A Systematic Review and Meta-Analysis of Pregnancy Outcomes in Patients with Systemic Lupus Erythematosus and Lupus Nephritis

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Background and objectives: Studies of the impact of systemic lupus erythematosus (SLE) and its pregnancy complications have yielded conflicting results. Major limitations of these studies relate to their small numbers of patients and retrospective designs. The aim of this study was to perform a systematic literature review of pregnancy outcomes in women with SLE and a meta-analysis of the association of lupus nephritis with adverse pregnancy outcomes.

Design, setting, participants, & measurements: We searched electronic databases from 1980 to 2009 and reviewed papers with validity criteria. Random-effects analytical methods were used to evaluate pregnancy complications rates.

Results: Thirty-seven studies with 1842 patients and 2751 pregnancies were included. Maternal complications included lupus flare (25.6%), hypertension (16.3%), nephritis (16.1%), pre-eclampsia (7.6%), and eclampsia (0.8%). The induced abortion rate was 5.9%, and when excluded, fetal complications included spontaneous abortion (16.0%), stillbirth (3.6%), neonatal deaths (2.5%), and intrauterine growth retardation (12.7%). The unsuccessful pregnancy rate was 23.4%, and the premature birth rate was 39.4%. Meta-regression analysis showed statistically significant positive associations between premature birth rate and active nephritis and increased hypertension rates in subjects with active nephritis or a history of nephritis. History of nephritis was also associated with pre-eclampsia. Anti-phospholipid antibodies were associated with hypertension, premature birth, and an increased rate of induced abortion.

Conclusions: In patients with SLE, both lupus nephritis and anti-phospholipid antibodies increase the risks for maternal hypertension and premature births. The presented evidence further supports timing of pregnancy relative to SLE activity and multispecialty care of these patients.

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Systemic lupus erythematosus (SLE) is a multisystem autoimmune connective tissue disorder that primarily affects women of childbearing age. Normal fertility and sterility rates have been reported, and as such, pregnancy is a frequent occurrence in these patients (1).

Two major issues exist regarding the risks and management of pregnancy in women with SLE and renal disease. First, pregnancy may increase SLE activity and the short- and long-term adverse effects on renal function, potentially leading to accelerated progression to end-stage renal disease. Second, these pregnancies are at high risk for maternal and fetal complications, including spontaneous abortion and premature delivery, intrauterine growth retardation (IUGR), and superimposed pre-eclampsia. However, multiple studies directed at elucidating the impact of SLE on pregnancy outcomes have yielded conflicting results.

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Although early studies suggested an association between SLE and poor pregnancy prognosis (2,3), more recent data have shown improved outcomes, (4,5), including recently quoted live birth rates in at least 85% of pregnancies. Published data have identified several risk factors for poor pregnancy outcomes, including hypertension (6), anti-phospholipid syndrome, and SLE renal involvement (7–9).

The impact of lupus nephritis on fetal and maternal prognoses is not fully understood and has been a subject of controversy. Stable renal disease throughout pregnancy has been observed in some SLE patients, even in those with lupus nephritis and diffuse glomerular lesions (10,11). In contrast, the rate of pregnancy loss in patients with active nephritis was reported to be as high as 60% (12). However, the studies supporting this association are retrospective in character, with relatively small numbers of patients. In this study, we perform a systematic review and meta-analysis by combining information from relevant studies to (*1*) examine the association of maternal and fetal complications and SLE and (*2*) study the effects of the activity of lupus nephritis, including the World Health Organization biopsy classification, and the presence of anti-phospholipid antibodies (APAs) on pregnancy outcomes.

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Materials and Methods

Study Selection

We conducted an electronic literature search from 1966 to April 2009 in Medline, PubMed, Embase, Lilacs, Science Citation Index, and the Cochrane Controlled Trials Register. We used a protocol that included the Cochrane Collaboration's search strategy for randomized controlled trials and the following terms: SLE, pregnancy outcome, lupus nephritis.

Studies were included if they addressed the outcome of SLE pregnancies and fulfilled the predefined requirements. Study quality was assessed using the study validation score (Table 1), developed by the investigators. Variables included are defined in Table 1. All variables were scored equally, with a value of four or greater used to classify papers for inclusion.

We contacted the authors of these papers to retrieve additional data not published in their analyses. Language was not an exclusion criterion, and translators were used when required. Data were extracted into a preformed Microsoft Excel database using predefined variables to obtain data about pregnancies and maternal and fetal outcomes. Study selection, data extraction, and assigning of a quality score were performed independently by two investigators, with discrepancies resolved by consensus.

Statistical Analyses

The primary fetal outcome was unsuccessful pregnancy, which included spontaneous abortion, stillbirth, or neonatal death. Secondary fetal endpoints included the individual outcomes for unsuccessful pregnancy and IUGR. For all fetal complications, induced abortions were excluded from further analysis. Maternal complications included maternal death, stroke, hypertension, pre-eclampsia or eclampsia, nephritis, and SLE flares.

Pooled event rate estimates and 95% confidence intervals (CIs) were computed using a fixed-effects approach, which reflects only the specific studies included in the analysis. Each complication was tested for study heterogeneity, with those detected as such further analyzed using the random-effects technique. Unlike the fixed-effects approach, the random-effects extends valid inferences to larger populations.

Random-effects meta-regression based on nonlinear mixed modeling was used to investigate the effect of nephritis on each of the maternal and fetal complications that showed heterogeneity across studies. P values for testing for heterogeneity or associations were computed based on the difference in log-likelihood statistics from two nested models compared with a χ^2 distribution. All tests are two-tailed, with $P < 0.05$ considered statistically significant.

Results

Study Selection and Demographics

Our literature search yielded 133 studies, of which 74 were deemed unsuitable by title alone. The remaining 59 were independently assessed, and 37 fulfilled study entry criteria (Figure 1). Twenty-nine studies were case series, five studies were case-control studies, and three were cohort studies. Twelve studies were prospective, and 25 studies were retrospective. The 37 studies (3–7,9,11,13–42) included a total of 1842 patients and 2751 pregnancies (Table 2).

Table 1. Study validation criteria

SLE defined using 1982 American College of Rheumatology criteria
Histology using World Health Organization classification
Defined hypertension in pregnancy
Defined pregnancy outcomes
Follow up for at least 1 month
At least 80% patients had follow up
SLE disease activity index used

Study heterogeneity was noted, with variable definitions of a history of nephritis, active nephritis and flare used in the included papers (Table 3). The 1982 American College of Rheumatology criteria for the diagnosis of systemic lupus erythematosus (43) were the most commonly used criteria, but others were also used (Table 3). Those patients who had a renal biopsy were classified according to the World Health Organization 1995 Classification System. The definitions of SLE activity varied; a few used the systemic lupus erythematosus disease activity index (SLEDAI) (Table 3).

Of the 37 papers included, varying terminology was used to identify women with a history of lupus nephritis, but inactive renal disease at conception, including "quiescent lupus nephritis." For the purposes of this study, we defined having a history of nephritis as those patients with clinical, laboratory, and/or histologic evidence of lupus nephritis at the time of conception. Active nephritis was defined as the presence of proteinuria >500 mg in 24 hours and/or having an active urine sediment, with or without an elevation in serum creatinine, at the time of conception; having a lupus nephritis flare during pregnancy; and having a new diagnosis of lupus nephritis during pregnancy. APAs were considered positive if any of the following were present: anti-cardiolipin antibodies, and/or lupus anticoagulant, and/or anti-phospholipid syndrome (positive APA and clinical manifestations, including arterial and/or venous thromboses). Flares were defined as having a flare of SLE and/or lupus nephritis during pregnancy and up to, on average, 6 months postpartum, attributable to pregnancy.

Significantly, not all participants in every study had biopsy-proven lupus nephritis, although all had a confirmed diagnosis of SLE upon entry into their respective studies. Some papers included exclusively those patients with biopsy-proven lupus nephritis ($n = 9$); others had a varying number of patients with biopsy-proven lupus nephritis (Ta-

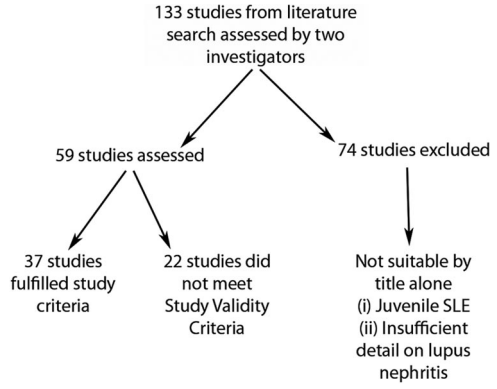

Figure 1. Flow diagram of studies assessed and used in this meta-analysis.

Table 2. Characteristics of the studies included in the analyses

No.	Author	Year	No. Patients	No. of Pregnancies	APA Positive	History of Nephritis	Active Nephritis	Flare During Pregnancy
1	Daskalakis *et al.* (6)	1998	11	12	6	12	7	4
2	Mintz *et al.* (13)	1986	75	102	n/a	58	9	55
3	Sittiwangkul *et al.* (14)	1999	42	48	n/a	24	13	16
4	Oviasu *et al.* (15)	1991	25	53	8	53	6	1
5	Le Houng *et al.* (16)	1997	38	62	28	17	1	17
6	Rahman *et al.* (9)	1998	73	141	17	n/a	23	72
7	Georgiou *et al.* (17)	2000	47	59	10	n/a	6	14
8	Imbasciati *et al.* (11)	1984	19	26	n/a	18	18	21
9	Le Thi Houng *et al.* (3)	1994	84	103	15	28	8	34
10	Packham *et al.* (18)	1992	41	64	21	46	34	16
11	Wong *et al.* (19)	1991	22	29	6	17	11	13
12	Ruiz-Irastorza *et al.* (41)	1996	68	78	33	0	12	63
13	Julkunen *et al.* (20)	1993	112	242	56	22	n/a	n/a
14	Nossent and Swaak (21)	1990	37	63	17	5	2	21
15	Houng *et al.* (7)	2001	22	32	17	32	4	5
16	Wagner *et al.* (22)	2009	58	90	n/a	43	23	2
17	Tandon *et al.* (23)	2004	53	78	0	78	65	33
18	Wong *et al.* (4)	2006	17	24	0	n/a	12	5
19	Whitelaw *et al.* (24)	2008	31	47	6	13	2	13
20	Soubassi *et al.* (25)	2004	22	24	12	24	12	20
21	Surita *et al.* (26)	2007	67	76	24	47	29	58
22	Molad *et al.* (27)	2005	20	29	11	2	n/a	6
23	Phadungkiatwattana *et al.* (28)	2007	68	122	0	0	8	20
24	Imbasciati *et al.* (29)	2008	81	113	27	113	34	34
25	Clowse *et al.* (30)	2005	203	267	124	52	42	32
26	Cortes-Hernandez *et al.* (31)	2002	60	103	17	20	8	39
27	Cavallasca *et al.* (32)	2008	61	72	20	20	12	14
28	Chandran *et al.* (33)	2005	31	52	17	17	0	3
29	Clark *et al.* (34)	2003	88	88	16	22	2	0
30	Moroni *et al.* (35)	2002	48	70	16	51	25	13
31	Carmona *et al.* (36)	2005	35	42	11	42	13	8
32	Wang *et al.* (37)	2006	66	66	n/a	26	26	15
33	Zhang *et al.* (38)	2007	26	34	n/a	34	n/a	8
34	Julkunen *et al.* (40)	1993	16	26	8	26	n/a	2
35	Lima *et al.* (42)	1995	90	108	44	14	14	74
36	Derksen *et al.* (5)	1994	25	35	16	14	9	6
37	Carmona *et al.* (39)	1999	46	60	16	10	2	15
	Totals (*n*)		1842	2751	619	1000	492	747

n/a, not available, *i.e.,* not reported in the original paper.

ble 3). The proportion of patients with histories of lupus nephritis varied, as did the number of patients with active lupus nephritis upon study entry (Table 3). Very few biopsies were performed to confirm the diagnosis of lupus nephritis during pregnancy. The majority of papers included patients with both active and inactive SLE at the time of conception; only three papers assessed inactive disease only (6,16,25) and one paper looked at stable disease (15).

Analysis

Among 37 studies selected and reviewed, 34 studies had data for active nephritis at the time of conception, whereas 33 reported data on history of nephritis. The fixed-effect and random-effect rates estimated for active nephritis were 19.0 and 16.1% of pregnancies, respectively. The interstudy rates of nephritis were highly variable, as were the overall rate estimates from the fixed-effect (40.5%) and random-effect (60.9%) approaches. Thirty-two studies included data on APAs, with a positive APA rate of 26.2 (fixed-effect) and 23.6% (random-effect) of pregnancies.

Fixed-effects and random-effects rates were estimated for both fetal events (Table 4) and maternal events (Table 5). In addition, a test for study heterogeneity was performed for each complication. For the sake of brevity, and because heterogene-

ity was detected for most complications, only the random-effects estimates are discussed.

The induced abortion rate across all studies was 5.9% (95% CI, 3.2 to 8.6%). When these pregnancies were excluded, the most common fetal complications included spontaneous abortion (16.0%), IUGR (12.7%), stillbirth (3.6%), and neonatal deaths (2.5%). In all, 23.4% (95% CI, 19.5 to 27.3%) of pregnancies, without induced abortion, were unsuccessful. Among all live births, the premature birth rate was considerably high at 39.4% (95% CI, 32.4 to 46.4%).

The most frequent maternal complications included lupus flare (25.6%), hypertension (16.3%), nephritis (16.1%), and pre-eclampsia (7.6%). Severe complications, including eclampsia, stroke, and maternal death, were observed in ~1% of subjects. Maternal deaths occurred because of opportunistic infections, sepsis, flares of lupus nephritis, and renal impairment (3,7,11,17,22,30,33,35). Of these deaths, three of the reported cases described the renal histologic subclass, and all had proliferative disease (7,17,22). Hemodialysis was rarely reported and included two patients who required hemodialysis during their pregnancies (32) and one patient who progressed to end-stage renal disease and continued dialysis therapy (35).

Random-effects meta-regression was performed to assess the effects of nephritis on maternal and fetal complications. Active nephritis was significantly associated with maternal hypertension ($P < 0.001$) and premature birth ($P = 0.020$), whereas a history of nephritis was associated with hypertension ($P < 0.001$) and pre-eclampsia ($P = 0.017$) (Table 6). After controlling for hypertension, the association between active nephritis and premature birth was still statistically significant ($P = 0.016$).

Additional analyses were performed to assess for an association between APAs and pregnancy outcomes. Similar to active nephritis, the presence of positive APAs was associated with hypertension ($P = 0.029$) and premature birth ($P = 0.004$). The presence of APAs correlated with an increased rate of induced abortion ($P = 0.016$). Importantly, there was not a statistically significant association between having APAs and the rate of active nephritis ($P = 0.82$).

Subgroup analyses were performed using only those studies with a 100% rate of biopsy-proven lupus nephritis on study entry ($n = 9$). These showed statistically significant associations between active nephritis and hypertension ($P = 0.010$) and between having a history of nephritis and hypertension ($P = 0.002$) and pre-eclampsia ($P = 0.040$). In addition, the presence of APAs was positively associated with premature birth rate ($P < 0.001$) in biopsy-proven patients. Associations approaching statistical significance were noted for premature birth rate with both active nephritis ($P = 0.079$) and history of nephritis ($P = 0.073$) and for positive APAs with both hypertension ($P = 0.068$) and unsuccessful pregnancy ($P = 0.089$).

We also analyzed pregnancy outcomes by histologic subtype in a subset of papers that correlated renal histology with maternal and/or fetal outcomes (11,13,15,16,19,22,29,31,36). Because of limited data, we grouped histologic subclasses into proliferative (classes III and IV), and nonproliferative (classes II and V) lesions. There was not a statistically significant association between histologic subclass and rate of unsuccessful pregnancy ($P = 0.39$) or rate of any maternal complication ($P = 0.58$).

Discussion

Our meta-analysis of 37 selected papers investigating the associations among pregnancy and SLE shows high rates of SLE flare, hypertension, nephritis, and pre-eclampsia. Fetal complications included spontaneous abortion, stillbirth, neonatal death, and IUGR. Overall, one quarter of pregnancies were unsuccessful, whereas among all live births, the premature birth rate was 39.4%. Active lupus nephritis seemed to increase the risk for adverse pregnancy outcomes, particularly premature birth and hypertension. Our findings provide further support for the current recommendations calling for avoidance of pregnancy until all manifestations of nephritis are quiescent. History of nephritis was associated with higher rates of pre-eclampsia, thus emphasizing the need for a multispecialty approach in the care of these patients with respect to close monitoring and early recognition of clinical signs of pre-eclampsia. Because positive APAs were associated with higher rates of hypertension, premature birth, and induced abortion, early screening for anti-cardiolipin antibodies and a lupus anti-coagulant may identify those at risk.

Studies of the associations of SLE and lupus nephritis with pregnancy outcomes showed significant variation with respect to study design, definitions, statistical methods, bias and outcomes. Early studies reported poor clinical outcomes, but a number of recent papers have shown that outcomes are better than previously thought. These differences may reflect the changing clinical environment and the emergence of new therapeutic options. In addition, discrepancies in reported pregnancy events may reflect the heterogeneity of the studies with respect to the patient populations studied, the activity of lupus nephritis, World Health Organization classification, and the presence of APAs. By performing a meta-analysis, we have more power to detect existing associations than the individual studies alone, especially given the low prevalence of these pregnancy outcomes. Furthermore, the random-effects approach to this meta-analysis allowed us to assess these rates in the larger population while appropriately accounting for all of the different types of study populations and designs used. Our results indicate that active lupus nephritis is a significant risk factor for both premature birth and hypertension, which may further contribute to maternal and fetal morbidity and mortality.

The presence of either APA or anti-phospholipid syndrome is frequently associated with SLE. When present, a high titer of anti-cardiolipin antibodies has been shown to be predictive of the clinical outcome of anti-phospholipid syndrome in SLE patients (43). A Greek study has shown that up to 50% of SLE patients may be anti-cardiolipin antibody positive (44). Similarly, the presence of a lupus anti-coagulant is also associated with adverse fetal outcomes, with an overall live birth rate of 73% and a prematurity rate of 37%, despite the use of a number of treatment modalities (45). To date, few papers have examined the associations among lupus nephritis, APAs, and pregnancy outcomes in a systematic manner. Our univariate regres-

Table 3. Biopsy rates, disease activity rates upon study entry, and definitions used in the studies included for analysis

No.	Author	Percent Biopsy Proven on Study Entry	Diagnostic Criteria	Disease Activity	Flare	Hypertension Definition
1	Daskalakis *et al.* (6)	100% (11/11)	1	1	n/a	BP >140/90 mmHg
2	Mintz *et al.* (13)	73% (55/75)	1, 2	1	1	n/a
3	Sittiwangkul *et al.* (14)	n/a	1	2	1, 2	SBP >140 mmHg and/or DBP >90 mmHg
4	Oviasu *et al.* (15)	100% (25/25)	3	n/a	n/a	n/a
5	Le Houng *et al.* (16)	29% (11/38)	1	n/a	1	DBP >90 mmHg
6	Rahman *et al.* (9)	n/a	1	3	1	SBP >140 mmHg and/or DBP >90 mmHg
7	Georgiou *et al.* (17)	n/a	1	1	1	n/a
8	Imbasciati *et al.* (11)	100% (19/19)	3	n/a	n/a	n/a
9	Le Thi Houng *et al.* (3)	n/a	1	1	n/a	DBP ≥90 mmHg
10	Packham *et al.* (18)	100% (41/41)	3	n/a	n/a	DBP ≥95 mmHg or drug therapy
11	Wong *et al.* (19)	77% (17/22)	1	4	1	SBP ≥130 mmHg and/or DBP ≥90 mmHg
12	Ruiz-Irastorza *et al.* (41)	n/a	1	5	3	n/a
13	Julkunen *et al.* (20)	12% (13/112)	1	n/a	n/a	n/a
14	Nossent and Swaak (21)	13% (95/37)	1	1, 6	n/a	>140/85 mmHg
15	Houng *et al.* (7)	100% (22/22)	4	n/a	n/a	DBP >90 mmHg
16	Wagner *et al.* (22)	33% (19/58)	4	1	1	BP >140/90 mmHg
17	Tandon *et al.* (23)	36% (19/53	1	1, 7, 8	1	n/a
18	Wong *et al.* (4)	n/a	1	1	1	n/a
19	Whitelaw *et al.* (24)	29% (9/31)	4	3	1	BP >140/90
20	Soubassi *et al.* (25)	100% (22/22)	5	1	n/a	n/a
21	Surita *et al.* (26)	n/a	1	3	1	n/a
22	Molad *et al.* (27)	n/a	1	3	1	BP 140/90 mmHg
23	Phadungkiatwattana *et al.* (28)	n/a	1	n/a	1	SBP >140 mmHg and/or DBP >90 mmHg
24	Imbasciati *et al.* (29)	100% (81/81)	4	1	1	SBP >140 mmHg and/or DBP >90 mmHg or drug therapy
25	Clowse *et al.* (30)	n/a	1	9	1	n/a
26	Cortes-Hernandez *et al.* (31)	20% (12/60)	1	3	1	SBP >140 mmHg and/or DBP >90 mmHg
27	Cavallasca *et al.* (32)	n/a	1	1	1	BP ≥140/90 mmHg
28	Chandran *et al.* (33)	29% (9/31)	1	1, 3	1, 4	SBP >140 mmHg and/or DBP >90 mmHg
29	Clark *et al.* (34)	n/a	1	3	n/a	n/a
30	Moroni *et al.* (35)	94% (45/48)	4	1	1	SBP >140 mmHg and/or DBP >90 mmHg
31	Carmona *et al.* (36)	100% (35/35)	1	6	1	BP >140/90 mmHg
32	Wang *et al.* (37)	n/a	4	3, 7	n/a	n/a
33	Zhang *et al.* (38)	46% (12/26)	1	3	n/a	n/a

Table 3. (Continued)

No.	Author	Percent Biopsy Proven on Study Entry	Diagnostic Criteria	Disease Activity	Flare	Hypertension Definition
34	Julkunen *et al.* (40)	100% (16/16)	3	1	1	n/a
35	Lima *et al.* (42)	n/a	1	1	1	n/a
36	Derksen *et al.* (5)	40% (14/25)	1	3	1	BP >140/90 mmHg
37	Carmona *et al.* (39)	n/a	1	6	n/a	n/a

Diagnostic criteria: 1, American College of Rheumatology (ACR) 1982 criteria (50); 2, paper-specific criteria (51); 3, clinical, laboratory, and histologic criteria; 4, updated ACR criteria (52); 5, paper-specific criteria (53). n/a, not available.

Activity: 1, organ involvement and laboratory abnormalities; 2, Mexican systemic lupus erythematosus activity index (54); 3, systemic lupus erythematosus disease activity index-SLEDAI (55); 4, paper-specific scoring system (56); 5, lupus activity index (57); 6, lupus activity criteria count (58); 7, systemic lupus erythematosus activity index 2000 (59); 8, adjusted mean systemic lupus erythematosus disease activity index (60); 9, physician's estimate of lupus activity (61).

Flare: 1, new signs of active disease by clinical and laboratory variables or change in therapy; 2, Change in Mexican systemic lupus erythematosus activity index (54) score (>1); 3, change in lupus activity index (57) score (≥0.26); 4, change in systemic lupus erythematosus disease activity index (60) score (>5).

Table 4. Analysis of fetal events

Event	Denominator	Fixed-Effects Analysis		Random-Effects Analysis	
		Test for Heterogeneity	Estimated Rate (95% CI)	Estimated Rate (95% CI)	SD Estimate[a]
Induced abortions	Number of pregnancies	<0.001	7.2% (6.0%, 8.4%)	5.9% (3.2%, 8.6%)	5.6%
Spontaneous abortions	Number of pregnancies without induced abortions	<0.001	16.6% (14.7%, 18.5%)	16.0% (12.1%, 19.9%)	7.6%
Stillbirths	Number of pregnancies without induced abortions	0.001	4.0% (2.9%, 5.1%)	3.6% (2.0%, 5.2%)	2.2%
Neonatal deaths	Number of pregnancies without induced abortions	0.050	2.8% (1.9%, 3.8%)	2.5% (1.2%, 3.8%)	1.5%
Unsuccessful pregnancies	Number of pregnancies without induced abortions	0.025	23.0% (20.3%, 25.6%)	23.4% (19.5%, 27.3%)	4.7%
Intra Uterine Growth Retardation (IUGR)	Number of pregnancies without induced abortions	<0.001	14.3% (12.4%, 16.2%)	12.7% (8.8%, 16.7%)	6.8%
Premature Birth Rate	Number of live births	<0.001	37.1% (34.8%, 39.4%)	39.4% (32.4%, 46.4%)	17.6%

[a]To compute an estimate of the random-effects SD, which depends on the value of the complication rate, the central value from the random-effects model (i.e., the random-effects estimated rate) was used in the calculation.

Table 5. Maternal events analysis

Event	Denominator	Fixed-Effects Analysis		Random-Effects Analysis	
		Test for Heterogeneity	Estimated Rate (95% CI)	Estimated Rate (95% CI)	SD Estimate[a]
Maternal death[b]	No. of Pregnancies	<0.001	2.1% (1.3%, 3.0%)	1.0% (0.0%, 2.0%)	1.3%
Stroke[b]	No. of Pregnancies	1.00	0.8% (0.0%, 1.5%)	—	—
Hypertension	No. of Pregnancies	<0.001	15.3% (13.3%, 17.3%)	16.3% (10.3%, 22.3%)	11.2%
Pre-eclampsia	No. of Pregnancies	<0.001	9.1% (7.4%, 10.8%)	7.6% (3.6%, 11.6%)	7.6%
Eclampsia	No. of Pregnancies	0.184	0.8% (0.0%, 1.6%)	—	—
Active nephritis	No. of Pregnancies	<0.001	19.0% (17.4%, 20.6%)	16.1% (9.0%, 23.2%)	18.9%
Flares	No. of Pregnancies	<0.001	29.2% (27.3%, 31.0%)	25.6% (17.4%, 33.8%)	22.8%

[a]To compute an estimate of the random-effects SD, which depends on the value of the complication rate, the central value from the random-effects model (i.e., the random-effects estimated rate) was used in the calculation.
[b]Random-effects estimates were not computed for maternal death or stroke because neither of the event rates showed study heterogeneity.

sion analysis showed positive associations between APAs and hypertension in pregnancy, premature birth, and induced abortion. Conceivably, an increased risk for hypertension in these patients may lead to a higher risk for pre-eclampsia, a well-recognized pregnancy complication among patients with antiphospholipid syndrome (46).

The main weakness of our paper is that of all meta-analyses: it is limited by the quality of the studies included. Because the studies were mainly observational in nature, the statistical combination of data might have been subject to selection and reporting biases (47). By establishing a strict methodology and a predefined review process, including a validity scale, we eliminated bias from our analysis where possible. Our review process was also designed to ensure that studies included were of appropriate quality because we excluded papers with insufficient methodological details, as well as those with apparent deficiencies in trial design. This is in keeping with internationally accepted approaches to meta-analysis (48). Furthermore, by using a random-effects approach for all parameters that showed study heterogeneity, we appropriately accounted for the study design variability in our analyses. We included papers of all languages by using translators when needed.

Our analysis showed positive associations between hypertension and both active nephritis and a history of nephritis in those patients with biopsy-proven lupus nephritis. We further stratified pregnancy outcomes by the World Health Organization lupus nephritis classification, which showed no differences in either fetal or maternal outcomes. However, a limited amount of data were available for this analysis, with only seven and five studies reporting sufficient data on fetal and maternal outcomes, respectively. In addition, the renal histologic pattern might not have influenced the pregnancy outcomes because of the fact that most of these biopsies were performed years before the pregnancies that were analyzed. Finally, data that were provided by the studies included in the meta-analysis were not sufficient to analyze the impact of the level of kidney function and the degree of proteinuria at the start of pregnancy on kidney function and pregnancy outcomes. These important clinical questions should be addressed by future prospective studies.

Table 6. Summary of meta-regression of nephritis and adverse pregnancy outcomes

Y-Variable	Meta-Regression (*X*)			
	Active Nephritis		History of Nephritis	
	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
Induced abortion rate	0.0508 (−0.0863, 0.1878)	0.412	0.0480 (−0.0426, 0.1385)	0.269
Spontaneous abortions	0.0604 (−0.1352, 0.2560)	0.507	0.0324 (−0.0772, 0.1420)	0.540
Stillbirths	0.0193 (−0.0510, 0.0896)	0.544	−0.0183 (−0.0754, 0.0387)	0.506
Neonatal death rate	0.0496 (−0.0296, 0.1289)	0.163	0.0312 (−0.0091, 0.0715)	0.136
Unsuccessful pregnancy	0.0502 (−0.1706, 0.2709)	0.622	0.0041 (−0.1200, 0.1282)	0.943
IUGR rate	−0.0855 (−0.3115, 0.1405)	0.457	−0.087 (−0.1450, 0.1277)	0.892
Premature birth rate	0.4261 (0.0627, 0.7896)	0.020	0.1717 (−0.0462, 0.3896)	0.111
Hypertension rate	0.5379 (0.2647, 0.8112)	<0.001	0.2931 (0.1763, 0.4009)	<0.001
Preeclampsia	0.1055 (−0.1237, 0.3348)	0.328	0.1352 (0.0176, 0.2528)	0.017
Eclampsia	0.0174 (−0.0423, 0.0772)	0.252	0.0174 (−0.0423, 0.0772)	0.252

Conclusions

Our meta-analysis of 2751 pregnancies in patients with SLE showed lupus nephritis to be associated with premature birth and hypertension during pregnancy. In addition, positive APAs were associated with an increased risk for hypertension in these patients. Of note, hypertensive pregnancy disorders are increasingly recognized as risk factors for future cardiovascular disease, which is a leading cause of morbidity and mortality in SLE patients (49). Therefore, optimal timing of pregnancy in SLE patients with lupus nephritis may both decrease hypertensive pregnancy events and have a long-term impact on cardiovascular events later in life.

Our data further support the importance of pre-pregnancy counseling of women with SLE and lupus nephritis with respect to optimal timing of pregnancy relative to disease activity. It also emphasizes the importance of screening for APAs in these patients. Because much of the evidence is derived from studies focused on different outcomes, heterogeneous study designs, and defined endpoints, our study highlights the need for prospective studies with well-defined SLE activity and pregnancy outcomes.

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Disclosures

None.

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