

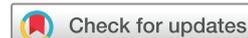
# Impact of low-dose acetylsalicylic acid on pregnancy outcome in systemic lupus erythematosus: results from a multicentre study

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**To cite:** Tani C, Zucchi D, Haase I, *et al.* Impact of low-dose acetylsalicylic acid on pregnancy outcome in systemic lupus erythematosus: results from a multicentre study. *Lupus Science & Medicine* 2022;**9**:e000714. doi:10.1136/lupus-2022-000714

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Received 15 April 2022  
Accepted 2 June 2022



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## ABSTRACT

**Objective** It is still a matter of debate whether low-dose acetylsalicylic acid (LDASA) should be prescribed to all patients with SLE during pregnancy. This study aimed at investigating the impact of LDASA on pregnancy outcomes in patients with SLE without history of renal involvement and without antiphospholipid antibodies (aPL).

**Methods** This is a retrospective analysis of prospectively monitored pregnancies at seven rheumatology centres. Previous/current renal involvement and aPL positivity were the exclusion criteria. Adverse pregnancy outcome (APO) is the composite outcome of the study and included proteinuric pre-eclampsia, preterm delivery <37 weeks, small-for-gestational age infant, low birth weight <2500 g, intrauterine growth restriction and intrauterine fetal death after 12 weeks of gestation of a morphologically normal fetus.

**Results** 216 pregnancies in 187 patients were included; 82 pregnancies (38.0%) were exposed to LDASA treatment. No differences in terms of age at conception, disease duration, clinical manifestations, comorbidities and disease flare during pregnancy were observed between patients taking LDASA and those who did not take LDASA during pregnancy. APO was observed in 65 cases (30.1%), including 13 cases (6.1%) of pre-eclampsia. The incidence of all complications was similar in the two groups. However, it is interesting to note that pre-eclampsia had lower frequency in patients taking LDASA versus those not taking LDASA (2.4% vs 8.3%,  $p=0.14$ ).

**Conclusions** In pregnant patients with SLE without renal involvement and were aPL-negative, there is a low risk of severe obstetric complications, such as early pre-eclampsia. LDASA treatment does not provide a statistically significant advantage over these complications. However, a careful individual risk–benefit balance is warranted.

## INTRODUCTION

Pregnant patients with SLE is considered at risk of maternal and fetal complications

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The protective role of low-dose acetylsalicylic acid (LDASA) treatment against pre-eclampsia is well established in patients with SLE with previous renal involvement and/or antiphospholipid antibodies (aPL), but whether LDASA should be prescribed to all patients with SLE during pregnancy is still a matter of debate.

### WHAT THIS STUDY ADDS

⇒ In our cohort, patients with SLE without renal involvement and were aPL-negative seem to have a low risk of severe obstetric complications such as early pre-eclampsia, and LDASA does not provide a significant advantage over these complications.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ In patients with SLE without renal involvement and were aPL-negative, LDASA does not seem to provide a significant protection against severe obstetric complications.

⇒ A careful individual risk–benefit balance is warranted.

resulting in high rates of preterm birth, pre-eclampsia and fetal loss compared with the general population, especially in the presence of antiphospholipid antibodies (aPL), active disease and renal involvement.<sup>1,2</sup>

The protective role of low-dose acetylsalicylic acid (LDASA) against pre-eclampsia is well established in non-autoimmune patients at high risk of this obstetric complication, as well as in patients with SLE with previous renal involvement and/or aPL.<sup>3–5</sup>

Indeed, LDASA is recommended by the 2017 European Alliance of Associations for Rheumatology recommendations for management of women's reproductive health<sup>6</sup> in patients with SLE at risk of pre-eclampsia, especially those with previous lupus nephritis or were aPL-positive. The 2020 American College of Rheumatology (ACR) Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases suggests treatment with LDASA in all pregnant women with SLE.<sup>7</sup> However, the committees acknowledge the lack of actual data. Also, the American College of Obstetricians and Gynecologists recommendations report autoimmune diseases among the high-risk factors, suggesting the use of LDASA.<sup>8</sup>

Although there are no studies on this target population, it has been postulated that LDASA could lower the risk of obstetric complications in SLE to an extent comparable with the risk reduction demonstrated in trials assessing LDASA treatment for other high-risk groups.<sup>5,9</sup>

This study aimed to test whether LDASA exposure during pregnancy in patients with SLE without history of renal involvement and without aPL is associated with better pregnancy outcomes, since published data on this topic are still scarce or absent.

## METHODS

This is a retrospective study involving pregnancies in patients with SLE prospectively followed by the pregnancy clinic at seven rheumatology referral centres (university medical centres of Brescia, Düsseldorf, Ferrara, Milano, Padova, Pavia and Pisa) between 1995 and 2021. Our multicentre cohort included patients with SLE fulfilling the ACR 1997 classification criteria.<sup>10</sup>

Previous/current renal involvement as defined by the ACR criteria<sup>11</sup> and any positive result by either lupus anticoagulant, IgG/IgM anticardiolipin antibodies and IgG/IgM anti-beta-2-glycoprotein I in medium or high titre on two or more consecutive occasions at least 12 weeks apart were the exclusion criteria.

Clinical and serological data were retrieved from clinical charts. Disease activity was recorded at first evaluation (within 8 weeks of gestation) and monitored thereafter every month. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score was used to categorise active disease (clinical SLEDAI >0) and disease flares have been defined according to the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI Flare Index.

Patients started LDASA at the first evaluation during pregnancy or at least within the first trimester; only pregnancies in which therapy was continued throughout the pregnancy were included. Twin pregnancies were excluded.

Adverse pregnancy outcome (APO) was the composite primary outcome of the study and included proteinuric pre-eclampsia,<sup>12</sup> preterm delivery before 37 weeks of gestation, small-for-gestational age infant, low birth weight less

than 2500 g, intrauterine growth restriction (IUGR) and intrauterine fetal death (IUFD) after 12 weeks of gestation of a morphologically normal fetus. Preterm delivery was defined severe when it occurred before 32 weeks of gestation, and birth weight was defined very low if the newborn weighed less than 1500 g.

Informed consent was obtained from all patients and was registered on medical records.

## Statistical analysis

The characteristics of the pregnancies, overall and by treatment, were described in terms of frequencies and percentages for categorical variables and median and IQR for continuous variables.

The data presented three nested levels of variations: pregnancy within a woman within a centre. The association of the composite outcome with the use of LDASA was assessed by a Bayesian mixed-effect logistic model<sup>13</sup> with woman as the random effect, with and without adjustment for potential confounders, including age at pregnancy, primiparity, hypertension, active disease at first visit and disease flares during pregnancy. The estimated OR and the corresponding 95% CI for the treatment effect were calculated. The variable centre was not included in the model because there was no evidence of heterogeneity in outcome among centres. The statistical software R V.4.1.1<sup>14</sup> with its package blmer was used for analyses.

## RESULTS

The study included 216 pregnancies from 187 women (162, 21 and 4 with one, two and three pregnancies, respectively) from seven referral centres. Four patients were African, and the others Caucasian.

### Baseline characteristics at conception

The characteristics of pregnancies are described in table 1.

The median age and disease duration at conception were 32 (IQR 30–36) years and 9 (IQR 5–13) years, respectively. From the clinical perspective, in 160 pregnancies (74.1%) women had a history of joint involvement, in 143 (66.2%) cutaneous involvement, in 68 (31.5%) haematological involvement, in 35 (16.2%) serositis and in 12 (5.5%) history of neuropsychiatric involvement. According to the study exclusion criteria, none had a history or present kidney involvement. In 10.8% of cases the disease was active at the first evaluation during pregnancy, and in active patients the median SLEDAI score was 5 (IQR 4–6).

As far as the serological profile is concerned, over the course of the disease, in all cases but one (99.5%) were patients ANA-positive, 50.5% anti-double stranded(ds) DNA, 49.5% anti-Ro, 19.4% anti-La, 6.9% anti-Nuclear Ribonucleoprotein (RNP) and 5.1% anti-Sm positive. According to the study exclusion criteria, none had current or history of positive aPL antibodies.

In 111 pregnancies (51.4%) patients received glucocorticoids during pregnancy (median daily dose of 5 mg

**Table 1** Baseline characteristics of pregnancies

	All (N=216) n (%)	No low-dose acetylsalicylic acid (n=134), n (%)	Low-dose acetylsalicylic acid (n=82), n (%)	P value*
Age at pregnancy, years†	32 (30–36)	33 (29–37)	32 (30–36)	0.75
Disease duration†	9 (5–13)	8 (4–13)	9 (6–13)	0.26
Joint involvement‡	160 (74.1)	98 (73.1)	62 (75.6)	0.75
Cutaneous involvement‡	143 (66.2)	85 (63.4)	58 (70.7)	0.30
Haematological involvement‡	68 (31.5)	37 (27.6)	31 (37.8)	0.13
Serositis‡	35 (16.2)	21 (15.7)	14 (17.1)	0.84
Hypertension	8 (3.8)	7 (5.3)	1 (1.2)	0.26
Obesity	6 (3.2)	5 (4.3)	1 (1.3)	0.41
Smoking	2 (1.8)	2 (3.4)	0 (0.0)	0.50
First pregnancy	96 (45.7)	57 (43.8)	39 (48.8)	0.57
Assisted reproduction techniques	3 (2.1)	1 (1.3)	2 (3.0)	0.60
Hydroxychloroquine§	141 (65.3)	81 (60.4)	60 (73.2)	0.07
Glucocorticoids§	111 (51.4)	66 (49.3)	45 (54.9)	0.48
Azathioprine§	24 (11.1)	16 (12.0)	8 (9.8)	0.66
Ciclosporin A§	4 (1.9)	0 (0.0)	4 (4.9)	0.04
Active disease at first visit	22 (10.8)	16 (12.5)	6 (7.9)	0.36
SLEDAI at first visit†	2 (0–2)	2 (0–3)	2 (0–2)	0.28
Disease flares during pregnancy	26 (12.3)	17 (12.8)	9 (11.5)	0.83

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

Number of missing data: active disease at first visit: 12; SLEDAI at first visit: 16; hypertension: 5; obesity: 26; smoking: 103; first pregnancy: 6; medically assisted procreation: 73; disease flares during pregnancy: 5.

\*P values from Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables.

†Median (IQR).

‡At any time during the disease course.

§During pregnancy.

prednisone equivalent/day), in 141 (65.3%) women were on hydroxychloroquine, in 24 (11.1%) on azathioprine and in 4 (1.9%) on ciclosporin A.

In 82 pregnancies (38.0%) patients received LDASA during pregnancy; no differences in terms of age at conception and disease duration, clinical manifestations, comorbidities and disease flare during pregnancy were observed between cases on LDASA with respect to cases in which patients did not take LDASA during pregnancy. As far as concomitant therapies are concerned, a slightly higher percentage of patients on LDASA were also on hydroxychloroquine (73.2% vs 60.4%,  $p=0.07$ ) or on ciclosporin A (4.9% vs 0%,  $p=0.04$ ), while no differences were observed for glucocorticoids and azathioprine (table 1).

### Pregnancy outcomes

Overall, APO was reported in 65 pregnancies (30.1%); in particular, pre-eclampsia was observed in 13 pregnancies (6.1%) and occurred before 34 gestational weeks in 7 cases (3.2%), IUFD in 3 (1.4%), IUGR in 12 (5.6%), very low birth weight in 13 (6.1%) and severe preterm birth in 11 pregnancies (5.1%). A detailed description of all pregnancy complications is reported in table 2. No significant association was observed between hypertension and

pre-eclampsia: among 8 women with hypertension, 1 had pre-eclampsia, while among 203 women without hypertension 12 had pre-eclampsia (Fisher's exact test  $p=0.37$ ). Of note, during pregnancy, in 12.3% of cases a disease flare occurred.

Interestingly, the frequency of all complications was similar in pregnancies of patients on LDASA and of patients who did not take LDASA during pregnancy.

When the correlation structure of the data was properly accounted for using mixed-effect logistic model, there was no evidence of association of the composite outcome with LDASA administration (unadjusted OR=1.37, 95% CI 0.39 to 4.76,  $p=0.62$ ); the adjustment for potential confounders did not materially change the result (adjusted OR=1.19, 95% CI 0.37 to 3.81,  $p=0.77$ ).

### DISCUSSION

In this study we described the outcomes of pregnancies in a particular subgroup of patients with SLE without evidence of aPL and history or current nephritis. We aimed to test whether LDASA could have a protective role against APO in this highly selected population without the classic risk factors for pregnancy complications. Thus, the study aimed to address a clinical issue which is raised

**Table 2** Pregnancy outcomes

	All (N=216) n (%)	No low-dose acetylsalicylic acid (n=134) n (%)	Low-dose acetylsalicylic acid (n=82) n (%)	P value*
Gestational diabetes	3 (2.1)	1 (1.3)	2 (3.0)	0.60
Pre-eclampsia	13 (6.1)	11 (8.3)	2 (2.4)	0.14
Early-onset pre-eclampsia ( $<34$ weeks)	7 (3.2)	6 (4.4)	1 (1.2)	0.90
Intrauterine fetal death	3 (1.4)	3 (2.2)	0 (0.0)	0.29
Intrauterine growth restriction	12 (5.6)	7 (5.3)	5 (6.2)	0.77
Gestational weeks at delivery†	39 (37–40)	39 (37–40)	39 (37–39)	0.55
Preterm delivery	40 (18.9)	23 (17.7)	17 (20.7)	0.59
Birth weight $<2500$ g	33 (15.6)	19 (14.4)	14 (17.5)	0.56
Birth weight $<1500$ g	13 (6.1)	11 (8.3)	2 (2.5)	0.14
Size for gestational age				0.09
Small	23 (11.0)	10 (7.7)	13 (16.5)	
Appropriate	182 (87.1)	118 (90.8)	64 (81.0)	
Large	4 (1.9)	2 (1.5)	2 (2.5)	
Composite outcome‡	65 (30.1)	38 (28.4)	27 (32.9)	0.54

Number of missing data: gestational diabetes: 74; pre-eclampsia: 2; intrauterine fetal death: 0; intrauterine growth restriction: 2; gestational week: 6; preterm delivery: 4; birth weight: 8; birth weight  $<2500$  g: 4; birth weight  $<1500$  g: 3; size for gestational age: 7.  
\*P values from Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables.  
†Median (IQR).  
‡Composite outcome: at least one of pre-eclampsia, intrauterine fetal death, intrauterine growth restriction, preterm delivery, birth weight  $<2500$  g and small for gestational age.

very frequently in clinical practice and for which the available literature does not provide a clear and definite answer: should we prescribe LDASA to all patients with SLE during pregnancy?

As a matter of the fact, a recent study from the Systemic Lupus International Collaborating Clinics (SLICC) cohort showed that LDASA was prescribed in only 25% of lupus pregnancies despite the presence of traditional risk factors for pre-eclampsia.<sup>15</sup>

The first important result that emerged from this study is that the incidence of severe obstetric complications in this particular population is low; in particular, pre-eclampsia was observed in 6.1% of patients, an incidence significantly lower than that observed in unselected SLE cohorts and similar to the frequency observed in the general population.<sup>16–19</sup> The incidence of pre-eclampsia in our cohort was also lower than that expected in high-risk pregnancies, where it is around 9%.<sup>20</sup>

The most frequent obstetric complication was preterm delivery, observed in 18.9% of pregnancies; however, severe preterm delivery was reported in a minority of cases. It is important to note that these patients were strictly monitored and most pregnancies were planned, and these aspects could have had an impact on the low number of severe adverse events.

Our results are in line with previous findings on stable patients with SLE without active nephritis or prednisone  $>20$  mg, as in the Predictors of Pregnancy Outcome:

Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus (PROMISSE) study, where no difference in per cent of LDASA use in patients with and without APO was reported.<sup>2</sup> While the study did not restrict to those without aPL or nephritis as in our analysis, the importance of a good control of disease activity was stressed similarly.

The second aspect that emerged from this study is that LDASA does not seem to have a significant impact on the occurrence of obstetric complications in this type of patients; indeed, the frequency of the composite outcome APO and of each adverse outcome is similar in patients on LDASA and not.

This is in line with literature data on the general population showing that the relative risk reduction of pre-eclampsia with LDASA is modest and strongly related to the baseline, individual pre-eclampsia risk.<sup>8,21</sup> It may therefore be assumed that the sample size of our study is not sufficient to detect the beneficial effect of LDASA in this type of patient at low risk of complications.

Moreover, a possible bias by indication should be considered; indeed, we can assume that LDASA was probably administered to patients at increased risk of pregnancy complications, at least according to physician judgement.

However, it is interesting to note that pre-eclampsia had a frequency of 2.4% in patients taking LDASA, while those not taking LDASA had 8.3%. Although this difference is not statistically significant, probably due to the low

number of observations included, this could suggest a protective effect of LDASA against the hypertensive disorders of pregnancy. On the other hand, chronic hypertension was more frequent, even if not significantly, in the control group than in the LDASA group (5.2% vs 1.2%); this comorbidity represents a well-known major risk factor for pre-eclampsia warranting the intake of LDASA irrespective of the diagnosis of SLE.

Thus, based on these findings, patients with SLE without aPL nor lupus nephritis seem to have a low risk of severe obstetric complications (especially pre-eclampsia) and LDASA treatment does not provide a significant advantage over these complications.

On the other hand, it should also be emphasised that a robust body of evidence showed no significant haemorrhagic risk or fetal risk associated with LDASA use during pregnancy. Thus, in the individual risk–benefit assessment, the potential protection from pregnancy complications seems to outweigh the risk of adverse events.<sup>8 22</sup> Unfortunately, we did not assess haemorrhagic complications that occurred in our pregnancies.

This study has some limitations. First of all, it is a retrospective analysis and the physician's judgement has a strong weight in the study. Indeed, we did not observe any cluster of risk factors in patients who received LDASA, but still it is not possible to reproduce the clinical reasoning made by the physician (or the multidisciplinary team) during preconception counselling.

However, our data derived from the real-life practice of seven European referral centres for pregnancy in SLE and were carefully collected; thus, good standardisation among the centres is expected. The second limitation is related to the small sample size and the resulting small number of obstetric complications, limiting the statistical analysis.

On the other hand, to the best of our knowledge, this is the first study to assess the impact of LDASA in a selected and homogeneous population of patients with SLE with a low-risk profile for obstetric complications.

In conclusion, these data highlight the importance of a careful individual risk assessment for pregnancy complications in patients with SLE, hopefully in the setting of a preconceptional counselling. Moreover, these data encourage a shared decision-making process between patients, rheumatologists and obstetricians, taking into account disease-related and non-disease-related factors.

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**Acknowledgements** The authors wish to thank all patients enrolled in the study and all clinicians, nurses and midwives who cared for the patients.

**Contributors** CT and DZ contributed to the conception and design of the study, to the acquisition and interpretation of data, and were responsible for writing the manuscript. IH, MG, ML, LC, AB, FC, JM, FALS, FM, EE, RE, EB, MP, LA, LAC, GZ, MG, LI, AT, AD and RF actively contributed to the acquisition of data and drafting of the manuscript. LB and MF were responsible for data analysis and contributed to the drafting of the manuscript. MM contributed to the conception and design of the study and to the acquisition of data. MM was also responsible for the interpretation of data, contributed to the drafting of the manuscript and was responsible for the overall content as the guarantor. All authors have read and approved the final version of the article.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Ethics approval** This study involves human participants and was approved by Comitato Etico Area Vasta Nord Ovest (approval number: 13660) and performed according to the principles of the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. The data underlying this article will be shared on reasonable request to the corresponding author.

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#### REFERENCES

- 1 Smyth A, Oliveira GHM, Lahr BD, *et al*. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol* 2010;5:2060–8.
- 2 Buyon JP, Kim MY, Guerra MM, *et al*. Predictors of pregnancy outcomes in patients with lupus: a cohort study. *Ann Intern Med* 2015;163:153–63.
- 3 Roberge S, Giguère Y, Villa P, *et al*. Early administration of low-dose aspirin for the prevention of severe and mild preeclampsia: a systematic review and meta-analysis. *Am J Perinatol* 2012;29:551–6.
- 4 Radu A, Dudu SC, Ciobanu A, *et al*. Pregnancy management in women with Antiphospholipid syndrome. *Maedica* 2019;14:148–60.
- 5 Rolnik DL, Wright D, Poon LC, *et al*. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017;377:613–22.
- 6 Andreoli L, Bertias GK, Agmon-Levin N, *et al*. EULAR recommendations for women's health and the management of family

- planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann Rheum Dis* 2017;76:476–85.
- 7 Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Care Res* 2020;72:461–88.
  - 8 ACOG Committee opinion no. 743: low-dose aspirin use during pregnancy. *Obstet Gynecol* 2018;132:e44–52.
  - 9 Gu W, Lin J, Hou Y-Y, et al. Effects of low-dose aspirin on the prevention of preeclampsia and pregnancy outcomes: a randomized controlled trial from Shanghai, China. *Eur J Obstet Gynecol Reprod Biol* 2020;248:156–63.
  - 10 Hochberg MC. Updating the American College of rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:40.
  - 11 Dooley MA, Aranow C, Ginzler EM. Review of ACR renal criteria in systemic lupus erythematosus. *Lupus* 2004;13:857–60.
  - 12 Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013;122:1122–31.
  - 13 Chung Y, Rabe-Hesketh S, Dorie V, et al. A nondegenerate penalized likelihood estimator for variance parameters in multilevel models. *Psychometrika* 2013;78:685–709.
  - 14 Team RC. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2021. <https://www.R-project.org/>
  - 15 Mendel A, Bernatsky SB, Hanly JG, et al. Low aspirin use and high prevalence of pre-eclampsia risk factors among pregnant women in a multinational SLE inception cohort. *Ann Rheum Dis* 2019;78:1010–2.
  - 16 Clowse MEB, Jamison M, Myers E, et al. A national study of the complications of lupus in pregnancy. *Am J Obstet Gynecol* 2008;199:127.e1–127.e6.
  - 17 Tani C, Zucchi D, Haase I, et al. Are remission and low disease activity state ideal targets for pregnancy planning in systemic lupus erythematosus? A multicentre study. *Rheumatology* 2021;60:5610–9.
  - 18 He WR, Wei H. Maternal and fetal complications associated with systemic lupus erythematosus: an updated meta-analysis of the most recent studies (2017-2019). *Medicine* 2020;99:e19797.
  - 19 Abalos E, Cuesta C, Grosso AL, et al. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol* 2013;170:1–7.
  - 20 Duley L, Meher S, Hunter KE. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev* 2019:CD004659.
  - 21 LeFevre ML, U.S. Preventive Services Task Force. Low-Dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. preventive services Task force recommendation statement. *Ann Intern Med* 2014;161:819–26.
  - 22 Yelnik CM, Lambert M, Drumez E, et al. Bleeding complications and antithrombotic treatment in 264 pregnancies in antiphospholipid syndrome. *Lupus* 2018;27:1679–86.