

Survey of Antimalarial Use in Lupus Pregnancy and Lactation

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ABSTRACT Objective. To obtain the experience of selected experts in the use of antimalarial drugs (AM) in pregnancy and lactation in systemic lupus erythematosus.

Methods. Seventy-eight lupus experts identified from North America and UK were mailed a 19 question survey regarding their experience using AM in pregnancy and lactation.

Results. The 52 (67%) respondents with usable questionnaires treated a median of 75 lupus patients/year, including 4–5 lupus pregnancies/year. Thirty-five (69%) continued AM sometimes, often, or always during pregnancy. Continuing AM increased with the number of pregnant lupus patients seen ($p < 0.01$). None reported having seen any fetal toxicity with AM use, and pregnancy was never terminated because of AM, other than at patient insistence ($n = 1$). Postpartum, 29 (63%) continued AM and advised breast-feeding. Responses were consistent among North American and UK experts.

Conclusion. The majority of lupus experts continue AM during pregnancy. This was particularly true for those who treated a larger number of pregnant lupus patients per year. The majority advise breast-feeding and continue AM postpartum. These practices are supported by the limited literature available. (J Rheumatol 2002;29:700–6)

Key Indexing Terms:

ANTIMALARIAL TREATMENT
PREGNANCY

LUPUS
LACTATION

Antimalarial drugs (AM) are a well established treatment for systemic lupus erythematosus (SLE). Several studies have shown their efficacy in controlling disease activity and others have documented that their discontinuation may precipitate flare^{1–4}. Although AM are widely used to control disease activity in lupus, their use in pregnancy and lactation remains controversial. Further, pregnancies in SLE are high risk with increased risk of preterm birth and fetal loss^{5–8}. SLE tends to flare during pregnancy^{6,9,10} and disease activity is one of the factors contributing to adverse pregnancy outcomes¹¹. It is therefore desirable to control disease activity before and throughout pregnancy.

Knowing that AM cross the placenta and are secreted in breast milk may discourage AM use during pregnancy and breast-feeding. Yet AM have a half-life of about 40 days, suggesting that discontinuation must occur many months prior to conception to completely protect the fetus from

exposure. Thus, the fetuses of many women who discontinued AM shortly before pregnancy likely had been exposed to AM.

In the absence of large controlled studies, many rheumatologists depend on the experience of others in prescribing AM in pregnancy and breast-feeding. In this study, selected lupus “experts” were surveyed about their experience.

MATERIALS AND METHODS

Lupus experts were identified through a combination of methods including a Medline search for authors of English language clinical studies using the key words antimalarial drugs, lupus, and pregnancy from 1966 to 1999, authors of lupus chapters in major rheumatology textbooks, and the British Isles Lupus Assessment Group. To contrast between-country differences, the study was limited to experts in North America (Canada, the USA, and Mexico) and the UK.

Identified lupus experts were mailed a 19 question survey (Appendix) that queried the demographic data of the specialist, a description of his/her practice, and management of SLE patients during pregnancy and breast-feeding. In the event of non-reply, a second copy of the survey was mailed or faxed. Respondents who reported they had no data from clinical experience were excluded.

The data were analyzed using SPSS version 9.0. A Spearman correlation matrix was calculated. Categorical variables were compared across levels of other categorical variables by means of chi-square tests; numerical variables were compared across levels of binary variables using Mann-Whitney tests and across multiple levels of categorical variables using Kruskal-Wallis tests; ordered categorical variables and numerical variables were related by means of Spearman correlations.

RESULTS

Seventy-eight experts were identified (Canada = 24, USA = 31, Mexico = 5, UK = 18). Fifty-eight (74%) responded and

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data from 52 (67%) were analyzed. Six respondents were not included either because they had no clinical experience ($n = 4$) or they were retired ($n = 2$). Because of small numbers, experts from Mexico were combined with those of the USA in the analysis. Twenty of the 52 (38%) were from Canada, 18 (35%) from the USA (including Mexico), and 14 (27%) from the UK.

Of the 52 respondents, 38 (73%) were male and 13 (25%) were female. Their mean age was 51 ± 9 years (range 35 to 71) and this did not differ between the sexes. The median year of graduation from medical school was 1974 (range 1955 to 1988). The mean percentage of time in clinical practice was $63 \pm 28\%$. The median number of lupus patients followed per year was 75, the median number of pregnant lupus patients seen yearly per respondent fell between 4 and 5, and the number of pregnant lupus patients seen yearly by all the respondents was around 234. With regard to these variables, there were no differences among the respondents from Canada, the US, and the UK except for age ($p = 0.007$) and year of graduation ($p = 0.032$). The UK experts in particular were significantly younger and had graduated more recently from medical school than the US respondents. There was also a trend for more US respondents to be female ($p = 0.05$) (Table 1).

When the experts were asked whether they continued AM during pregnancy they replied as follows: 12 (24%) never; 4 (8%) rarely; 14 (27%) sometimes; 12 (24%) often; and 9 (18%) always (Figure 1). The responses did not differ statistically among Canadian, US, and UK experts (Figure 2).

Although the correlation between continuing AM and the number of lupus patients followed per year ($r = 0.25$, $p = 0.07$) was not significant, continuing AM during pregnancy increased with the number of pregnant lupus patients seen ($r = 0.55$, $p < 0.001$) (Figure 3). Continuing AM in pregnancy correlated with the year of graduation from medical school. The more recent the year of graduation, the greater the tendency to continue AM ($r = 0.30$, $p = 0.04$).

While the majority of lupus experts continued AM in pregnancy, only 13% initiated them for a flare in pregnancy. The respondents were not asked why they were reluctant to start AM in pregnancy. However, reasons might include the

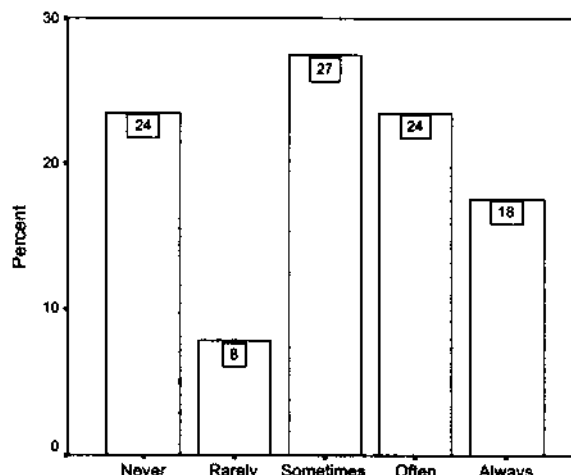


Figure 1. Responses to the question, "Do you continue AM during pregnancy?"

delayed onset of action of antimalarials or a general reluctance to initiate any drug in pregnancy for which safety for the fetus is unproven. Respondents with a greater tendency to continue AM also had a greater tendency to initiate them in pregnancy regardless of whether the patient had ever received them previously ($r = 0.49$, $p = 0.002$) or had benefited from them prior to the pregnancy ($r = 0.56$, $p < 0.001$).

When prescribing AM in pregnancy, 34/40 (85%) maintained the same dose of AM as prior to the pregnancy, whereas 6/40 (15%) reduced the dose.

Although the use of AM during pregnancy varied among the experts, 51/52 (98%) stated they believed that there was no increase in stillbirths or spontaneous abortions with the use of the drug. None reported ever having seen any fetal toxicity with AM use. With the respondents each caring for a median of 4 to 5 lupus pregnancies a year, this reflects no fetal toxicity in more than 200 pregnancies per year. Only one of the 52 respondents had terminated a pregnancy because of AM use and this was at the patient's preference.

When rheumatologists were asked whether they continued AM during breast-feeding, it was found that when a pregnant patient taking AM gives birth, 29 (63%) advised continuing AM and starting breast-feeding, 11 (24%) advised against breast-feeding, and 6 (13%) discontinued AM and advised patients to breast-feed (Figure 4). Responses were consistent among Canadian, US, and UK experts. When asked if they would start treatment with AM in a lupus patient that was breast-feeding, if the clinical manifestations of the flare were those likely to respond to AM, the majority (53%) said they would do so often or always (Figure 5). Rheumatologists who tended to restart AM for a flare in pregnancy tended also to restart them during breast-feeding ($r = 0.34$, $p = 0.02$) (Figure 6).

Respondents were asked to indicate their level of confidence in managing a pregnant patient with lupus (Figure 7). Not surprisingly, given that the respondents were selected based on published experience, the median score was 9/10

Table 1. Characteristics of the respondents.

	Male, %	Age, yrs, Mean \pm SD	Year of Graduation, Median	Percentage of Time in Clinical Practice, Mean \pm SD
Canada	90	51 ± 7	1972	60 ± 28
USA*	56	56 ± 10	1970	64 ± 32
UK	77	45 ± 9	1979	66 ± 25
Total	75	51 ± 9	1974	63 ± 28

*Includes Mexico.

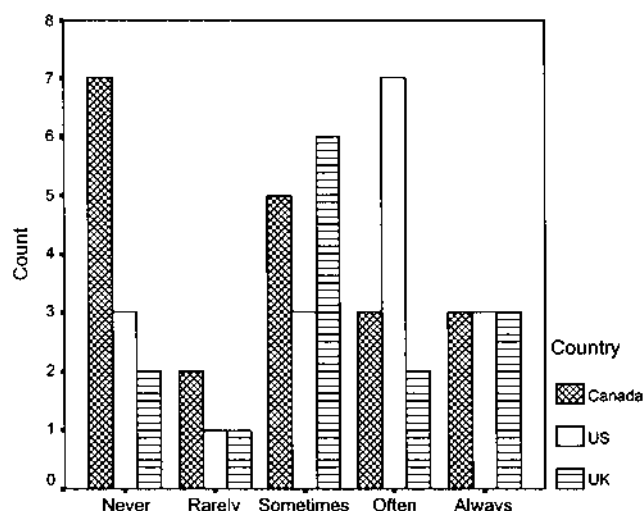


Figure 2. A comparison between Canadian, US, and UK respondents in their responses to the question whether they continue AM during pregnancy.

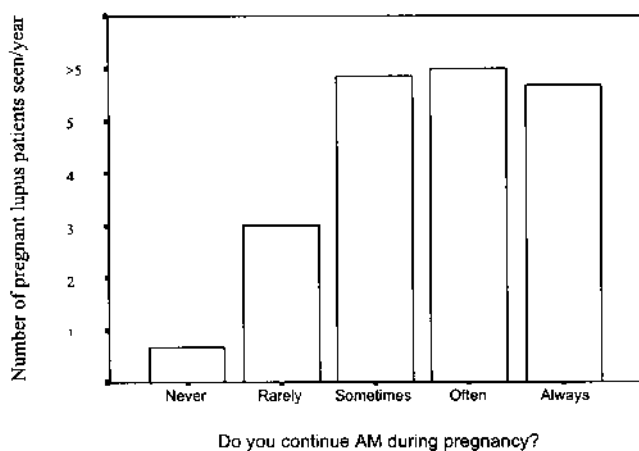


Figure 3. A comparison of the likelihood of continuing AM during pregnancy and the number of pregnant patients with lupus seen by a respondent per year.

for all respondents, regardless of country of practice. The confidence level of the respondent correlated with the number of lupus patients they followed ($r = 0.33$, $p = 0.02$) and with the number of pregnant lupus patients they treated ($r = 0.35$, $p = 0.01$). There was no significant correlation, however, between confidence and continuing AM during pregnancy or breast-feeding.

DISCUSSION

Most of the experts who responded to our survey continue AM during pregnancy and breast-feeding. This practice is supported by most of the case series and the limited number of controlled studies published.

The major concerns about AM in pregnancy arise from

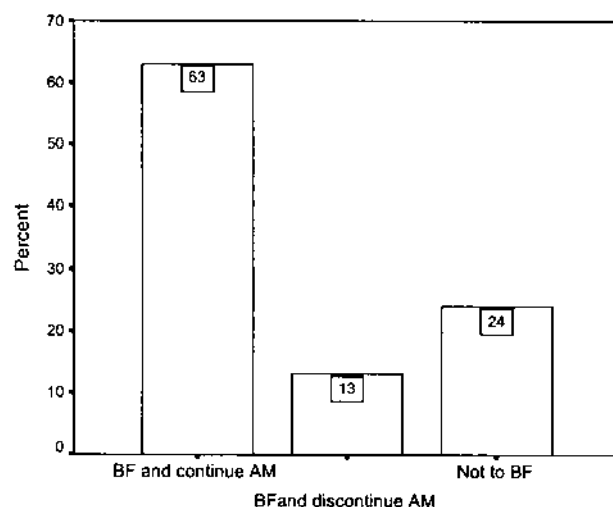


Figure 4. Responses to the question, "What do you advise your lupus patient when she gives birth?" BF: Breast-feed.

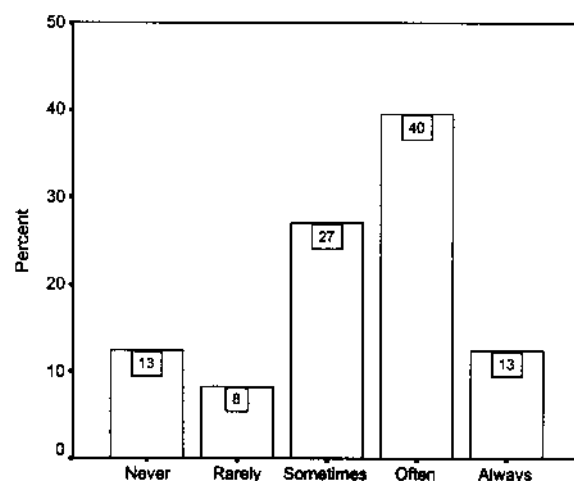


Figure 5. Percentage of respondents initiating AM during breast-feeding if findings are likely to improve with treatment.

the 1964 report by Hart and Naunton¹², who described a 30-year-old mother of 6 children who was diagnosed with discoid lupus after the birth of her first child. Subsequently, she had 6 additional pregnancies (5 live births). In 4 pregnancies she had at least some exposure to chloroquine, either 250 mg daily or 250 mg BID. Two children had posterior column defects and vestibulocochlear abnormalities. One of the 2 was retarded mentally and the other had several convulsions. Of the other 2 pregnancies with exposure to chloroquine one resulted in a child who had Wilms' tumor and hemihypertrophy of the body and the other in a spontaneous abortion. The 2 pregnancies that occurred after the diagnosis of discoid lupus and without the concomitant use of chloroquine resulted in healthy offspring, although it is

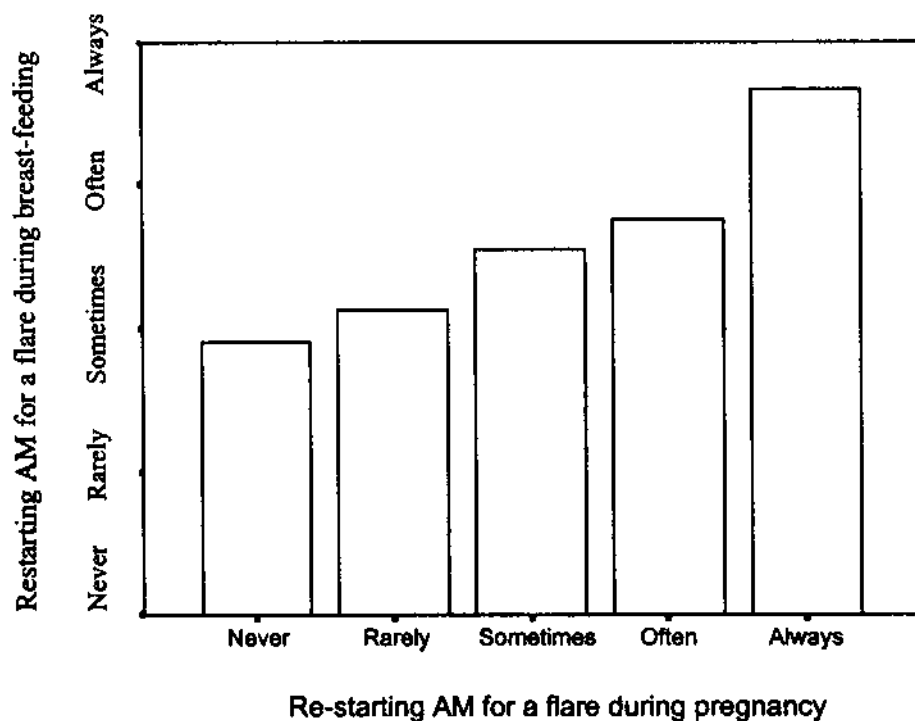


Figure 6. A comparison of the likelihood of restarting AM for a flare during pregnancy versus during breast-feeding.

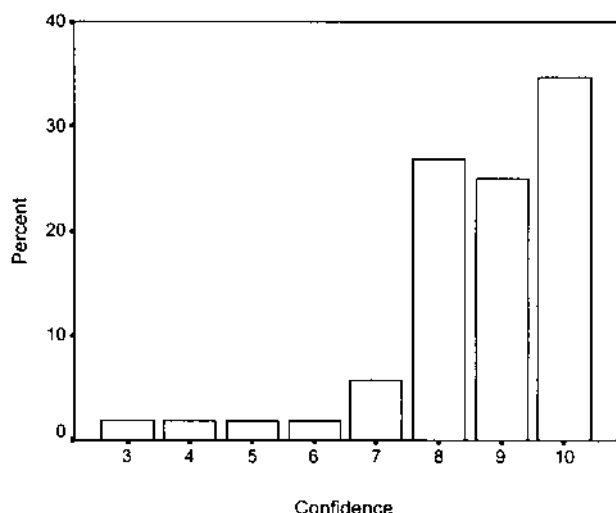


Figure 7. Confidence level reported by the respondents in managing patients with lupus during pregnancy.

unclear exactly when chloroquine was discontinued in relation to pregnancy. It is possible that there had been at least some exposure to chloroquine even when the patient was not taking it during her pregnancy given the long half-life of the drug.

In contrast to the Hart and Naunton report, 2 case series were published^{13,14} of pregnant patients taking hydroxy-

chloroquine (HCQ) and chloroquine amounting to 30 pregnancies in total (Table 2). These pregnancies resulted in 18 full term births, 5 preterm, 4 spontaneous abortions, and 3 stillbirths. There were no congenital abnormalities reported in the offspring.

In addition, there have been 3 studies¹⁵⁻¹⁷, 2 of which included patients with SLE, comparing pregnancies in which patients were exposed to AM with pregnancies without the exposure to AM. These studies failed to find any increase in adverse pregnancy outcomes in patients taking AM during pregnancy (Table 3). Ross and Garatsos¹⁸ reported a 27-year-old patient with discoid lupus: while taking 400 mg HCQ sulfate daily, she requested abortion because of her concerns about congenital abnormalities to her fetus. Abortion was performed at 14 weeks of gestation and pathological examination of the fetus revealed no congenital abnormalities including of the aural apparatus. A recent double blind and placebo controlled trial of HCQ was conducted¹⁹ in 20 pregnant patients with SLE or discoid lupus in Brazil. In those randomized to HCQ, there was no toxicity or congenital anomaly, but there was a decrease in prednisone dose and in SLEDAI score. Fetal age and Apgar scores at delivery were higher in the HCQ compared to the placebo group.

In regard to lactation, a number of studies have measured the amount of chloroquine or HCQ delivered to the newborn during breast-feeding. Ette, *et al*²⁰ measured chloroquine

Table 2. Case series of women using AM during pregnancy.

Study	Pregnancies No. of Patients	Diagnosis	AM Taken During Pregnancy	Pregnancy Outcome
Parke & West	9 (8)	SLE	HCQ 200 mg daily in all but one (200 mg every other day)	Active disease (n = 4): All PTL Inactive disease (n = 5): 4 NFT, 1 PTL
Levy ¹⁴	21 (18)	SLE, RA MP	CQ 125–500 mg or HCQ 200–500 mg daily during the first trimester	Active disease (n = 11): 8 NFT, 2 SA, 1 SB Inactive disease (n = 6): 3 NFT, 2 SA, 1 SB MP (n = 4): 3 NFT, 1 SB

HCQ: hydroxychloroquine, PTL: preterm labor, NFT: normal full term, CQ: chloroquine, MP: malaria prophylaxis, SA: spontaneous abortion, SB: still birth.

Table 3. Controlled studies of AM use in pregnancy.

Study	Diagnosis	No. of Pregnancies	AM Taken During Pregnancy	Pregnancy Outcome
Khamashta ¹⁵	SLE, discoid lupus	Taking AM: 36	HCQ 200–400 mg daily	2 SA, 3 fetal death, 31 live births (17 premature, 6 IUGR, 10 fetal distress, 1 Down's syndrome)*
		No AM: 53	—	4 SA, 5 fetal death, 44 live births (21 premature, 18 IUGR, 16 fetal distress, 1 extra 6 th finger) [†]
Parke ¹⁶	SLE	Taking AM: 14	CQ 250–500 mg, or HCQ 200–400 mg daily	Active disease (3): 3 SB Inactive disease (11): 6 NFT, 4 SA, 1 SB
		No AM: 6	—	Active disease (4): 3 SA, 1 NND Inactive disease (2): 1 NFT, 1 SA
Wolfe ¹⁷	MP	Taking AM: 169	CQ 300 mg weekly	1 TOF, 1 hypothyroidism ^{††}
		No AM: 454	—	1 microcephaly, 1 CHD, 1 clubfoot, 1 hamartoma ^{††}

CQ: chloroquine, HCQ: hydroxychloroquine, SA: spontaneous abortion, IUGR: intrauterine growth retardation, SB: still birth, NFT: normal full term, NND: neonatal death, MP: malaria prophylaxis, TOF: Tetralogy of Fallot, CHD: congenital heart disease. * The disease was active in 62% of cases. † The disease was active in 58% of cases. †† Fetal wastage was not reported.

sulfate in breast milk and saliva after 2 tablets of the drug, containing 300 mg chloroquine base, were given orally to 5 healthy nursing mothers. It was estimated that 0.55% of the given dose was secreted in the breast milk. This would be equivalent to 1.65 mg of chloroquine secreted daily. However, secretion of chloroquine in breast milk was not evaluated based on repeated AM dosing as would occur clinically. Another study²¹ on 11 nursing mothers who received one dose of 600 mg chloroquine base showed a maximum of 4.4 ± 2.6 mg received by the breast-feeding infant — 1.4 mg/kg on a body weight basis. Nation, *et al*²² described a 27-year-old lactating mother of a 9-month-old infant, who was taking 400 mg HCQ sulfate daily for 6 weeks to control active SLE. The concentration of HCQ was measured in breast milk, plasma, and whole blood at different intervals during breast-feeding. The milk to plasma concentration ratio was roughly 5.5 and the milk to whole

blood ratio was 0.6. Assuming steady-state conditions and a daily milk consumption of 1 liter, it was calculated that the infant received a daily dose of 1.1 mg, which was equivalent to 0.35% of the daily maternal dose of HCQ base. After correction for body weight, the maternal and the infant doses correspond to 5.96 and 0.11 mg/kg, respectively. On a body weight basis, the infant received 2% of the maternal dose. Østensen, *et al*²³ described a 24-year-old lactating mother with seronegative rheumatoid arthritis who restarted 200 mg HCQ twice daily after a relapse of her arthritis. Multiple samples of plasma and breast milk were taken and it was found that after 4 doses of HCQ, only 3.2 µg (0.0003% of the total dose) was secreted in the milk over 48 hours.

These studies show that only a small amount of the ingested AM is delivered to the infant through breast-feeding. However, the clinical significance of this small

dose and its safety for the infant have not been described. Nonetheless, the literature lacks any evidence of a specific risk for the breast-feeding infant of a mother taking AM. This may explain why the majority of the lupus experts in our study advised their postpartum patients to breast-feed and continue AM.

A recent insight that is important in deciding whether to continue AM during pregnancy concerns new information on AM pharmacokinetics. While the half-life of HCQ was thought to be several days, it is now recognized to be at least 40 days²⁴. HCQ was detected in whole blood and urine up to 91 and 85 days, respectively, following a single oral dose of 200 mg HCQ sulfate²⁵. The metabolites of HCQ sulfate can be detected 5 months after the last dose given^{24,26}. The prolonged half-life results from its extensive tissue sequestration and its slow redistribution from the tissues back to the blood. The volume of distribution of HCQ was estimated to be roughly 8000 liters after a single oral dose and 5500 liters after the same dose injected^{25,26}.

Considering that AM rapidly cross the placenta^{27,28} and their metabolites can be detected in cord blood, neonatal systemic blood, and neonatal urine²⁹, discontinuation of AM even several months prior to conception will not protect the fetus from exposure to AM. Accordingly, it is probably unrealistic to discontinue AM when pregnancy is discovered since the fetus will continue to be exposed to the drug throughout the first trimester in spite of the medication being stopped.

When the possibility of pregnancy is discussed in advance, the physician can discuss with the patient the pros and cons of continuing AM. Should the patient decide to discontinue AM, this should likely be done at least 6 months prior to conception. It is probably advisable for the physician to be proactive with SLE patients at potential risk of pregnancy that discussion of medications needs to be considered well in advance of conception.

The majority of respondents to our questionnaire, particularly those who treat larger numbers of pregnant patients with lupus, are comfortable to continue AM during a lupus pregnancy. No respondent reported seeing fetal toxicity. This practice is consistent with the limited, but nonetheless supportive, literature. However, increased adverse pregnancy outcomes in lupus in general may render it difficult to exclude even relatively common adverse fetal outcomes with using AM.

The natural caution to avoid use of any drugs in pregnant women must be balanced by the possible increase in adverse fetal outcomes with active SLE in the mother. To the extent AM control SLE activity, they may well reduce adverse outcomes, thereby justifying drug use during pregnancy where active disease seems likely or even possible.

With regard to breast-feeding, the majority of lupus experts advised continuing AM during breast-feeding. To the extent that AM suppress lupus activity and maintain

better health in a mother, this is likely an advantage for both the mother and the infant. This benefit must be weighed against the unknown risk of very low AM exposure for the fetus via breast milk. Initiating AM while breast-feeding, however, is another issue that remains to be agreed on.

With increasing use of antimalarial drugs in SLE, further study of AM safety is required. Both pharmacological and epidemiological approaches will be needed to confirm the limited clinical data presently available. In the meantime, some reassurance can be obtained from those with considerable experience, most of whom appear to believe that AM are safe in pregnancy and lactation.

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APPENDIX.

The survey questionnaire mailed to participants.

QUESTIONNAIRE

1. Age:
2. Gender:
3. Year of graduation from medical school:
4. Do you currently practice in: USA, Canada, UK
5. What percentage of your time is allocated to seeing rheumatic disease patients?
6. How many lupus patients on antimalarial therapy do you follow on average per year? (0–10, 11–25, 26–50, 51–100, 100)
7. How many of your lupus patients have ever become pregnant on antimalarial therapy? (None, 1, 2–3, 4–5, > 5)
8. Do you continue antimalarial therapy during pregnancy? (Always, often, sometimes, rarely, never)
9. In a lupus patient that becomes pregnant, never having previously received antimalarial therapy, have you ever started treatment during pregnancy? (Yes, no)
10. In a lupus patient that has previously benefited from antimalarial therapy, but has a disease exacerbation during pregnancy while not taking antimalarials, do you restart the drug? (Always, often, sometimes, rarely, never)
11. In general, if you decide to continue with the antimalarial treatment throughout pregnancy, do you decrease the dose? (Yes, no, not applicable — I never continue antimalarial therapy in pregnancy)
12. Have you ever seen any fetal toxicity with antimalarial treatment? (No, yes. Please describe)
13. Do you believe that there is an increase in stillbirths or spontaneous abortions in pregnancies of lupus patients taking antimalarials, compared to other lupus pregnancies? (Yes, no)
14. If your answer to question 13 is “yes”, is this based on experience? (Yes, no)
15. Have you ever terminated a pregnancy because of antimalarial use? (Yes, no)
16. Was this because of the patient’s wishes? (Yes, no)
17. A lupus patient who took antimalarial drugs during pregnancy now gives birth and asks you for advice regarding breast-feeding. In general, do you advise her (Not to breast-feed? To breast-feed and discontinue the antimalarials? To breast-feed and continue the antimalarials?)
18. If your lupus patient who has been well controlled off antimalarial treatment now flares up when she is breast-feeding and has findings likely to improve with antimalarials, do you start her on treatment? (Always, often, sometimes, rarely, never)
19. On a scale from zero to 10, how confident do you feel managing a

lupus patient when she gets pregnant? (Zero = not confident at all, 10 = very confident). Please circle the number which best describes your level of confidence.

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