SYSTEMATIC REVIEW

High-dose vs low-dose steroid in pregnancy patients with systemic lupus erythematosus and lupus nephritis: A systematic review and meta-analysis [version 1; peer review: 1 approved]

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Abstract

Background: Management of systemic lupus erythematosus (SLE) and lupus nephritis (LN) in pregnancy has been improving in recent decades. However, SLE can still lead to adverse pregnancy outcomes if not appropriately treated. Optimal dose of steroids, as one of the most commonly used for the treatment of SLE and LN in pregnancy is still a subject of debate. In this review, we determine the pregnancy outcomes in SLE and LN patients treated with low vs high doses of steroids.

Methods: ProQuest, Pubmed, Science Direct, Scopus, and Web of Science were carefully searched for relevant studies published in English. A total of 2,596 studies were reviewed. We extracted the data from previous studies showing the use of steroids treatment in high-dose and low-dose related to pregnancy outcomes. We provide larger data about maternal (preterm rupture of membrane, fetal loss, pre-eclampsia, and flare up) and fetal outcomes (prematurity, small gestational age, low birth weight) receiving high vs low steroid in patients with SLE and LN in this systematic review and meta-analysis.

Results: A total of 13 studies were included. Of these, one study

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discussed a group with LN and 12 other studies discussed SLE with related maternal and fetal outcomes. Maternal outcome in the group with low-dose steroid showed a lower risk of fetal loss (odds ratio (OR): 1.93; 95% confidence interval (CI) 1.01-3.70), but there were no differences in other maternal outcomes. The low-dose steroid group showed a better fetal outcome, with a lower risk of prematurity (OR: 3.06; 95% CI 1.98-4.71), small gestational age (OR: 2.63; 95% CI 1.15-6.00), and low birth weight (OR: 2.43; 95% CI 1.23-4.79).
Conclusions: In pregnant patients with SLE or LN, high-dose steroids are associated with the high risk of fetal loss during pregnancy, preterm birth, small gestational age, and low birth weight.

Keywords
systemic lupus erythematosus, lupus nephritis, steroid, high dose, low dose, health

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Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease that can manifest as mucocutaneous, hematologic, neurologic, and renal.[1] This condition affects mostly women of childbearing age. In 1996, the prevalence of women diagnosed with SLE in the United Kingdom in 18 to 65 year olds was 54 per 100,000 cases,[2,3] while prevalence in 2012 increased significantly into 97.04 per 100,000 cases with the mean age of 49 years old.[4] It makes SLE one of the most common autoimmune diseases in pregnancy.

Pregnancy and SLE worsen each other. Adverse effects of SLE in pregnancy include pre-eclampsia or eclampsia, preterm birth, preterm premature rupture of the membrane, intrauterine growth restriction (IUGR), and fetal loss.[5] Hypertensive complications, such as pre-eclampsia (PE)/eclampsia (eclampsia), pregnancy-induced hypertension (PIH), and hemolysis, and elevated liver enzymes and low platelets (HELLP) syndrome, are major concern for SLE pregnant patients, especially those with anti-phospolipid autoantibodies (aPL) positivity/antiphospholipid syndrome (APS) and lupus nephritis (LN).[6] On the other hand pregnancy may increase SLE activity or induce flare that may lead to unfavorable symptoms.[7] In the past decade, physicians contraindicated pregnancy in SLE.[8] Nevertheless, with the improvement of therapy and management, pregnant women with SLE could have better outcomes and prognosis.[9] A recent comprehensive review of several countries within the past 40 years showed that the rate of fetal loss has decreased from 40% to 17%, whereas the most recent studies found a pregnancy loss rate of 10% to 25%.[6]

Steroids are the most common therapy for autoimmune and inflammatory disease including SLE to manage flare or maintain therapy.[10–12] It has a dual contradicting effect in the treatment of SLE with pregnancy, either making it better and worse. Data showed that increasing dose are also followed by increasing risk of adverse effects.[13] During pregnancy, steroid exposure can affect placental growth and gene expression resulting in poor nutrition and gas exchange for the fetus,[14,15] hence it should be limited to a minimum level. High doses during pregnancy have been linked to a higher risk of diabetes, hypertension, pre-eclampsia, and premature membrane rupture.[16] Short courses of high dosages and/or intravenous pulse methylprednisolone can be administered in the case of disease flares.[17] With the lack of information about steroids dose for therapy of SLE in pregnancy, we examine the outcome of pregnancy after low or high dose steroids in this systematic review and meta-analysis.

Objectives

The objective of this systematic review and meta-analysis was to examine the effect on high-dose vs low dose of steroid in maternal and fetal outcomes in patients with SLE and LN.

Methods

Databases and search

We conducted an electronic literature search from online databases, ProQuest, Pubmed, Scopus, Science Direct, and Web of Science. In addition, reference lists from previous reviews that had articles related to our criteria for inclusion were searched and literature was included where appropriate. The search was conducted in October 2021 and the last search on each database was on 26 November 2021. Literature searching was done according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[18] We used a protocol included in the Cochrane Collaboration's search strategy for randomized control trials with the following terms used to search each database: (systemic lupus erythematosus) OR (SLE) OR (lupus nephritis) OR (LN) AND (pregnancy outcome*) OR (pregnancy complication*) OR (maternal outcome*) OR (maternal complication*) OR (fetal outcome*) OR (fetal complication*) OR (adverse pregnancy outcome*) OR (obstetrical outcome*). No filters and limit used in our search strategy. The search terms used for each database can be found as *Extended data*.[47]

Selection criteria

We included studies based on the following criteria:

(1) The studies were randomized control trials, cohort, case-control, or cross-sectional;

(2) Studies reported maternal and fetal complications in pregnant women with SLE or LN;

(3) Studies reported high-dose steroid and low-dose steroid groups;

(4) English language publication.

Studies were excluded when meeting the following criteria:

(1) They were case report, case series, literature review, systematic review, and meta-analysis;

(2) Studies did not report the outcome of pregnancy-related to the group of steroids;

(3) Duplicated studies.

The searches were performed by author RH. Two authors (EP and IS) independently screened all titles and abstracts, and retrieved the full text of any articles that met the aforementioned criteria. Both authors reviewed full text articles' eligibility, and disagreement between two authors was resolved by discussion. This process of selection, including the removal of duplicate studies, and reviewing abstracts and full texts was carried out using platform COVIDENCE, a web-based platform designed for the process of systematic reviews.

Outcome measures

The following maternal outcomes were reported: pre-eclampsia/eclampsia, premature rupture of membranes (PROM), flares, oligohydramnios, pregnancy-induced hypertension (PIH), and fetal loss. The fetal outcomes studied were: live birth, preterm birth (under 37 weeks gestational age), small gestational age (SGA), and low birth weight (LBW).

We defined the outcomes as follows:

Maternal outcomes definition:

(1) Preeclampsia: Preeclampsia is gestational hypertension with one of the following new-onset disorders at or after 20 weeks of pregnancy such as proteinuria, other organ dysfunction including kidney, liver, neurological and hematological involvement, and uteroplacental dysfunction;[19]

(2) Eclampsia: Seizure that occurs in pregnant women with preeclampsia;[20]

(3) Preterm Rupture Of the Membranes (PROM): Ruptures of the amniotic sac membranes in pregnant women at gestational age at or 37 weeks before the onset of labor;[21]

(4) Oligohidramnion: Decreased amniotic fluid volume less than expected gestational age. it can be identified by procedures using ultrasonography with the result of amniotic fluid index lower than 5 centimeters;[22]

(5) Gestational Hypertension (GH): Chronic de novo hypertension which occurs at or after 20 weeks' pregnancy with no manifestations of preeclampsia;[19]

(6) Pregnancy loss: 1) spontaneous abortion: loss of pregnancy less than 20 weeks of gestational age 2) Intrauterine Fetal Death (IUFD): loss of pregnancy more than 20 weeks of gestational age or fetal weight over than 350 gram 3) stillbirth: loss of pregnancy before or during pregnancy. We defined three of them as pregnancy loss;[23]

(7) SLE flare: 1) signs of new active disease observed through clinical and laboratory factors or change in therapy; 2) elevation of Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score;[24] 3) elevation of Lupus Activity Index in Pregnancy;[25] 5) elevation of physician global assessment;[26] 4) elevation of Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2k) score.[27]

Fetal outcomes definition:

(1) Live birth: baby born alive during labor[28];

(2) Preterm birth: the birth of a baby at gestational age before 37 weeks[29];

(3) Small gestational age (SGA) or Intrauterine growth retardation (IUGR): newborn baby or fetal weight less than 10th percentile for gestational age[30];

(4) Low birth weight (LBW): newborn baby weight less than 2500 grams.[28]

Data extraction

Data extraction was carried out by pairs of reviewers (EP, IS), and any disagreements were determined by consensus in the team. The studies were then screened for relevance, and those meeting the eligibility criteria were included in the review. In this process, we utilized COVIDENCE, though RevMan 5.4 could be used as an open-source alternative. If the data represented in the article were unclear, we contacted the corresponding authors of each study to clarify and ask for additional data if needed.

We extracted data from each study using a predesigned table. Data collected were methodological data, mean maternal age during pregnancy, group of high-dose, low-dose steroid, and the related pregnancy outcomes. We used each study's definition of high-dose or low-dose steroid and the doses were equalized to prednisone equivalent. If the study did not mention the definition of high-dose and low-dose of steroid, we used recommendations from the 2020 American College of Rheumatology (ACR) Guideline[31]; i.e. if a group received >10 mg/day of prednisone equivalent, it would be considered as high-dose.

Quality assessment

The quality of the observational studies was reviewed independently by EP and IS using the Newcastle-Ottawa Scale (NOS).[7] The bias was reviewed by the following parameters: selection, comparability, and exposure or outcome. The total score will be 9 for cohort and 8 for cross-sectional studies. Total score ≥ 7 for cohort and ≥ 6 for cross-sectional studies were used to conclude high-quality studies.[7] Disagreements were resolved by consensus. The funnel plots were used to help assess bias of missing results in each study.

Statistical analysis

We used RevMan (5.4) software for statistical analysis. Data were represented by Odds Ratio (OR) with 95% confidence intervals calculated for maternal and fetal outcomes. Heterogeneity among studies was assessed by the Q-test and I^2 statistic. Subgroup analysis with a p-value equal to or less than.05 was considered statistically significant. Low heterogeneity was defined by an I^2 value in the range of 25% and 50 between 50% and 75% for moderate heterogeneity, and greater than 75% as high heterogeneity. We did Egger's test and a funnel plot for publication bias ($p<0.05$ was considered statistically significant).

Ethics statement

This study was approved by Airlangga Hospital's ethical board, certificate number 189/KEH/2019. All analyses for the present study were based on previous published research, thus no patient consent was required. This article is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[47]

Results

Study selection

A flow chart of the study selection process is shown in Figure 1. We identified a total of 2,596 studies using search terms from our aforementioned databases. A total of 1,441 duplicated studies were removed. Following screening title and abstract we excluded irrelevant 797 studies, 305 full-text studies were reviewed for eligibility, and finally, a total of 13 studies were included in our quantitative synthesis for systematic review and meta-analysis.

Study characteristics

Of 13 studies, nine studies were cohort retrospective, while four studies were cohort prospective. The main characteristics are shown in Table 1. The studies were conducted in various regions such as Canada, China, Italy, Ghana, London, Thailand, Japan, and USA. The patient's enrollment was from 1996 to 2020. The majority of women included in the study were Asian (53%) (Table 1). The average maternal age was 29 $\pm$ 3,09 years old. From the data, most women with SLE received a low-dose steroids (72,2%) than high-dose steroids (27,8%) treatments, with the average cut-off used to classify high-dose steroids was 11,78 mg. A total of participants in the experimental (high dose steroids) group were 448 patients (48 patients were LN) and the control (low dose steroids) group were 1,289 patients (82 patients were LN) (Table 3).

Pregnancy outcomes

This research divided the outcomes into two groups: maternal outcomes and fetal outcomes. The maternal outcomes reported were as follows: fetal loss, PROM, pre-eclampsia, oligohydramnios, PIH, and flares. Five of 13 studies discussed fetal loss as a maternal outcome. In the fetal outcomes group, the studies analyzed pre-term, LBW, and SGA. The majority of studies (8/13) discussed pre-term labor as an outcome (Table 2). The SLE diagnostic criteria used for these studies have many variations. The majority of studies were using the ACR 1997 Criteria as reference (Table 2). The criteria used for disease activity also varied in each study. In most studies, the disease severity was defined by organ

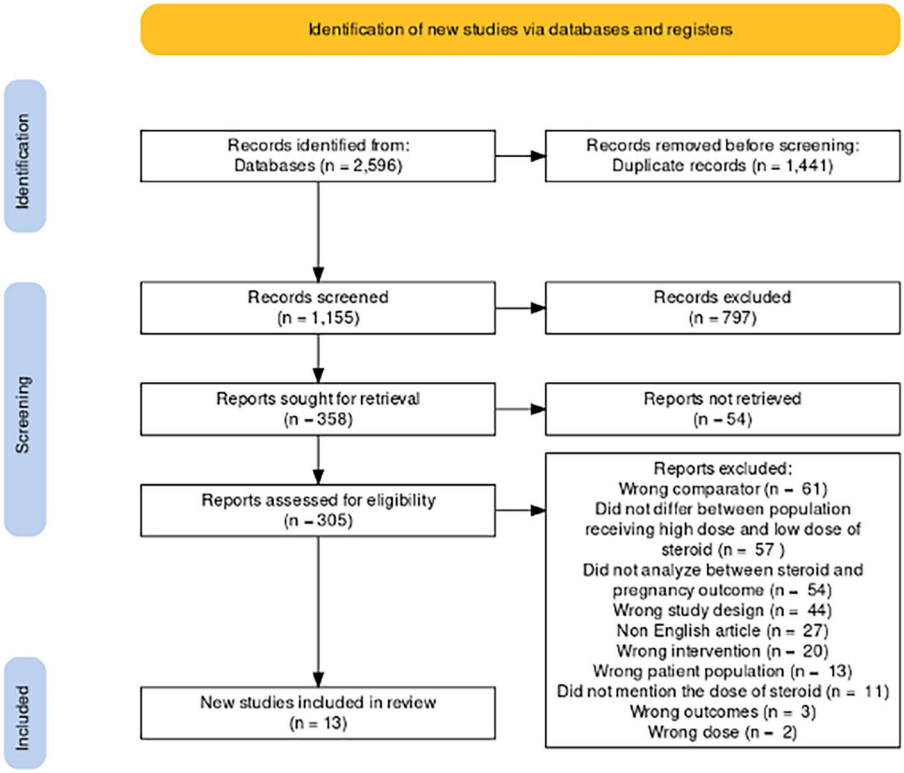

Figure 1. PRISMA flowchart for included studies.

involvement and laboratory abnormalities, whereas five studies used the systemic lupus disease activity index (SLEDAI) (Table 2). There were also various criteria for defining flares in patients. Most of the studies used flares criteria based on signs of new disease activity either by clinical or laboratory and change in therapy, and 3 other studies used the SLEDAI score (Table 2).

Risk of bias assessment

For cohort and cross-sectional studies, The Newcastle-Ottawa Score (NOS) was used to evaluate the risk of bias in this study. Table 2 shows the NOS scores from each study. For the cohort studies, the total NOS score was 9. The majority of studies (11/13) have an average score of 8, and two other studies have a score of 7. All of the studies are high quality and have low-risk of bias. We used Egger's test to evaluate the possibility of publication bias. No indication of publication bias ($p<0.05$) for all outcomes were detected.

Preterm rupture of membrane (PROM)

Four studies (n=202) with outcomes of PROM were included in the meta-analysis. The risk of PROM in high-dose steroids were not significantly difference compared with low-dose steroids group (OR 1.14, 95% CI 0.44 to 2.98, p=0.79, I^2=38%) (Table 3).

Fetal loss

Five studies (n=217) with the fetal loss evaluated were included in the meta-analysis. High-dose steroids were associated with a higher risk of fetal loss as compared to low-dose steroids (OR 1.93, 95% CI 1.01 to 3.70, p=0.05, I^2=0%) (Table 3).

Pre-eclampsia

Only three studies (n=168) were included in the meta-analysis in relation to preeclampsia outcomes. The risk of preeclampsia in high-dose steroids were not significantly difference compared with low-dose steroids group (OR 1.30, 95% CI 0.51 to 3.30, p=0.58, I^2=35%) (Table 3).

Table 1. Main and baseline features of the included studies. OR, odds ratio; ROC, receiver operating characteristic; RR, risk ratio; HR, hazard ratio.

Study	Year	Design	Region	Years of patients' enrolment	Maternal age ± (years)	Patients receive high-dose steroid* (n)	Patients receive low-dose steroid* (n)	Cut off for high-dose steroid* (/day)	Statistical outcomes	Additional data
Clark *et al.*[32]	2003	Cohort Retrospective	Canada	1999-2001	30.96 ± 3.9	14	5	≥10 mg	*p* value	-
Dey *et al.*[33]	2016	Cohort Retrospective	Ghana	2013-2014	30.1	4	3	>10 mg	prevalence	-
Doria *et al.*[34]	2002	Cohort Prospective	Italy	NR	30.5	7	7	>10 mg	prevalence	-
Englert *el al.*[35]	1988	Cohort Prospective	London	1983-1985	NR	9	11	≥15 mg	prevalence	-
Foocharoen *et al.*[36]	2009	Cohort Retrospective	Thailand	1997-2006	27.3 ± 3.26	9	9	>15 mg	prevalence	-
Kobayasshi *et al.*[37]	1999	Cohort Prospective	Japan	1982-1997	29.7 ± 3.8	5	61	>15 mg	prevalence	-
Louthrenoo *et al.*[38]	2021	Cohort Prospective	Thailand	1993-2007	26.94 ± 4.80	10	61	>10 mg	-	OR
Murata *et al.*[39]	2021	Cohort Retrospective	Japan	2006-2020	31.4 ± 4.6	5	47	>15 mg	*p* value	ROC
Oishi *et al.*[40]	2021	Cohort Retrospective	Japan	1996-2018	30.0	20	49	≥10 mg	-	OR, ROC analysis
Palmsten *et al.*[13]	2021	Cohort Retrospective	USA	2007-2013	27.9 ± 5.8	49	174	Average 15.2 ± 6.4	-	RR, HR
Takahashi *et al.*[41]	2013	Cohort Retrospective	Japan	1995-2013	30.7 ± 4.6	47	26	≥7.5 mg	*p* value	-
Ueda *et al.*[42]	2020	Cohort Retrospective	Japan	2005-2019	32.5 ± 1.16	5	43	>10.5 mg	*p* value	-
Zhang *et al.*[43]	2020	Cohort Retrospective	China	2012-2017	25.74 ± 4.67	28	55	≥10 mg	Mean SD	OR, ROC analysis

*Prednisone equivalent dose.

Table 2. Outcomes reported, diagnosis criteria and Newcastle-Ottawa Score (NOS).

Study	Disease population	Maternal outcomes related to steroid dose	Fetal outcomes related to steroid dose	SLE diagnostic criteria	Disease activity	Flare	NOS Score
Clark *et al.*[32]	SLE	-	Pre-term	2	3	3	8
Dey *et al.*[33]	SLE	Fetal loss	-	1	4	4	8
Doria *et al.*[34]	SLE	PROM, pre-eclampsia, oligohidramnion	Pre-term	2	5	4	7
Englert *el al.*[35]	SLE	Fetal loss	Pre-term, LBW	2	NR	NR	7
Foocharoen *et al.*[36]	SLE	Abortion (fetal loss)	-	1	4	4	8
Kobayasshi *et al.*[37]	SLE	PROM	Pre-term, SGA	2	4	4	8
Louthrenoo *et al.*[38]	SLE	PROM, PIH, flares, fetal loss	Pre-term, SGA, LBW	1	2	5,6,7	8
Murata *et al.*[39]	SLE	PROM, pre-eclampsia	Pre-term, SGA, LBW	1	3,4	3	8
Oishi *et al.*[40]	LN	-	Pre-term, LBW	1	1,4	4	8
Palmsten *et al.*[13]	SLE	-	Pre-term	3	NR	NR	8
Takahashi *et al.*[41]	SLE	Pre-eclampsia, flare up	-	1	3,4	4,8	8
Ueda *et al.*[42]	SLE	Flare	-	1	3,4	3,4	8
Zhang *et al.*[43]	SLE	Fetal loss	-	1	3	5	8

Diagnostic: 1) ACR 1997 Criteria, 2) ACR 1982 Criteria, 3) ICD 9th revision. Disease activity: 1) SLEDAI-2k, 2) Modified SLEDAI-2k, 3) SLEDAI, 4) Organ involvement and laboratory abnormalities, 5) ECLAM Score. Flare: 1) SLEDAI-2k, 2), Modified SLEDAI-2k, 3) SLEDAI score, 4) Signs of new active disease either by clinical or laboratory and change in therapy, 5) change in LAI-P, 6) change in PGA, 7) SLE flare index, 8) SELENA trial.
Abbreviations: SLE, systemic lupus erythematosus; LN, lupus nephritis; PROM, preterm rupture of membrane; PIH, pregnancy induce hypertension; SGA, small gestational age; LBW, low birth weight; NR, not reported.

Table 3. Comparison high vs low-dose steroid for maternal and fetal outcomes.

			Maternal outcome								
Outcomes	**N**	**Mode**	**Value**				**pE**	**pHet**	**P**	**OR**	**95% CI**
			High-dose steroid		**Low-dose steroid**						
			n	**Total**	**n**	**Total**					
PROM	202	Fixed	6	41	25	161	0.81	0.19	0.79	1.14	0.44-2.98
Fetal Loss	217	Fixed	24	61	37	156	0.42	0.50	0.05	1.93	1.01-3.70
Pre-eclampsia	163	Fixed	9	60	17	103	0.61	0.22	0.58	1.30	0.51-3.30
Flare up	235	Random	23	68	67	167	0.89	0.03	0.50	1.77	0.33-9.41
			Fetal Outcome								
Outcomes	**N**	**Mode**	**Value**				**pE**	**pHet**	**P**	**OR**	**95% CI**
			High-dose steroid		**Low-dose steroid**						
			n	**Total**	**n**	**Total**					
Prematurity	526	Fixed	78	134	139	392	0.32	0.53	<0.00001	3.06	1.98-4.71
SGA	178	Fixed	13	31	33	147	0.35	0.47	0.02	2.63	1.15-6.00
LBW	216	Fixed	33	53	71	163	0.49	0.19	0.01	2.43	1.23-4.79

Abbreviations: N, total number of patients; OR, odds ratio; pE, p Egger; pHet, p Heterogeneity; CI, confidence interval; PROM: preterm rupture of membrane; SGA, small gestational age; LBW, low birth weight.

Flare

Three studies (n=235) were included in the meta-analysis. The risk of disease flare in high-dose steroids were not significantly difference compared with low-dose steroids group (OR 1.77, 95% CI 0.33 to 9.41, p=0.50, I^2=73%) (Table 3).

Preterm birth

Eight studies (n=526) were included in the meta-analysis for preterm birth outcome. One study discussed LN. Higher risk or preterm delivery were more associated with high-dose steroids than low-dose steroids (OR 3.06, 95% CI 1.98 to 2.22, p<0.00001, I^2=0%) (Table 3).

Small gestational age (SGA)

Four studies (n=178) were included in the meta-analysis. High-dose steroids were associated with a higher risk of SGA as compared with low-dose steroids (OR 2.63, 95% CI 1.15 to 6.00, p=0.02, I^2=0%) (Table 3).

Low birth weight (LBW)

Five studies (n=216) were included in the meta-analysis. The risk of LBW in high-dose steroids were not significantly difference compared with low-dose steroids group (OR 2.43, 95% CI 1.23 to 4.79, p=0.01, I^2=34%) (Table 3).

Funnel plots were also done which can be found as *Extended data*.[47] Comparison and detail about outcomes are provided in Figures 2, 3, 4, 5 and Table 3.[47]

Maternal outcomes

Fetal loss during pregnancy

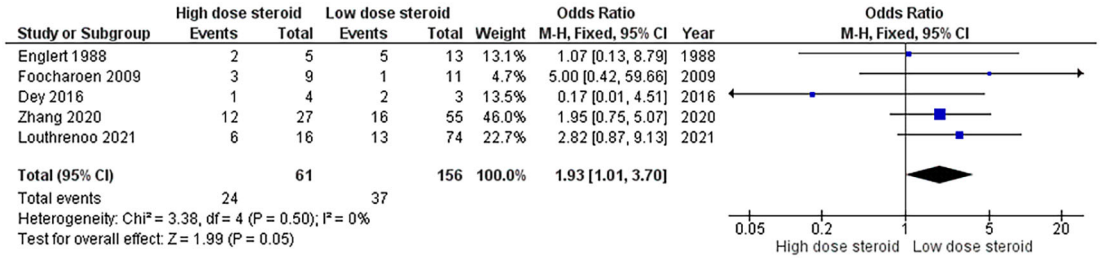

Figure 2. Fetal loss during pregnancy in high-dose versus low-dose steroids.

Fetal outcomes

Prematurity

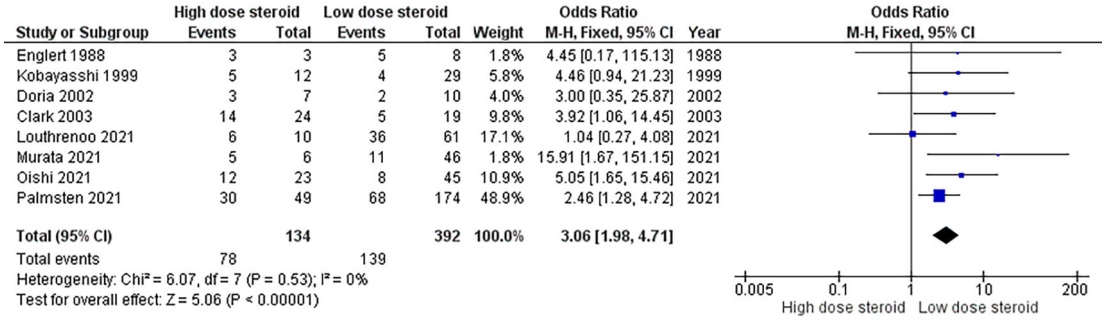

Figure 3. Prematurity in high versus low-dose steroids.

Small gestational age

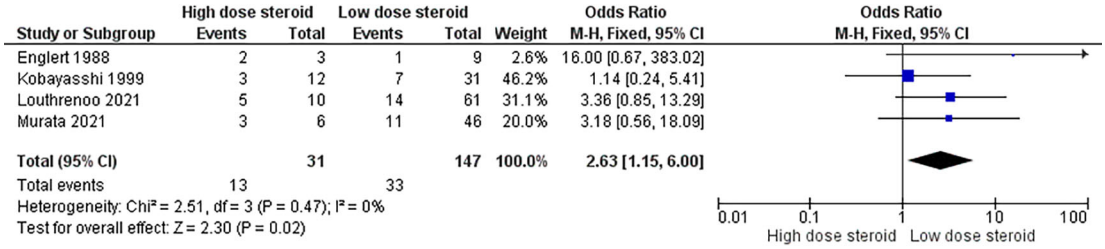

Figure 4. Small gestational age in high versus low-dose steroids.

Low birth weight

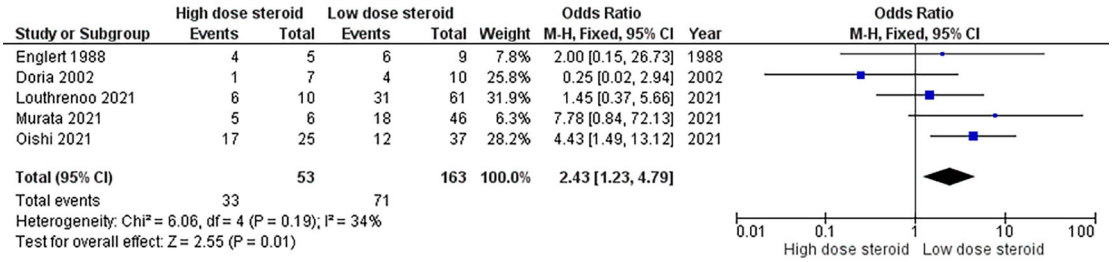

Figure 5. Low birth weight in high versus low-dose steroids.

Discussion

In this systematic review, we examine 13 papers that evaluate at how steroid dose affects pregnancy outcomes in SLE and LN patients. Overall, we discovered that high steroid doses were linked to a higher risk for adverse maternal outcomes, particularly pregnancy loss. Furthermore, increased risks of poor fetal outcomes, such as premature birth, low birth weight, and small gestational age, were linked to high-dose steroid use during pregnancy. Low-dose steroids were given to more SLE patients in this study than high-dose steroids, which were classified as >10 mg/day of prednisone equivalent. The number of pregnancy losses was considerably higher in the high-dose steroid group than in the low-dose steroid group. Furthermore, the premature delivery rate was 58 percent among all live births.

We used a comprehensive search strategy and careful appraisal following a standard protocol for systematic review to assess the validity of study results. The selected studies mostly have similar characteristics of enrolled patients with respect to age, race, criteria used for diagnosis and disease activity. All of the studies were high quality with low-risk of bias and no indications of publication bias from Egger test. Premature delivery, intrauterine development retardation, and fetal death in pregnant women with SLE were highly associated with steroid dose reflecting managed disease, as well as disease flare-ups during pregnancy, according to our findings. To the best of our knowledge, this is the first meta-analysis that discussed the relationship between steroids and fetal or maternal outcomes in SLE and LN patients.

In a previous systematic review, Wu *et al.* reported prevalence of adverse pregnancy outcomes in SLE with LN and identified their significant association.[7] However, the study did not look at the differences in the occurrence of the aforementioned outcomes between individuals who were given a high steroid dose and those who were given a low steroid dose. Another meta-analysis showed that higher rates of maternal and fetal complications including preeclampsia, hypertension, fetal loss, premature birth, SGA and congenital defects were strongly associated with SLE.[44] Nevertheless, the included studies were limited and antenatal management using steroids was not mentioned. High blood pressure, active nephritis, and the antiphospholipid syndrome (APS) in SLE flares up seemed to be the major factors behind the adverse pregnancy outcomes.

The role of steroids to control the flare and maintenance therapy in patients with remission are widely used. In both acute and chronic settings, the use of steroids during pregnancy is the preferred choice for a myriad of maternal and fetal purposes.[45] In many fetal tissues, such as the liver, lungs, stomach, skeletal muscle, and adipose tissue, steroids are vital for the growth and development to prepare for the life outside the womb. Steroids control prostaglandin production, which has been linked to key roles during implantation by improving stromal vascular permeability and employed in

the treatment of mothers who are at risk of preterm delivery.[45,46] Their abilities to inhibit the immune system and reduce inflammation are frequently used to control the severity of a patient's condition and flares in pregnant women with autoimmune disorders, such as SLE.[46]

In a cohort study on preterm deliveries in women with SLE, Clark *et al.* demonstrated that lower dose of steroid maintained through pregnancy was associated with extending SLE pregnancies to full term, thus lowering maternal and fetal morbidity.[32] On the other hand, Zhang *et al.* stated that increased fetal loss was not associated with the prednisone dose in pregnant women with SLE, whereas combined APS and SLEDAI were the key risk factors of those complication. All abovementioned results represent limited discussion about optimal doses of steroids to improve the outcome of SLE women. Along with varying population, study design, diagnostic criteria, statistical method, and outcomes reported. This systematic review combined a larger population to provide the risk of steroids in pregnancy outcomes to support the need for dose adjustment of steroid in patients with active SLE and consideration for avoidance of pregnancy until all manifestations are quiscent.

This study came with some limitations. Our team did not find eligible randomized control trials that study about pregnancy outcome related to the dose of steroid due to limited studies and ethically improper to perform. Most of our included studies were retrospective-observational studies that are more prone to bias and cofounding. We only include the English studies, as consequence the non-English studies that met our criteria could not be reviewed. We did not conduct subgroup analysis of the dosage, route of administration, and kind of steroid. Each center has customary steroid administration in patients with SLE and LN; therefore, to apply the result of this study, clinicians should firstly ensure the indication and determine the most optimal and safe dosage to achieve a good maternal and fetal outcome. Some studies only had small samples with insufficient total samples to be generalized to the entire population. Further observation with larger population on the side effects of steroid in combination with another agent, e.g., immunosuppressants, is required to evaluate maternal and fetal outcome.

Conclusions

Steroids are used to overcome SLE and LN in pregnancy. High-dose steroids may increase the risk of preterm birth and miscarriage during pregnancy. Besides, it may also cause deterioration, seen in other variables of the maternal and fetal outcome.

Data availability

Underlying data

Figshare: Data of High-dose vs Low-dose Steroid in Pregnancy Patients with Systemic Lupus Erythematosus and Lupus Nephritis: A Systematic Review and Meta-analysis, https://doi.org/10.6084/m9.figshare.18514970.v5.[47]

This project contains the following underlying data:

- High vs Low Dose Steroid in Pregnancy Patients with SLE.rm5 (the data of each study used to create the forest and funnel plots. The open source software RevMan is required to open this file).

Extended data

Figshare: Data of High-dose vs Low-dose Steroid in Pregnancy Patients with Systemic Lupus Erythematosus and Lupus Nephritis: A Systematic Review and Meta analysis, https://doi.org/10.6084/m9.figshare.18514970.v5.[47]

This project contains the following extended data:

- PubMed 25 Nov.png (search terms in Pubmed database).
- Proq-96-25nov.png (search terms in ProQuest database).
- SciDir-25nov-138.png (search terms in Science Direct database).
- Scopus-nov-670.png (search terms in Scopus database).
- Wos-467-25nov.png (search terms in Web of Science database).
- PRISMA flow.png (PRISMA flow diagram)

- Funnel plot_PROM.svg
- Funnel plot_Fetal Loss.svg
- Funnel plot_Flare up.svg
- Funnel plot_LBW.svg
- Funnel plot_Prematurity.svg
- Funnel plot_Pre eclampsia.svg
- Funnel plot_SGA.svg

Reporting guidelines

Figshare: PRISMA checklist for 'High-dose vs low-dose steroid in pregnancy patients with systemic lupus erythematosus and lupus nephritis: A systematic review and meta-analysis', https://doi.org/10.6084/m9.figshare.18514970.v5.[47]

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Reviewer Report 30 August 2022

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✔ **Eduardo F. Borba**
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The objective of this paper is to perform a systematic review and meta-analysis in order to evaluate the effect on high-dose vs low dose of steroid in maternal and fetal outcomes in patients with systemic lupus erythematosus (SLE) and lupus nephritis (LN). This is a very important issue in this disease.

Some minor questions arise:

1. Authors should revise all the text for grammatical errors.

2. Title: OK.

3. Abstract: OK.

4. Keywords: Please use “therapy” instead of “health”.

5. Introduction: Please insert some comments about a recent review that provide recommendations for therapy during pregnancy in SLE (reference #31) and provide a short description of it in order to describe the main suggestions of this paper. In fact, authors used these recommendations for defining high and low steroid dose (Methods section).

6. Patients and methods: Interesting design and selection. Outcomes were well-defined. Methods were appropriate for analysis.

7. Results: No further comments.

8. Discussion: In the same way, authors should include comments in this section about the review that provides recommendations for therapy during pregnancy in SLE (reference #31). Authors should describe these recommendations and compare to those identified in

their study. This suggestion will highlight their findings and make clear their conclusions.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical Reserch in Rhematology - Associate Professor in my Institution - University of Sao Paulo - Brazil

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.