Then, on initial review of the title and/or abstracts, 929 articles that did not address SLE monitoring in pregnancy and were removed, leaving 53 articles that were reviewed in depth. Upon full review of the 53 articles, it was found that 6 more did not address SLE monitoring in pregnancy, 6 did not use any scoring system for SLE disease activity, 1 was a review, 1 was a case series, and 1 was a metaanalysis. These were removed, leaving 38 original observational studies for review. Final studies were selected based on reporting of adverse obstetrical or maternal outcomes related to monitoring variables (Figure 1) in SLE.
Participant characteristics. The majority of studies evaluated monitoring of SLE during pregnancy and immediately postpartum. Only a few studies looked specifically at lupus nephritis or focused solely on pregnancies in mothers who were anti-Ro- and/or La-antibody positive. The study populations were multiethnic, with patients from across the world

Table 1. PRISMA-P checklist for preferred reporting of systematic reviews.

Section and Topic	Item No.	Checklist Item
Administrative information		
Title		
Identification	1a	Identify the report as a protocol of a systematic review.
Update	1b	If the protocol is for an update of a previous systematic review, identify as — *This is not an update of a previous protocol for a systematic review.*
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number — *This systematic review was not registered*.
Author		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author — *Emily Gibson McDonald[1], Royal Victoria Hospital, 1001 Decarie St., Montreal, Quebec H4A 3J1, Canada. Evelyne Vinet[1], Stephanie Keeling[2], Natalie Dayan[1], Lyne Bissonette[3], Sasha Bernatsky[1], Stephanie Ensworth[4], Ann E. Clarke[5]. [1]McGill University Health Centre, [2]University of Alberta, [3]University of Laval, [4]Mary Pack Arthritis Centre, [5]University of Calgary.*
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review — *Emily McDonald and Evelyne Vinet were involved in reading the abstracts, excluding unrelated abstracts, drafting the manuscript including reading articles in full and collating the data. Lyne Bissonette read and excluded unrelated abstracts. Natalie Dayan was involved in the supervision of Lyne Bissonette. Evelyne Vinet developed the PICO question and the search strategy and supervised Emily McDonald. Stephanie Keeling provided content expertise and supervision of the GRADE recommendations. Stephanie Ensworth and Ann E. Clark are part of the Canadian SLE Working Group. Evelyne Vinet is the guarantor of the manuscript.*
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments — *This manuscript does not represent a protocol amendment*.
Support		
Sources	5a	Indicate sources of financial or other support for the review — *EV received salary funding from the Fonds de Recherches Santé Québec (FRSQ). EGM received funding from an FRSQ Master's award and the McGill Clinician Investigator Program. SK received funding through a CIHR Dissemination Event. This work will be used by the Canadian SLE Working Group to develop recommendations for the diagnosis and monitoring of SLE.*
Sponsor	5b	Provide name for the review funder and/or sponsor — *The review was not funded*.
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol — *Cochrane Review was involved in the development of the PICO question*.
Introduction		
Rationale	6	Describe the rationale for the review in the context of what is already known — *Pregnant patients with SLE have higher rates of adverse obstetrical outcomes and SLE has a high likelihood of flaring in pregnancy, which in term can lead to worse obstetrical outcomes; there exist few guidelines for the monitoring of pregnancy in SLE; it is known that quiescent disease for several months prior to conception is associated with improved outcomes. It is not known what should be monitored throughout pregnancy in terms of blood and urine tests, serologies, ultrasounds, and disease activity and at what frequency.*
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO). P – pregnant SLE patients including all women of child-bearing age. I – laboratory investigations: antiphospholipid antibodies, Ro/SSA and La/SSB antibodies, anti-DNA antibody, complement levels, ESR, CRP, uric acid; renal function: disease activity, SLEPDAI, SLEDAI, BILAG, SLAM, ECLAM, SRI, CBC differential, lupus activity index, DNA antibodies; other: SLICC, monitoring of the baby, blood pressure. C – frequency. O – Preterm birth, preeclampsia/eclampsia, stillbirth, small for gestational age, intrauterine growth restriction, congenital heart block, fetal heart block, neonatal lupus, stillbirth, miscarriage, SLE flare; gestational hypertension: renal insufficiency, maternal death, thromboembolism event, premature rupture of membranes, premature labor/delivery; secondary: gestational diabetes, cesarean delivery.
Methods: For the following section please refer to the Materials and Methods section of the manuscript		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review.
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage.
Search strategy	10	Present draft of search strategy to be used for at least 1 electronic database, including planned limits, such that it could be repeated.
Study records		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review — *All records were managed in an Excel spreadsheet that included author, year, population, exposure, outcomes, and results*.

Table 1. Continued.

Section and Topic	Item No.	Checklist Item
Selection process	11b	State the process that will be used for selecting studies (such as 2 independent reviewers) through each phase of the review (that is, screening, eligibility, and inclusion in metaanalysis) — *Three authors were involved in screening the abstracts [2 authors initially — EM and LB, and a third author (EV) was involved if the first 2 authors did not agree on the eligibility of a study]. Two authors read the articles included for in-depth review and decided on the final exclusions (EM and EV).*
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators — *Two authors reviewed the articles included for the final review and based on an Excel spreadsheet extracted the data and collated it.*
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications — *For variables please refer to the in-depth description of the PICO question above where each component of the I and O are described in detail.*
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale – *Refer to the PICO question above where all elements of the outcomes are described.*
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis – *Studies were evaluated for quality using the Newcastle-Ottawa Scale (described in depth in the body of the thesis).*
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized — *Preliminary recommendations for monitoring of pregnancies complicated by lupus are prepared based on GRADE analysis of the data quality (for more details please refer to the methods section) of the thesis.*
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) – *Not applicable for this systematic review (relevant for metaanalysis only).*
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, metaregression) — *Not applicable for this systematic review (relevant for metaanalysis only).*
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned — *Not applicable for this systematic review (relevant for metaanalysis only).*
Metabias(es)	16	Specify any planned assessment of metabias(es), such as publication bias across studies, selective reporting within studies – *Not applicable for this systematic review (relevant for metaanalysis only).*
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) — *This is described in great detail in the methods section of the thesis.*

PRISMA-P: Preferred Reporting Items for Systematic Review and Metaanalysis Protocols; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; SLE: systemic lupus erythematosus; CIHR: Canadian Institutes of Health Research; PICO search strategy: Participants — Intervention — Comparison/Comparator — Outcome; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SLEPDAI: SLE in Pregnancy Disease Activity Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; BILAG: British Isles Lupus Assessment Group index; SLAM: Systemic Lupus Activity Measure; ECLAM: European Consensus Lupus Activity Measure; SRI: SLEDAI-2K Responder Index 50; CBC: complete blood count; SLICC: Systemic Lupus International Collaborating Clinics.

including North America, Europe, Latin America, Asia, and the Middle East.

Monitoring variables characteristics. Of 38 final articles evaluated, 22/38 (58%) addressed the value of measuring serology, including the measurement of aPL antibodies prior to pregnancy and/or during the first trimester, and 18/38 (47%) assessed monitoring for SLE flare with a validated scoring system, such as the SLEDAI (Figure 2). The utility of umbilical and/or uterine artery Doppler monitoring for predicting poor obstetrical outcomes was evaluated in 5/38 (13%) articles. Disease activity scoring systems modified to account for the physiologic changes of pregnancy were observed in 4 articles, such as the SLE in Pregnancy Disease Activity Index[54] and the Lupus Activity Index in Pregnancy[55]. Of note, none of them have been formally validated.

Outcomes. Findings from each study are summarized and presented in Table 3[2,9,13,15,20-53]; studies were evaluated for risk of bias using the Newcastle-Ottawa scale and the quality of data is presented in Table 4[2,9,13,15,20-53]. Across the studies included for full review, the presence of active disease (measured by various scoring systems), aPL antibodies positivity, and abnormal uterine and umbilical artery Doppler studies predicted poor pregnancy outcomes. Low complement and thrombocytopenia at the beginning of pregnancy were also predictors of poor obstetrical outcomes. No studies that assessed the value of serological and disease activity monitoring evaluated an evidence-based approach to the frequency of monitoring. Studies that addressed uterine and umbilical artery Doppler monitoring discussed the frequency at which these tests were performed but did not address the evidence behind the practice.

DISCUSSION

Summary of findings. In this systematic review examining monitoring in SLE pregnancies, 38 articles were included, after an initial screening of 1106 abstracts and 53 articles that were reviewed in depth. Final articles addressed the monitoring of SLE-related pregnancy and focused on 3 main

Table 2. Study characteristics.

Author and Year	Study	Study Population	Monitoring Variables
Al Arfaj 2010[20]	RC	Pre- and post-SLE pregnancies	Serology, renal, BP
Alshohaib 2009[21]	PC	Stable class 4 LN	Serology, renal, BP
Bertolaccini 2007[22]	CC	SLE vs non-SLE pregnancies	Anti-fX11
Brucato 2002[23]	PC	Anti-Ro–positive pregnancies	Serology, disease activity
Buyon 2015[2]	PC	SLE pregnancies	Serology, disease activity, PLT, antihypertensive use
Clowse 2011[24]	RC	SLE pregnancies	Serology, disease activity
Clowse 2013[9]	PC	SLE pregnancies	Serology, AFP, estradiol, CRP, disease activity, UA
Cortés-Hernández 2002[25]	PC	SLE pregnancies	Serology, BP, disease activity
Daskalakis 2009[26]	PC	LN pregnancies	Serology, renal, CBC
Derksen 1994[27]	PC	SLE pregnancies	Serology, disease activity
Farine 1998[28]	RC	SLE pregnancies	Disease activity, Dopplers
Surita 2007[29]	PC	SLE pregnancies	Renal, disease activity
Gaballa 2012[30]	PC	SLE vs non-SLE pregnancies	Serology, disease activity, Dopplers
Gheita 2011[31]	PC	SLE pregnancies	Serology, disease activity, Dopplers
Le Thi Huong 2006[32]	PC	SLE pregnancies	Serology, renal, BP, Dopplers
Ideguchi 2013[33]	RC	SLE pregnancies	Serology, fetal cardiac ultrasound
Jaeggi 2010[34]	CC	Anti-Ro–positive pregnancies	Serology
Jara 2007[35]	RC	SLE vs non-SLE pregnancies	Serology, prolactin, disease activity
Liu 2012[15]	RC	SLE pregnancies	Disease activity, presence of LN, thrombocytopenia
Mokbel 2013[36]	PC	SLE pregnancies	Disease activity
Molad 2005[13]	PC	SLE pregnancies	Serology, CBC, chemistry, disease activity
Moroni 2002[37]	RC	LN pregnancies	Renal, BP, serology
Petri 1995[38]	CC	SLE vs non-SLE pregnancies	AFP
Salazar-Páramo 2002[39]	RC	SLE vs non-SLE pregnancies	Disease activity
Stagnaro-Green 2011[40]	RC	SLE pregnancies	Hypothyroidism
Andrade 2006[41]	RC	SLE pregnancies	Disease activity
Clark 2003[42]	RC	SLE pregnancies	Serology, disease activity
Mavragani 1998[43]	RC	Anti-Ro vs healthy pregnancies	Ro/La
Ogasawara 1995[44]	PC	SLE pregnancies	Serology
Salomonsson 2002[45]	RC	Anti-Ro–positive pregnancies	Ro/La
Tandon 2004[46]	RC	SLE pregnancies	Renal
Leanos-Miranda 2007[47]	PC	SLE pregnancies	Anti-PRL antibodies, disease activity
Mosca 2007[48]	PC	SLE pregnancies	Serology, C1q antibodies, disease activity
Zhao 2013[49]	RC	New-onset SLE in pregnancy	Serology
Giancotti 2011[50]	PC	SLE pregnancies	Dopplers
Gladman 2002[51]	RC	Anti-Ro–positive pregnancies	Fetal echocardiogram
Lockshin 2012[52]	PC	Antiphospholipid pregnancies	Serology
Spence 2006[53]	RC	Anti-Ro–positive pregnancies	Hypothyroidism

Renal = serum creatinine, urinalysis, urine microscopy, and/or urine protein-to-creatinine ratio. RC: retrospective cohort; PC: prospective cohort; CC: case control; SLE: systemic lupus erythematosus; PRL: prolactin; BP: blood pressure; PLT: platelets; AFP: alpha fetal protein; CRP: C-reactive protein; LN: lupus nephritis; UA: uric acid; CBC: complete blood count.

types of monitoring (blood and urine tests, SLE disease activity monitoring, and uterine or umbilical Doppler studies), as well as other types of monitoring. There have been no randomized controlled studies on this topic and so all articles were observational studies. The majority of studies were cohort studies that investigated predictors of poor maternal and fetal outcomes related to measures of SLE activity (both disease-specific and otherwise) throughout pregnancy. Studies included SLE women with varying degrees of disease activity, with some including only women with inactive or mildly active SLE, which might have influenced their findings.

Possible recommendations. Based on our systematic review of the literature, there may be a role for monitoring aPL (LAC and aCL), dsDNA, complement, and anti-Ro and anti-La antibodies prior to conception and early in pregnancy. Complement and dsDNA are likely helpful measures when a flare is suspected because these tests were shown in numerous studies that we examined to be predictive of poor outcomes (20/37 or 54% of studies addressed the predictive value of 1 or more of these monitoring variables). Because patients with quiescent SLE (i.e., with no or low disease activity) have fewer negative outcomes in pregnancy, if these autoantibodies and blood tests are measured prior to conception, it might help physicians stratify pregnancy risk in pregnant women and/or women planning a pregnancy. However, dsDNA, for example, does not always correlate with disease flare and/or activity in all patients and so this is

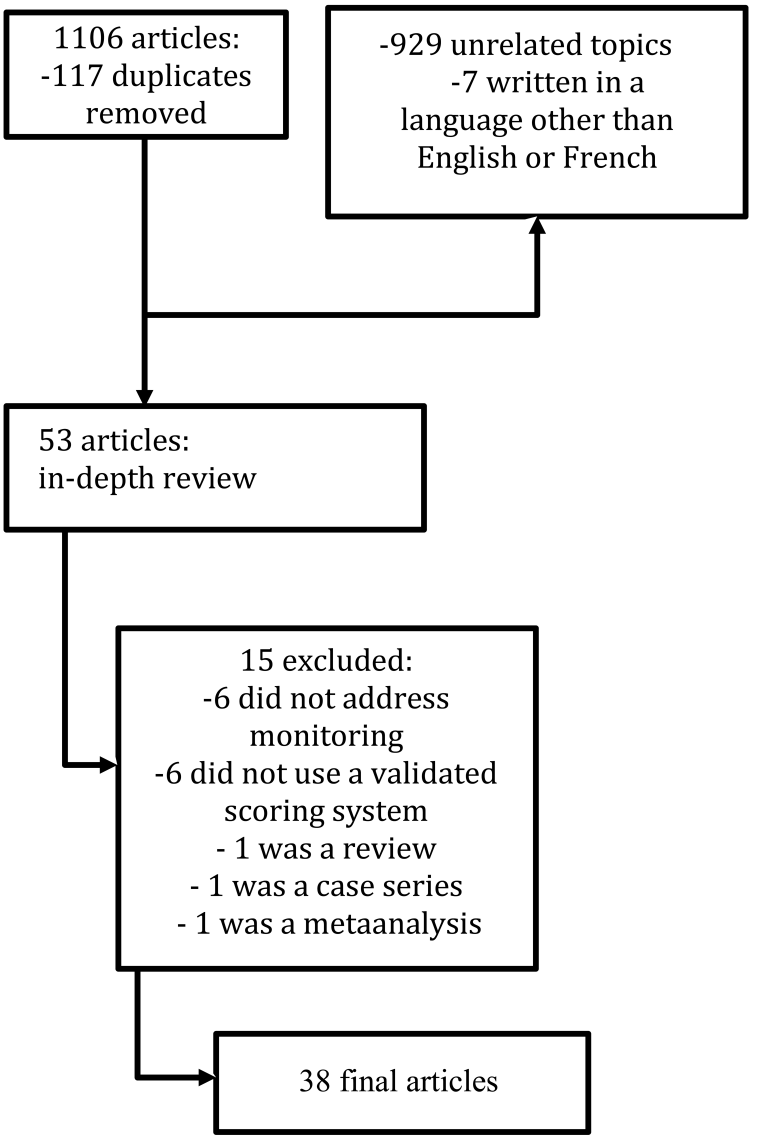

Figure 1. Flowchart of the article selection process.

not universally true, but might still contribute useful information. In addition, complement levels normally increase during pregnancy, which might further complicate its role as a reliable disease activity marker[27].

The available literature also suggests that laboratory testing should be combined with evidence of increased disease activity index as measured by a validated scoring system, such as the SLEDAI, which has also shown to be associated with poor maternal and obstetrical outcomes in numerous studies included in this systematic review (18/38 or 47%). However, no study has directly compared the predictive value of laboratory or clinical data alone as compared to SLEDAI (which combines clinical activity as well as laboratory data).

One expanding area of monitoring in SLE pregnancies relates to the role of uterine and umbilical Doppler studies. Absent end-diastolic velocities of the umbilical artery predict early pregnancy-induced hypertension/preeclampsia and fetal or neonatal death in non-SLE pregnancies[56,57]. Abnormalities demonstrating increased resistive indices, notching of the arteries, or in very severe cases, reversal of end-diastolic flow, are highly predictive of poor fetal outcomes in SLE pregnancies[28,32]. This type of monitoring is minimally invasive and could be considered in the second and third trimester if the expertise exists in the center where the patient's pregnancy is followed. This monitoring could therefore be used at the time of a suspected flare, or at the discretion of the maternal-fetal

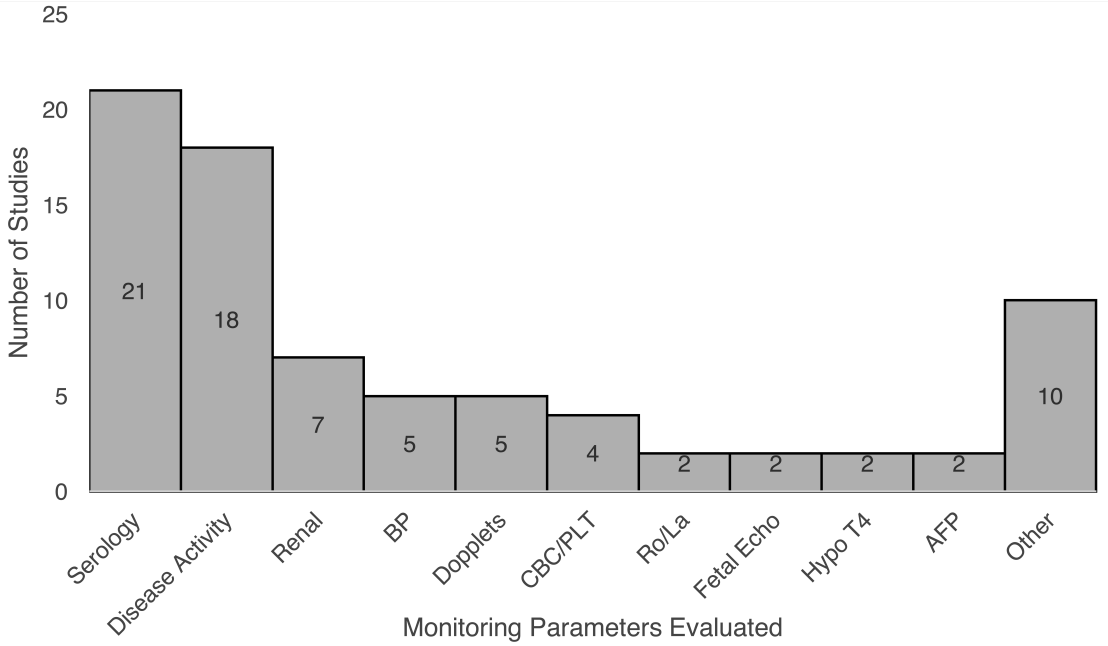

Figure 2. Histogram of the frequency of monitoring variables evaluated in the studies included in the systematic literature review. Serology = anti-DNA, antiextractable nuclear antibody, IgG and IgM anticardiolipin antibodies, lupus anticoagulant, and/or complement levels. Disease activity measured using a validated scoring system (examples include the SLEDAI and ECLAM scores; studies that did not use any type of scoring system to measure disease activity were not included). Renal = serum creatinine, urinalysis, urine microscopy and/or urine creatinine-to-protein ratio. Other = variables evaluated by only 1 included study (e.g., antifactor X11, C1q, and anti-PRL antibodies). AFP: alpha fetal protein; Hypo T4: hypothyroidism; CBC: complete blood count; PLT: platelets; BP: blood pressure; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; ECLAM: European Consensus Lupus Activity Measure; PRL: prolactin.

medicine or obstetrical medicine specialist who is involved in the patient's care.

Four studies looked at alternative or novel tests for predicting poor outcomes in pregnancy such as anti-C1q antibodies, antiprolactin antibodies, antifactor X11, and alpha-fetal protein. Given that these studies have not been reproduced, and many of these serological tests are not widely available, we would not recommend their routine use at this time for monitoring of SLE pregnancies.

Regarding other tests, it is reasonable to measure thyroid stimulating hormone levels early in pregnancy, because hypothyroidism was found to be associated with an increased risk of prematurity in pregnant women from the general population as well as pregnant women with SLE, and was associated with an increased incidence of complete CHB among the offspring of mothers with anti-Ro antibodies[40,53].

Prior to our study and the meeting of the Canadian SLE Working Group, guidelines did not exist regarding what monitoring variables should be measured in SLE pregnancies and at what frequency. A systematic review of the literature revealed there is no evidence to guide the frequency of routine monitoring of complete blood count, chemistry profile including liver enzymes, and urinalysis (routine or microscopy) or urine protein to creatinine levels, during pregnancy with SLE. There is some evidence for a role for measuring anti-Ro and anti-La antibodies prior to conception and early in SLE-related pregnancy, to risk-stratify pregnancies regarding the development of complete CHB. Similarly, the presence of aPL is predictive of poor outcomes, particularly preeclampsia and fetal loss, and so may be reasonable to measure prior to conception or early in pregnancy. Monitoring SLE disease activity should be done, potentially with a validated scoring system such as the SLEDAI because it relies on assessment of different clinical aspects of the disease (i.e., clinical manifestations and specific blood tests). If a flare is suspected, measuring anti-dsDNA antibodies and complement levels may be helpful. Women with SLE should be considered for referral to an expert in maternal-fetal medicine for fetal monitoring with umbilical artery Doppler studies, given that Doppler abnormalities are predictive of adverse outcomes; among pregnant populations without SLE, this monitoring modality has improved fetal outcomes. This systematic review will inform guidelines for the type of and frequency of monitoring of SLE in pregnancy, which are being developed by the Canadian SLE Working Group.

Table 3. Outcomes related to monitoring variables.

Author, Year	Country, No. Patients, No. Pregnancies	Criteria	Conclusions
Al Arfaj 2010[20]	Saudi Arabia, 319 women, 396 pregnancies	1997 ACR	Any history of LN was associated w/prematurity (36.4% w/LN vs 21.1% w/o LN; p 0.01). Active LN was more associated w/pregnancy loss than quiescent LN (26/44, 59.1% vs 27/109, 24.8%; p < 0.001) and more associated w/prematurity (61.1% vs 30%; p = 0.014). Presence of aPL was associated w/fetal loss (128 live births/205 deliveries were aPL+, 62.4% vs 141/178 deliveries were aPL–, 79.2%; p = 0.004). SLE flare was associated w/fetal loss (71 live births/118 deliveries w/flare, 60.2% vs 198/265 pregnancies w/o flare, 74.7%; p = 0.004). Flare was associated w/IUGR (38.1% pregnancies w/flare vs 20.3% w/o flare, p < 0.003). HTN was associated w/IUGR (44.6% HTN pregnancies vs 20.2% non-HTN; p = 0.01). HTN was associated w/prematurity (48.9% HTN pregnancies vs 21.2% non-HTN; p < 0.0001).
Alshohaib 2009[21]	Saudi Arabia, 20 women, 20 pregnancies	LN on biopsy	20 pregnant women w/quiescent class IV LN. Proteinuria increased significantly from 32 weeks GA to 34–36 weeks GA (p < 0.05). APO occurred in 6 of 20 patients and all were associated w/the development of anti-dsDNA+ (no p value available for comparison).
Andrade 2006[41]	USA, 63 women and pregnancies	1997 ACR	The SDI score after pregnancy was significantly higher than before it (mean SDI score before: 0.19; mean SDI score after: 0.60, p < 0.0001). Damage accrual was strongly associated w/pregnancy duration, disease activity, and damage accrual at the visit immediately prior to the pregnancy outcome (p = 0.006, p < 0.001 and p < 0.001, respectively), and moderately associated w/total disease duration (p = 0.039).
Bertolaccini 2007[22]	England, 83 pregnant women (control 123 healthy deliveries)	1982 criteria	Patients w/APO were more likely to have anti-fXII IgG but not IgM [37% vs 4%, OR 14 (95% CI 4.5–43) and 9% vs 3%, OR 2.8. (95% CI 0.6–13)]. Patients w/miscarriage and fetal death were more likely to have anti-fXII IgG [35% vs 4%; OR 12 (95% CI 3.7–42) and 40% vs 4%, OR 16 (95% CI 4–62)].
Brucato 2002[23]	Italy, 53 SLE Ro+ vs 58 SLE Ro–	1997 ACR	There was no significant difference in APO between women w/ and w/o Ro antibodies (p = NS for multiple comparisons); CHB was more common among Ro+ (no p value for comparison; only 2 cases of CHB).
Buyon 2015[2]	USA and Canada, 385 women w/SLE	1997 ACR	First trimester predictors of APO included LAC (OR 8.32, 95% CI 3.59–19.26), antihypertensive use (OR 7.05, 95% CI 3.05–16.31), PGA score > 1 (OR 4.02, 95% CI 1.84–8.82), and platelet count (OR 1.33, 95% CI 1.09–1.63 per decrease of 50×10^9 cells/l).
Clark 2003[42]	Canada, 88 women and pregnancies	1997 ACR	SLE patients w/preterm deliveries were more likely to be taking ≥ 10 mg/day prednisone during their pregnancy (50.0% vs 22.2%, p = 0.028) and had more aCL IgG positivity (p = 0023). The mean weeks of gestation was shorter for aCL+ IgG compared to the aCL– group (34.9 ± 4.4 vs 37.5 ± 3.2 weeks, respectively; p = 0.032). There was no difference in second trimester disease activity between the term and preterm groups (33.3% and 36.4% of each group had a SLEDAI of 0). More women in the term group received no medication during their pregnancies compared to women in the preterm group (20.0% vs 0.0%, p = 0.031).
Clowse 2011[24]	USA, 203 women, 267 pregnancies	1997 ACR	The presence of anti-dsDNA in the second trimester was associated w/fetal loss (11 vs 9, p = 0.039) and preterm birth (34 vs 46, p = 0.032). Low C3 in the second trimester was associated w/fetal loss (7/131 vs 13/92, p = 0.021). High disease activity (PGA ≥ 2) in the second trimester was associated w/prematurity (62/194 vs 18/29, p = 0.0003).
Clowse 2013[9]	USA, 39 women, 40 pregnancies	1997 ACR	When measured at mid-gestation (20–28 weeks) low estradiol (R = 0.44, p = 0.01), increased ferritin (R = –0.37, p = 0.05), or increased uric acid (R = –0.43, p = 0.02) may correlate w/prematurity and earlier gestational age at delivery. Disease activity did not correlate w/prematurity (measured w/SLEPDAI and PGA). Overall, the cohort had low SLE disease activity.

Table 3. (Continued) Outcomes related to monitoring variables.

Author, Year	Country, No. Patients, No. Pregnancies	Criteria	Conclusions
Cortés-Hernández 2002[25]	Spain, 60 women, 103 pregnancies	1982 criteria	Among those w/a history of LN, aCL Ab positivity was associated w/fetal loss: 0/5 normal births vs 9/11 (82%) w/a fetal loss were aCL Ab+, $p < 0.05$. HTN was associated w/ APO: 0/5 normal births vs 2/3 (67%) pregnancies w/ APO were hypertensive, $p < 0.005$. Among all SLE pregnancies, aCL Ab positivity was associated w/ APO: 11/43 (26%) normal births vs 11/25 (44%) births w/ APO were aCL Ab+, $p < 0.05$. HTN at conception was associated w/ fetal loss: 0/43 normal births vs 6/27 (22%) births w/ a fetal loss were hypertensive, $p < 0.05$. Low C3 associated w/ fetal loss: 11/43 (26%) normal births vs 12/27 (44%) of births w/ APO had low C3, $p < 0.05$. Women who flared (n = 34) tended to have a history of > 3 flares/yr up until 3 mos PTC compared to those who did not flare in pregnancy (n = 67, p = 0.035), and tended to have a higher mean SLEDAI in the 3 mos PTC (3.13 vs 1.64, p = 0.03).
Daskalakis 2009[26]	Greece, 11 women, 12 pregnancies	1982 criteria	All patients w/ LN on renal biopsy. Renal function deteriorated in 3/12 (25%). Preeclampsia occurred in 3/12 (25%). An APO was observed in 10/12 pregnancies (83%). No comparisons were made.
Derksen 1994[27]	The Netherlands, 25 women, 35 pregnancies	1982 ARA criteria	Disease activity monitored w/ SLEDAI. Up to 14/35 pregnancies (40%) manifested evidence of disease flare in pregnancy. aPL+ tended to have fewer live births and more preeclampsia: 10/16 (63%) vs 15/19 (79%) had live births w/ aPL+ and 42% vs 13% had preeclampsia. No p values calculated.
Farine 1998[28]	Canada, 56 women and pregnancies	1982 ARA criteria	R/AEDF was associated w/ APO. Preeclampsia occurred in 6/50 (12%) of those w/ NEDF vs 4/6 (67%) w/ R/AEDF (OR 14, 95% CI 2.19–98.13; p = 0.007). IUGR occurred in 12/50 (24%) w/ NEDF vs 4/6 (67%) w/ R/AEDF (OR 6.3, 95% CI 1.03–38.98; p = 0.049). Preterm delivery occurred in 12/50 (24%) w/ NEDF vs 83% w/ R/AEDF (OR 15.8, 95% CI 1.68–149.17; p = 0.008).
Gaballa 2012[30]	Egypt, 40 women and pregnancies w/ SLE (control 35 nonpregnant SLE)	1997 ACR	There was a tendency for flare among pregnant SLE more than nonpregnant SLE: 21/35 (60%) vs 14/40 (37.5%), p = 0.052. Those who flared were more likely to have a SLEDAI > 2 at conception: 15/25 (60%) vs 20%, p = 0.013. APO was associated w/ more severe flare in pregnancy: 0/15 full term pregnancies vs 7/16 (43.8%) APO had a severe flare, $p < 0.05$. aPL positivity was associated w/ fetal loss: 1/15 (0.07%) term pregnancies vs 6/9 (67%) fetal losses were aPL +ve, $p < 0.05$. Active renal disease was associated w/ APO: 1/15 (0.07%) term pregnancies vs 8/16 (50%) w/ APO had active renal disease at conception, $p < 0.05$.
Gheita 2011[31]	Egypt, 36 women and pregnancies	1997 ACR	There was a higher SLEDAI and SLICC in those w/ APO and the difference reached significance for the disease activity at the 24th week (12.13 ± 3.27 and 7.57 ± 2.18, respectively, p = 0.005). Umbilical RI and PI were significantly higher in those w/ APO starting from the 30th week until full term: 0.71 ± 0.05 vs 0.66 ± 0.04, p = 0.018 for RI and 1.22 ± 0.26 vs 0.98 ± 0.09, p = 0.03 for PI at 30 weeks GA.
Giancotti 2011[50]	Italy, 20 women and pregnancies	1997 ACR	Doppler of the uterine arteries was altered in 9/20 (45%) pregnancies w/ mean RI > 0.79. Two of these women had spontaneous abortion during the first trimester of pregnancy; the other 7 pregnancies ended w/ preterm deliveries. 11 women (7 w/ altered uterine artery US Doppler and 4 w/ altered fetal US Doppler) had preterm deliveries.
Gladman 2002[51]	Canada, 105 women, 118 pregnancies	Anti-Ro or -La–positive	No case of CCHB was observed in 102 pregnancies w/o a history of CCHB. Among 12 pregnancies w/ a history of CCHB, 1 fetus developed CCHB. Results suggest that the risks of CCHB w/o a history are low.
Le Ti Huong 2006[32]	France, 84 women, 116 pregnancies	1997 ACR	Abnormal umbilical artery Doppler in the second trimester predicted fetal death: 3/8 (37.5%) fetal deaths had an abnormal umbilical artery Doppler vs 3/92 (3.3%) live births (OR 17.8, 95% CI 2.84–111.68; p = 0.006). Notched uterine artery Doppler predicted fetal death: 5/8 (62.5%) fetal deaths were abnormal vs 10/92 (10.9%) of live births (OR 13.67, 95% CI 2.83–66, p = 0.002).
Ideguchi 2013[33]	Japan, 41 women, 55 pregnancies	1997 ACR	IUFD was associated w/ aPL positivity: 2/8 (25%) fetal deaths vs 1/42 (2%) term pregnancies were aPL+. IUFD was associated w/ low C3: 4/8 (50%) of fetal deaths vs 6/42 (14%) had low C3.
Jaeggi 2010[34]	Canada, 40 fetuses/neonates w/ CCHB compared to 146 w/o	N/A	All mothers of children w/ cardiac involvement had moderate to high anti-Ro antibody levels (> 50 U/ml) as compared w/ only 44% of mothers of healthy infants ($p < 0.0001$). In prospectively screened fetuses only, the event rate of CCHB was 5% (3 of 59 cases) for fetuses w/ exposure to anti-Ro levels > 50 U/ml, OR 7.8 (0.4–159).
Jara 2007[35]	Mexico, 15 women and pregnancies w/ SLE	1997 ACR	Elevated prolactin levels correlated w/ M-SLAM: r = 0.43, $p < 0.01$ in pregnancies complicated by preterm birth.

Table 3. (Continued) Outcomes related to monitoring variables.

Author, Year	Country, No. Patients, No. Pregnancies	Criteria	Conclusions
Leanos-Miranda 2007[47]	Mexico, 99 SLE pregnancies (control 151 healthy pregnancies)	1997 ACR	Women w/ SLE and anti-PRL Ab were less likely to flare in pregnancy than women w/o: 2/13 (15.4%) vs 54/86 (62.8%), p = 0.004. Fetal complications were more common among women w/o anti-PRL Ab than women w/ Ab+: 57.5% vs 1/13 (7.7%), p = 0.002.
Lockshin 2012[52]	USA, 144 women and pregnancies	1997 ACR	LAC was the primary predictor of APO after 12 weeks of gestation in aPL-associated pregnancies. aCL antibody and anti-β2-GPI, if LAC is not also present, did not predict APO. LAC conferred an RR of 12.15 (95% CI 2.92–50.5) for APO, p = 0.0006. SLE conferred an RR of 2.16 (95% CI 1.27–3.68) for APO, p = 0.05. Prior thrombosis conferred a RR of 1.9 (95% 1.14–3.17) for APO, p = 0.01.
Liu 2012[15]	China, 105 women, 111 pregnancies	1997 ACR	Active SLE (SLEDAI > 4) vs quiescent SLE was associated w/ the following: Prematurity: 25/47 (53.2%) vs 3/34 (8.8%), p < 0.001 SGA: 21/48 (43.8%) vs 3/35 (8.6%), p < 0.001 Preeclampsia: 23/53 (43.4%) vs 2/35 (5.7%), p < 0.001 Fetal loss: 9/53 (17%) vs 1/35 (2.9%), p = 0.047 Preeclampsia was a predictor of pregnancy loss (OR 14.83, 95% CI 3.83–57.41, p < 0.001), prematurity (OR 8.04, 95% CI 2.00–32.34, p = 0.003), and SLE flare in pregnancy (OR 8.92, 95% CI 2.25–35.44, p = 0.002). Thrombocytopenia was a predictor of pregnancy loss (OR 4.43, 95% CI 1.12–17.6, p = 0.035), and SLE flare in pregnancy (OR 4.03, 95% CI 1.24–17.25, p = 0.022).
Mavragani 1998[43]	China, 154 Ro+ women (78 SLE and 76 non-SLE) vs 142 Ro– (71 SLE)	1997 ACR	Anti-Ro positivity was not associated w/ an increase in APO between SLE patients 28/78 (35.9%) vs 31/71 (43.7%), p = NS or between SLE patients and healthy controls 53/154 (34.4%), p = NS.
Mokbel 2013[36]	Egypt, 34 women, 37 pregnancies	1997 ACR	Planned pregnancy and SLEDAI at the beginning of pregnancy were significantly associated w/ fetal loss at univariate analysis. However, there were no significant predictors of fetal loss at binary logistic regression analysis. Effect measures not reported.
Molad 2005[13]	Israel, 20 women, 29 pregnancies	1997 ACR	In this study, no multivariate models reached statistical significance. Increased dsDNA (r = 0.5, p = 0.03), proteinuria (r = 0.6, p = 0.02), and leukopenia (r = 0.6, p = 0.01) were associated w/ postpartum flare in univariate analyses. Increased pregestational SLEDAI did not have a statistically significant effect on risk for postpartum flare. APO (including preeclampsia, IUGR, and prematurity) were associated w/ low pregestational albumin (r = 0.5, p = 0.01) and increased dsDNA (r = 0.5, p = 0.03). SLEDAI was not statistically associated w/ APO.
Moroni 2002[37]	Italy, 48 women, 70 pregnancies w/LN	1997 ACR	Predictors of fetal loss in multivariate analysis included arterial hypertension (OR 6.4, 95% CI 1.4–28.9; p = 0.05), proteinuria (OR13.3, 95% CI 2.6–66.6; p = 0.025), and aPL (OR 17.8, 95% CI 3.8–81.4, p = 0.01). The presence of any sign of activity of renal disease (plasma creatinine > 1.2 mg/dl or proteinuria > 0.5 g/24 h, w/ urinary red blood cells > 5 cells/HPF) at the beginning of pregnancy was the only predictor of renal flares. Renal flares occurred in 1/20 pregnancies (5%) w/ quiescent renal disease vs 12/31 pregnancies (39%) w/ active renal disease (p < 0.01).
Mosca 2007[48]	Italy, 19 women, 21 pregnancies	1997 ACR	aPL was associated w/ APO (p < 0.05); no effect measure reported. Anti-C1q and anti-dsDNA antibodies were not predictive of APO or of SLE flare (p = NS); no effect measures reported.
Ogasawara 1995[44]	Japan, 12 women and pregnancies	1982 ARA	aPL was associated w/ IUFD in a small number of women studied; 6/7 (85.7%) of aPL– women had live births vs 2/4 (50%) of aPL+ women. One aPL– woman had an SAB. No p value available for comparison.
Petri 1995[38]	USA, 55 women and pregnancies (control 1001 women w/o SLE)	1982 ARA	AFP was higher in SLE pregnancies (1.425 ± 0.73 vs 1.169 ± 0.5, p = 0.001). The 4 patients w/ abnormal AFP (> 2.3) were more likely to have preterm deliveries (31.5 vs 36.3 weeks, p = 0.02) and were more likely to have aCL (p = 0.03).
Salazar-Páramo 2002[39]	Mexico, 15 SLE pregnancies (control 15 non-SLE pregnancies)	1997 ACR	IgG aCL was associated w/ fetal loss (RR 7.8 ,95% CI 1.1–58; p = 0.01). Anti-dsDNA was associated w/ fetal loss (RR 12, 95% CI 1.7–86; p = 0.01). Mild SLE flare was not associated w/ APO, p > 0.05. Severe flare was associated w/ fetal loss (RR 13.9, 95% CI 1.7–100; p = 0.01).

Table 3. (Continued) Outcomes related to monitoring variables.

Author, Year	Country, No. Patients, No. Pregnancies	Criteria	Conclusions
Salomonsson 2002[45]	Sweden, 8 Ro/La+ pregnancies w/ CCHB, and 26 Ro/La+ w/o CCHB	N/A	IgG anti-Ro 52-kd antibodies could be detected in all mothers (9 of 9) who gave birth to children w/ CCHB, as well as in all 8 of their affected children. In mothers of unaffected children, IgG anti-Ro 52-kd occurred less frequently and at lower levels ($p < 0.02$).
Spence 2006[53]	Canada, 87 Ro+ women, 102 pregnancies	N/A	5/9 (56%) of children born to women w/ anti-Ro and hypothyroidism had CCHB compared to 10/78 (13%) of children born to women w/ anti-Ro and normal thyroid function; OR 8.63 (95% CI 1.63–48.08; $p = 0.006$).
Stagnaro-Green 2011[40]	USA, 63 women and pregnancies	1997 ACR	Preterm delivery was higher among SLE cases w/ thyroid disease 10/15 (67%) as compared to women who were euthyroid 6/34 (18%), $p < 0.002$.
Surita 2007[29]	N/A	N/A	Active SLE was associated w/ poor obstetrical outcomes. Disease flare was more common in women w/ renal involvement and was related to a greater prevalence of preeclampsia.
Tandon 2004[46]	N/A	1997 ACR	Pregnancy in patients w/ renal disease and SLE was not associated w/ a more significant deterioration of renal function compared to nonpregnant patients w/ SLE and renal disease ($p = NS$).
Zhao 2013[49]	China, 48 women w/ SLE onset in pregnancy, matched w/ 65 women w/ SLE and not pregnant	1997 ACR	LN and severe thrombocytopenia were more commonly seen in new-onset SLE during pregnancy than in patients w/o pregnancy (68.8 vs 35.4% and 25 vs 9.2%, respectively, $p < 0.05$). Compared to LN patients w/o pregnancy ($n = 23$), LN patients w/ pregnancy ($n = 33$) had more prominent proteinuria and nephrotic syndrome ($p < 0.05$).

ACR: American College of Rheumatology; SLE: systemic lupus erythematosus; LN: lupus nephritis; SDI: Systemic Lupus International Collaborating Clinics/ACR Damage Index; HTN: hypertension; IUFD: intrauterine fetal death; CCHB: complete congenital heart block; LAC: lupus anticoagulant; aPL: antiphospholipid antibodies; HPF: high-power field; APO: adverse pregnancy outcomes; GA: gestational age; SGA: small for GA; IUGR: intrauterine growth restriction; PGA: physician's global assessment; R/AEDF: reversed or absent end-diastolic flow; NEDF: notched end-diastolic flow; SLICC: Systemic Lupus International Collaborating Clinics; PTC: prior to conception; PRL: prolactin; anti-β2-GPI: apolipoprotein H; SAB: spontaneous abortion; NS: not significant; aCL: anticardiolipin antibodies; RI: resistance index; PI: pulsatility index; US: ultrasound; M-SLAM: modified systemic lupus activity measurement; ARA: American Rheumatism Association; AFP: alpha fetal protein; N/A: not available; SLEDAI: SLE Disease Activity Index; Ab: antibody .

Table 4. Quality assessment by Newcastle-Ottawa scale.

Author and Year	Selection (/4)	Comparability (/2)	Outcome (/3)	Total (/9)
Al Arfaj 2010[20]	4	2	3	9
Alshohaib 2009[21]	2	1	2	5
Brucato 2002[23]	3	1	3	7
Buyon 2015[2]	4	2	3	9
Clowse 2011[24]	3	1	3	7
Clowse 2013[9]	3	1	2	6
Cortés-Hernández 2002[25]	1	1	3	7
Daskalakis 2009[26]	3	1	3	5
Derksen 1994[27]	3	1	3	6
Farine 1998[28]	3	1	3	7
Surita 2007[29]	3	1	3	6
Gaballa 2012[30]	3	2	1	6
Gheita 2011[31]	3	1	1	5
Le Ti Huong 2006[32]	2	1	2	5
Ideguchi 2013[33]	3	1	2	6
Jara 2007[35]	2	1	1	4
Liu 2012[15]	3	2	2	7
Mokbel 2013[36]	3	2	2	7
Molad 2005[13]	3	1	2	6
Moroni 2002[37]	2	1	2	5
Salazar-Páramo 2002[39]	2	1	2	5
Stagnaro-Green 2011[40]	3	1	3	7
Andrade 2006[41]	3	2	2	7
Clark 2003[42]	3	1	2	6
Mavragani 1998[43]	3	2	2	7
Ogasawara 1995[44]	3	1	2	6
Tandon 2004[46]	3	2	3	8
Leanos-Miranda 2007[47]	2	1	2	5
Mosca 2007[48]	3	0	2	5
Giancotti 2011[50]	3	1	3	7
Gladman 2002[51]	3	1	3	7
Lockshin 2012[52]	4	2	3	9
Spence 2006[53]	1	1	3	5
Bertolaccini 2007[22]	1	1	2	4
Jaeggi 2010[34]	3	1	3	7
Petri 1995[38]	3	2	3	8
Salomonsson 2002[45]	3	1	3	7
Zhao 2013[49]	4	1	3	8

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