


Health Outcomes of 215 Mothers of Children With Autoimmune Congenital Heart Block: Analysis of the French Neonatal Lupus Syndrome Registry

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ABSTRACT. *Objective.* Transplacental passage of maternal anti-SSA and anti-SSB antibodies, potentially associated with maternal autoimmune diseases, can cause neonatal lupus syndrome. Given the paucity of data in this setting, we report short- and long-term outcomes of mothers of offspring with congenital heart block (CHB).

Methods. This retrospective study included anti-SSA/SSB antibody-positive mothers of fetuses with high-degree CHB and focused on their health status before pregnancy, at CHB diagnosis, and thereafter.

Results. We analyzed 215 women with at least 1 pregnancy with CHB. Prior to this diagnosis, only 52 (24%) mothers had been diagnosed with an autoimmune disease, mainly systemic lupus erythematosus (SLE; n = 26, 12%) and Sjögren syndrome (SS; n = 16, 7%). Six more were diagnosed with an autoimmune disease during the index pregnancy. Of the 157 mothers (73%) with no such diagnosis at childbirth, 77 (49%) developed one after a median follow-up of 11 years (range: 21 days to 54 years). By the end of follow-up, 135 women (63%) had an autoimmune disease diagnosis, mainly SLE (n = 54, 25%) and SS (n = 72, 33%). Three patients with SLE had renal involvement, and only 6 (3%) had required an immunosuppressive drug at any point. The symptoms best predicting autoimmune disease development were arthralgia and myalgia ($P < 0.001$), dry syndrome ($P = 0.01$), and parotid swelling ($P = 0.05$).

Conclusion. One-quarter of the patients had an autoimmune disease diagnosis at the time of the fetal CHB diagnosis. Nearly half of those without an initial diagnosis progressed during follow-up, most without severe manifestations. Severe diseases such as lupus nephritis were rarely seen, and immunosuppressive drugs were rarely required.

Key Indexing Terms: anti-SSA/Ro antibodies, congenital heart block, maternal diseases, neonatal lupus erythematosus syndrome, pregnancy, systemic lupus erythematosus

Neonatal lupus syndrome (NLS) caused by transplacental passage of maternal anti-SSA and/or anti-SSB antibodies is a rare disorder that includes cardiac neonatal lupus with congenital heart block (CHB) and skin rash.^{1,2} Its prevalence is

approximately 1% in anti-SSA-positive women; 1 of 154 (0.65%) in the prospective study by Buyon et al,³ 1 of 99 (1%) in a study by Costedoat-Chalumeau et al,⁴ and 2 of 100 (2%) in a study by Brucato et al.⁵

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Mothers with anti-SSA and anti-SSB antibodies can have diseases, or be asymptomatic or pauci-symptomatic when NLS is discovered in their offspring^{6,7}; those who are asymptomatic may later develop an autoimmune disease.⁶ Long-term outcomes have been described in previous series of 15 to 83 mothers, not all positive for anti-SSA/Ro antibodies.⁸⁻¹² More recently, Rivera et al described disease progression in 229 mothers of children with NLS enrolled in the US registry, 171 of whom had a child with CHB. The specific data of the mothers with CHB were not available, and the mean follow-up was limited to 4 years for asymptomatic mothers.⁶

Given that the outcome of the mothers of children with cutaneous or cardiac NLS may be different,¹³ we report here a long-term descriptive analysis of 215 mothers of offspring with high-degree CHB associated with maternal anti-SSA, with or without anti-SSB, antibodies.

METHODS

Patients. As described previously, the French NLS registry, established in 2000 with institutional review board approval (Comité de la Protection des Personnes, Ile-de-France VI, Groupe Hospitalier Pitié-Salpêtrière, updated on July 7, 2010) includes fetuses and children with NLS and their mothers with anti-SSA and/or anti-SSB antibodies.⁷ Women were included in this study if (1) they had a fetus or child enrolled in the registry by September 2019; (2) the child had second- or third-degree CHB, documented by in utero echocardiography and/or electrocardiography at birth; and (3) the mother had anti-SSA and/or anti-SSB antibodies.

Methods. As previously described,^{7,14} data were collected as thoroughly as possible from the different physicians (obstetricians, pediatricians, pediatric cardiologists, internists, and rheumatologists) involved in each case. The index pregnancy for mothers with > 1 offspring with CHB was the first pregnancy complicated by advanced CHB.

By September 2019, our registry was updated for each mother with rheumatologic or internal medicine medical reports and/or telephone interviews with the mothers. These used a standardized questionnaire for rheumatologic symptoms: arthritis/arthralgia, Raynaud phenomenon (RP), dry eyes or dry mouth, parotid enlargement, and/or rash. We were interested in any systemic autoimmune diseases (SAIDs) or rheumatic diseases. By SAIDs, we mean that we have not reported organ-specific autoimmune diseases (such as diabetes and thyroiditis). Maternal diseases were classified according to the international classification criteria, including the revised American College of Rheumatology (ACR) criteria for systemic lupus erythematosus (SLE),¹⁵ the revised European criteria for Sjögren syndrome (SS)¹⁶ and the revised ACR criteria for rheumatoid arthritis (RA).¹⁷ Undifferentiated connective tissue disease (UCTD) was defined by the presence of signs and symptoms suggestive of a connective tissue disease (CTD), but not fulfilling the criteria for any defined SAID, with positive antinuclear antibodies.¹⁸

We excluded patients who declined to participate and to answer the questionnaires as well as those lost to follow-up (no medical reports and no way of reaching them for standardized interview).

Statistical analysis. Quantitative variables were expressed as means \pm SD for normal distributions, otherwise as medians (range: minimum-maximum), and qualitative variables as the number of patients (percentages). The associations of the occurrence of diseases with different symptoms were evaluated by the chi-square test. Disease-free survival rates based on time since delivery and disease onset, as well as analysis of time to progression for mothers without any diagnosis of an autoimmune disease at entry, were based on the Kaplan-Meier survival function and verified by the Cox regression model with the ascending Wald method. The relations between time to disease onset and antibody status or various symptoms were analyzed with the log-rank test. All statistical analyses were 2-tailed, and differences with

$P < 0.05$ were considered statistically significant. The statistical analysis was performed with IBM SPSS version 10 for Windows (IBM Corp).

RESULTS

Patient characteristics. By September 2019, the French registry included 280 pregnancies complicated by CHB, corresponding to 255 individual women with at least 1 such pregnancy. Unavailable data resulted in the exclusion of 40 women: 22 who declined to participate in this study, and 18 lost to follow-up, including 3 who died from causes unrelated to autoimmune disease (among the total of 4 deaths in our registry). We analyzed the data of the remaining 215 women (Figure 1), updated to 2019 with medical records ($n = 154$) and/or a standardized questionnaire ($n = 159$).

The mean age at delivery of the infant with CHB was 30.6 ± 5.0 years (range 18.0-43.8); 135 were of European origin (63%), 63 North African (29%), 10 Afro-Caribbean (5%), and 7 Asian (3%). All had anti-SSA/Ro antibodies, and 132 (61%) also had anti-SSB/La antibodies. Only 187 women delivered a live-born baby (87%); the others had either fetal deaths attributed to CHB ($n = 15$) or medically indicated terminations of pregnancy ($n = 13$).

Maternal symptoms and diseases at the discovery of CHB. Before their child's CHB diagnosis, 163 mothers (76%) had not been diagnosed with any autoimmune disease, whereas 52 (24%) were already seeing a doctor for at least 1 SAID: SLE ($n = 26$, 12%), SS ($n = 16$, 7%), UCTD ($n = 7$, 3%), and/or another autoimmune disease ($n = 5$, 2%) including RA, systemic sclerosis, and autoimmune hepatitis (Figure 1).

The CHB diagnosis led to testing for and identifying a maternal SAID in 6 additional women: SLE ($n = 4$) and SS ($n = 2$). Finally, 58 patients (27%) had a SAID diagnosis at the index delivery (Figure 2).

At delivery, the remaining 157 women who had not met classification criteria for any SAID were either totally asymptomatic ($n = 93$, 59%) or had some symptoms ($n = 64$, 41%): arthralgia and myalgia ($n = 42$, 66%), dry eyes and/or dry mouth ($n = 36$, 56%), photosensitivity ($n = 18$, 28%), parotid swelling ($n = 22$, 34%), and/or RP ($n = 14$, 22%).

Long-term outcomes of the 157 mothers with no initial SAID. After a median follow-up of 11 years (range: 21 days to 54 yrs), 77 mothers (49%) had developed a SAID after a median delay of 2 years (range: 1 month to 38 yrs; Table 1 and Figure 1). The leading diagnosis was SS ($n = 54$, 34%), followed by SLE ($n = 24$, 15%), UCTD ($n = 7$; 4%) and/or RA ($n = 5$; 3%). Thirty-two (34.4%) women developed a SAID among 93 with no symptoms initially vs 45 among 64 (70.3%) with at least 1 initial symptom ($P < 0.001$). The estimated median time to progression for symptomatic and asymptomatic mothers was 12 and 72 months, respectively ($P = 0.02$; Figure 3). Symptoms associated with rapid onset of diseases were parotid swelling ($P = 0.03$) and erythema ($P = 0.03$).

The estimated disease-free survival probability at 5 years was 69.4% and at 10 years was 58.6%. The probability of developing SLE within 5 years was 10.2% and within 10 years 12.7%; the estimated median time to progression was 12 months. The

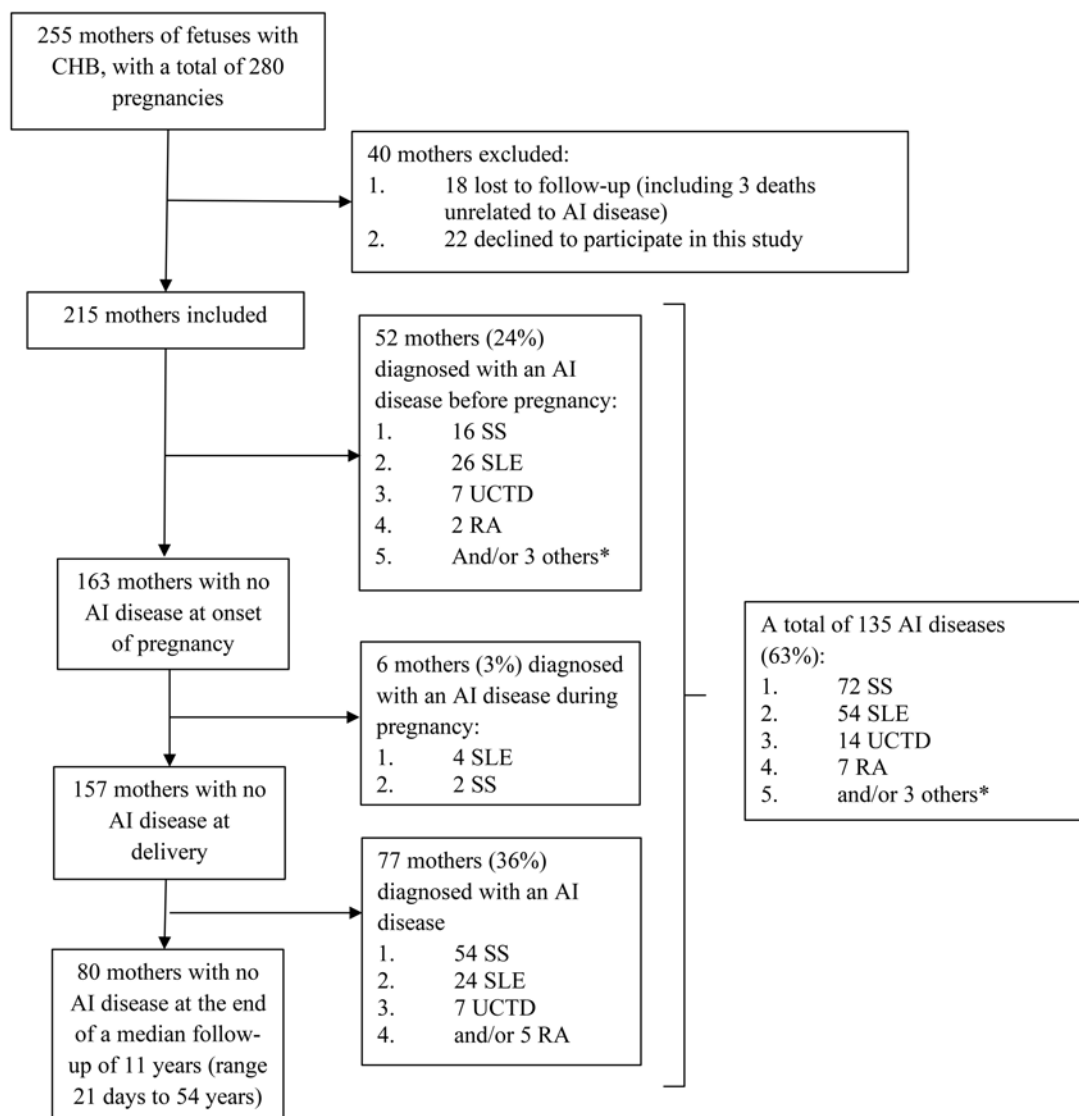


Figure 1. Flow chart. * Others included RA, systemic sclerosis, and autoimmune hepatitis. AI: autoimmune; CHB: congenital heart block; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SS: Sjögren syndrome; UCTD: undifferentiated connective tissue disease.

probability of developing SS within 5 years was 19.7% and within 10 years 28.1%, with an estimated median time to progression of 36 months. The estimated distributions of time from delivery to disease progression are shown in Figure 4.

SAID development did not differ significantly between mothers with only anti-SSA/Ro and those with both autoantibodies (32/63 vs 45/93, $P = 0.77$). The symptoms that best predicted the onset of a SAID were arthralgia and myalgia ($P < 0.001$), dry syndrome ($P = 0.01$), and parotid swelling ($P = 0.05$; Table 2).

Long-term outcomes for the entire population (215 mothers). Finally, at the end of follow-up, 135 mothers had a SAID: 72 with SS (33%), 54 with SLE (25%), 14 with UCTD (6%), and 10 other autoimmune diseases, including 7 with RA (Figure 2). Three patients had lupus glomerulonephritis (class V in 2 and class IV in 1), 1 associated with “neurolyupus” and requiring

cyclophosphamide (CYC) pulses. The others reported only cutaneous and articular manifestations.

Among the 215 mothers, 36 (17%) had been treated at some point with hydroxychloroquine (HCQ), 33 (15%) with steroids, and 6 (3%) with immunosuppressive drugs (methotrexate [MTX, $n = 4$], CYC [$n = 1$], and mycophenolate mofetil [$n = 1$]).

One maternal death occurred in a woman with SS who died from breast cancer after a follow-up of 7 years.

DISCUSSION

We report short- and long-term data on maternal disease progression in 215 mothers of children with CHB after a median follow-up of 11 years (range: 21 days to 54 years). We found that 52 (24%) mothers had a diagnosis of autoimmune disease at CHB diagnosis (6 more were diagnosed with such a

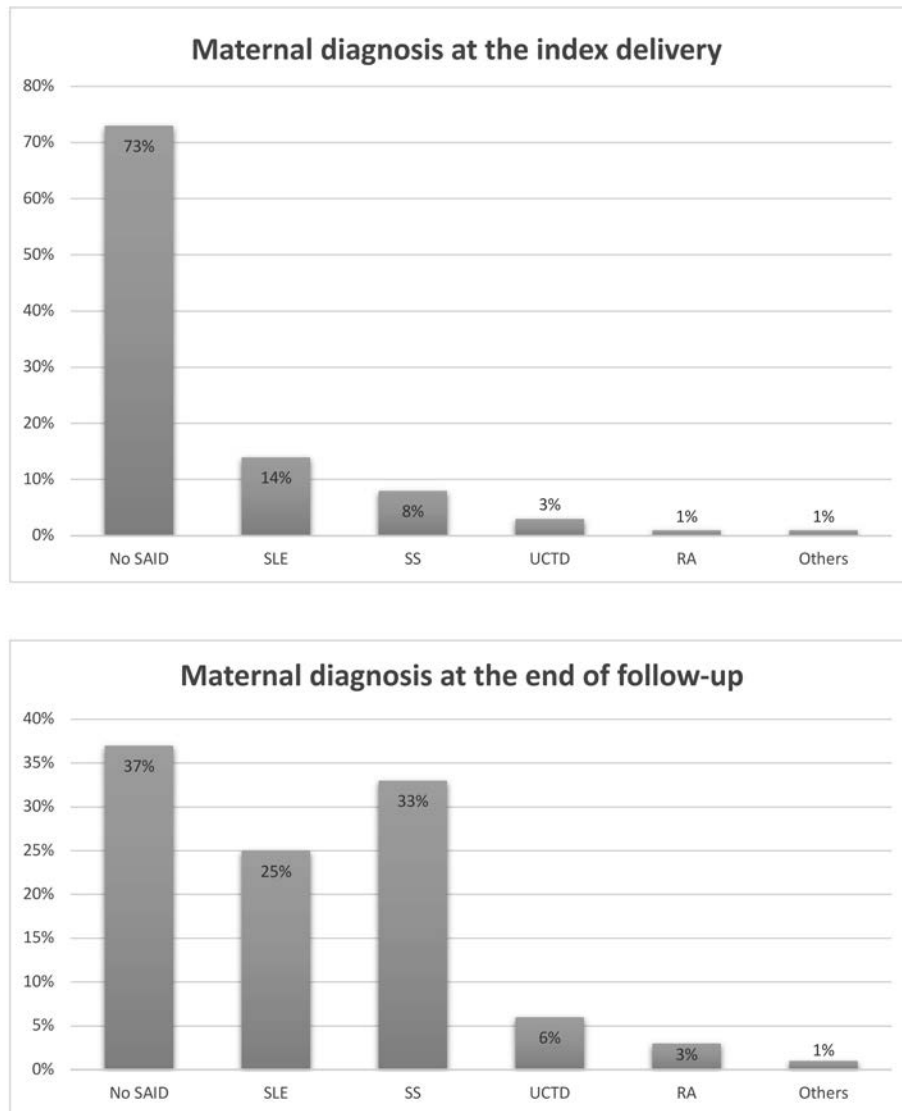


Figure 2. Maternal diagnosis at the index delivery and at the end of follow-up (n = 215). * Others included systemic sclerosis and autoimmune hepatitis. RA: rheumatoid arthritis; SAID: systemic autoimmune disease; SLE: systemic lupus erythematosus; SS: Sjögren syndrome; UCTD: undifferentiated connective tissue disease.

disease during the index pregnancy). This finding is important for making recommendations about CHB monitoring during subsequent pregnancies because, in the absence of generalized anti-SSA antibody screening, three-quarters of the women whose fetus will develop CHB will not have access to specific follow-up to detect it.¹⁹ This finding is consistent with a previous systematic review of the literature on underlying maternal autoimmune diseases. It included 856 mothers of children with CHB—greater than half were classified as asymptomatic carriers of anti-SSA and anti-SSB antibodies, with nearly 14% of cases classified as incomplete or undifferentiated autoimmune disease.¹

After a median follow-up of 11 years (range: 21 days to 54 yrs), 77 of the 157 (49%) mothers with no initial diagnosis of SAID had developed such a disease. The review by Brito-Zerón et al includes no data on this point.¹ Our results are consistent with the 2 largest studies on this topic, 1 from the US including

229 mothers of children with NLS⁶ and the other from Finland, covering 83 mothers of children with autoimmune CHB.¹² In these 2 studies, 25 of 51 (49.0%) and 10 of 23 (43.5%) mothers asymptomatic at enrollment remained asymptomatic after a mean follow-up of 4.1 years (range 0.5-9.0) and 9.6 years (range 0.0-21.0), respectively. The low number of asymptomatic mothers in the US study by Rivera et al might be explained by the frequency of the pauci-UCTD group, which the authors defined by the presence of up to 2 of the following symptoms: arthralgia, oral or nasal ulcers, photosensitivity, lymphopenia, RP, dry eyes or dry mouth, or parotid swelling.⁶

Our analysis of the 215 women included in our registry showed that 135 had a SAID at last follow-up: 72 had SS (33%) and 54 had SLE (25%). Maternal disease was severe in only 3 women (lupus nephritis [LN] and/or neurolupus) and required immunosuppressive drugs, mainly MTX, in 6. None had died from a SAID. The literature on the diagnoses of diseases

Table 1. Estimated median time to progression to systemic autoimmune diseases (SAIDs) for mothers with no SAID at delivery.

| Progression to SAID After Delivery | No. of Mothers Who Progressed, n | Median Time to Progression, Months (Range) |
|------------------------------------|----------------------------------|--|
| SLE | 24 | 12 (2-30) |
| SS | 54 | 36 (1-456) |
| UCTD | 7 | 24 (12-276) |
| RA | 5 | 60 (12-108) |
| All diseases | 77 | 24 (1-456) |

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SS: Sjögren syndrome; UCTD: undifferentiated connective tissue disease.

developed after the birth of a child with CHB is sparse. The Finnish study reported that mothers of children with CHB had clinical and immunologic characteristics more closely related to primary SS than to SLE.¹² Thus only 9 had SLE (11%) whereas 33 (39.8%) had primary SS after a mean follow-up of 9.9 ± 9 years, and severe manifestations of the disease were rare.¹² In the US study, among 229 mothers, 70 had SLE at enrollment and 24 additional mothers had developed SLE at the end of follow-up. Only 4 had developed LN (class IV in 2, class II/III and class II in 1 each).⁶ Among these 24 women, 5 were initially asymptomatic, 12 had undifferentiated autoimmune syndrome, and 7 had SS.⁶ Eight women who developed SS were initially asymptomatic, 13 had undifferentiated autoimmune syndrome, and 2 had SLE.⁶ An asymptomatic mother had an 18.6% probability of developing SLE within 10 years, and a 27.9% probability of probable/definite SS⁶ compared with 12.7% and 28.1%, respectively, in our study. Of note, the influence of ethnicity on the phenotypic expression of SAIDs has previously been described,

with less favorable outcomes in non-White populations, especially in SLE.²⁰⁻²² Thus, we could not rule out the possibility that SLE and SS phenotypes were less severe than in previous studies, given that non-White women accounted for only 37% of our cohort.

We found no statistically significant difference between mothers with anti-SSA/Ro only and those who also had anti-SSB antibodies in terms of risk of developing a SAID (32/63 [51%] vs 45/93 [48%], $P = 0.77$). In contrast, the US study reported that significantly more mothers with only anti-SSA/Ro remained asymptomatic or did not progress beyond pauci-UCTD, compared with mothers with both antibodies (24/27 [89%] vs 13/24 [54%], $P = 0.01$).⁶ We found that arthralgia and myalgia ($P < 0.001$), dry mouth and/or eye syndrome ($P = 0.01$), and parotid swelling ($P = 0.05$) best predicted the development of a SAID (Table 2). These symptoms were unsurprising given that this progression was mainly toward SS. Finally, while SLE used to be considered the key maternal autoimmune disease related to CHB onset,^{23,24} we, like others, found that SS was more prevalent in our cohort.^{6,12,24}

The principal limitation of our study is its retrospective nature and the absence of a standardized evaluation of SAID. It is therefore possible that we missed some diagnoses. Most symptomatic patients had mild CTDs, and their classification as SLE, SS, and especially UCTD might have changed if they had undergone thorough investigations at each timepoint. In addition, comparison with the US study by Rivera et al is difficult because we chose to apply international classification criteria for CTDs, including UCTD, whereas they defined a group called "pauci-CTD."⁶ It is also difficult to compare various studies from the literature, since some included isolated cutaneous NLS,⁶ while others included patients negative for anti-SSA

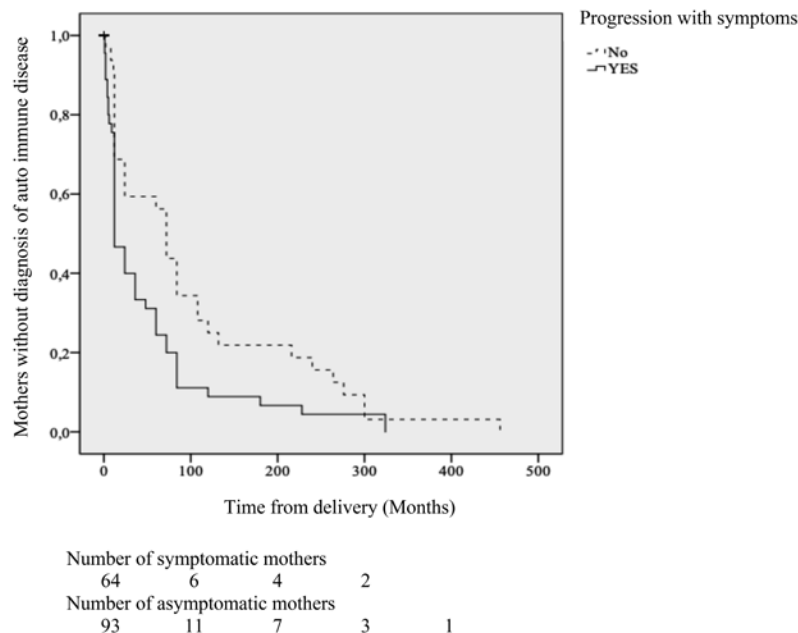


Figure 3. Estimates of distribution of time to disease progression by symptoms. The estimated median time to progression was 12 months for symptomatic mothers and 72 months for asymptomatic mothers ($P = 0.019$).

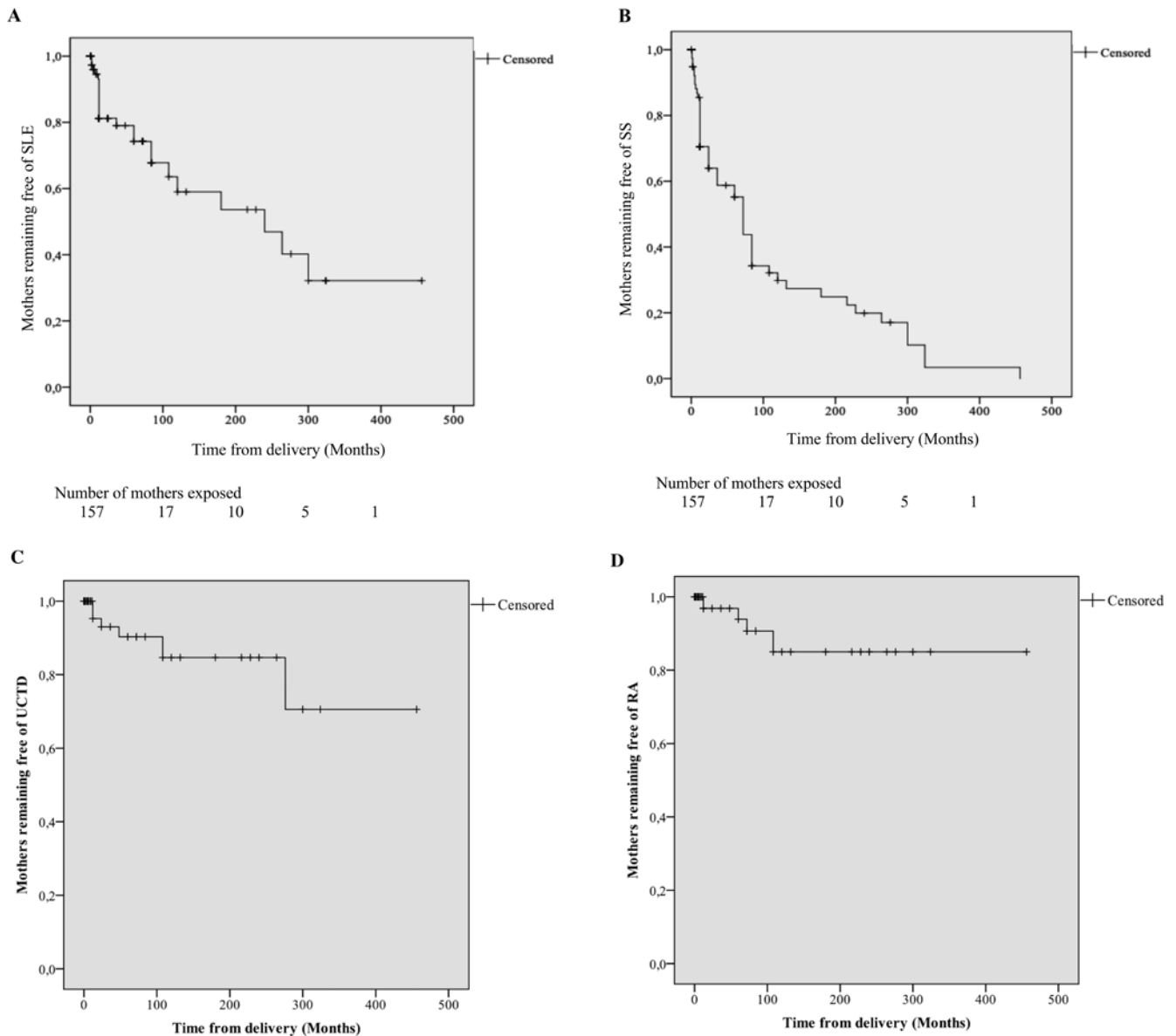


Figure 4. The estimated distribution of time from delivery to disease progression. The number of patients developing each disease diagnosis was compared to the number of those without a rheumatic disease diagnosis ($n = 157$). Each figure considers the same population, regardless of whether its members have or have not been diagnosed with one of the other diseases. (A) Estimated distribution of time to development of SLE in initially healthy mothers. (B) Estimated distribution of time to development of SS in initially healthy mothers. (C) Estimated distribution of time to development of UCTD in initially healthy mothers. (D) Estimated distribution of time to development of RA in initially healthy mothers. (Censored: mothers developing diseases except SLE in A, SS in B, UCTD in C, and RA in D). RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SS: Sjögren syndrome; UCTD: undifferentiated connective tissue disease.

or anti-SSB antibodies.⁹ To overcome this issue, we chose to describe a homogeneous and well-defined group (ie, high-degree CHB only and positive for anti-SSA antibodies). We recognize that this prevented us from analyzing non-CHB NLS cases, but these will be the subject of future studies. In addition, we cannot exclude an immortal person-time bias as a result of inclusion of follow-up time preceding enrollment for some women, nor the possibility that the estimates of autoimmune disease diagnoses in the mothers included in our cohort is inflated, because CHB cases may have been more frequently reported for women already followed for an autoimmune disease, and because women not

lost to follow-up may be more likely to develop such a disease. Another limitation is that we did not have detailed information on when medications were introduced, especially HCQ in pauci-symptomatic women, as this could have affected the development of overt CTD. Finally, the specificity of anti-SSA antibodies was not always available and we could not analyze the respective effect of anti-SSA52 and anti-SSA60 antibodies.

In conclusion, one-quarter of the women had a diagnosis of SAID at diagnosis of fetal CHB. Nearly half of the mothers with no initial diagnosis progressed toward a SAID during follow-up, most developing only mild symptoms. SS was more frequent than

Table 2. Symptom frequencies among the 157 mothers with no diagnosis of autoimmune disease at delivery, by subsequent development of SAID.

| Maternal Symptoms At Delivery | Development of a SAID | | P |
|---------------------------------|-----------------------|-------------|---------|
| | No, n = 80 | Yes, n = 77 | |
| No symptoms | 61 (76) | 32 (42) | < 0.001 |
| Arthralgia, myalgia | 10 (13) | 32 (42) | < 0.001 |
| Dry syndrome (mouth and/or eye) | 9 (11) | 27 (35) | 0.001 |
| Raynaud phenomenon | 6 (8) | 8 (10) | 0.52 |
| Parotid swelling | 7 (9) | 15 (19) | 0.05 |
| Cutaneous rash | 6 (8) | 12 (16) | 0.11 |
| Anti-SSB/La positive | 48 (60) | 45 (58) | 0.84 |

Values are n (%). Values in bold are statistically significant. SAID: systemic autoimmune disease.

SLE. Severe diseases such as LN were rarely seen, and immunosuppressive drugs were rarely required. These women should receive regular follow-up to monitor symptom onset. In addition, ocular and salivary gland function tests could be routinely performed, as with minor salivary gland biopsy when required.

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