Short running head: CHB and maternal outcome.

Health Outcome of 215 Mothers of Children with Autoimmune Congenital Heart Block: Analysis of the French Neonatal Lupus Syndrome Registry.

Imene Miniaoui (1)*, Nathalie Morel (1)*, Kateri Lévesque (1), Alice Maltret (2), Marine Driessen (3), Agathe Masseau (4), Pauline Orquevaux (5), Jean-Charles Piette (6), Francois Barriere (7), Jérome Le Bidois (2), Sophie Georgin-Lavialle (8), Gaëlle Guettrot-Imbert (1), Véronique Le Guern (1), Luc Mouthon (1), Moez Jallouli (1), Christophe Deligny (9), Eric Hachulla (10), Bénédicte Romefort (11), « Lupus néonatal » group, Damien Bonnet (2), and Nathalie Costedoat-Chalumeau (12).

* These 2 authors contributed equally to this work.

(1) I. Miniaoui, MD, N. Morel, MD, K. Lévesque, MD, G. Guettrot-Imbert, MD, V. Le Guern, MD, L. Mouthon MD, PhD, M. Jallouli, MD, N. Costedoat-Chalumeau, MD, PhD, AP-HP, Hôpital Cochin, Centre de référence maladies auto-immunes et systémiques rares d'Ile de France, Paris, France;

(2) A. Maltret, MD, J. Le Bidois, MD, D. Bonnet, MD, PhD, APHP, Centre de référence Malformations Cardiaques Congénitales Complexes - M3C, Hôpital Necker-Enfants malades, Université de Paris, Paris, France;

(3) M. Driessen, MD, Obstetrics and materno-fœtal unit / APHP Hôpital Necker-Enfant Malades, Université de Paris, Paris, France;

(4) A. Masseau, MD, Service de Médecine Interne, CHU Nantes, France;

(5) P. Orquevaux, MD, CHU de Reims, Centre de compétence maladies auto-immunes et systémiques rares, Reims, France;

(6) J.-C. Piette MD, PhD, UPMC; AP-HP, Hôpital Pitié-Salpêtrière, Centre de référence maladies auto-immunes et systémiques rares, Paris, France;

(7) F. Barriere, MD, AP-HM, Hôpital Timone Enfants, Unité de Réanimation Pédiatrique, Marseille, France;

(8) S. Georgin-Lavialle, MD, PhD, AP-HP, Hopital Tenon, Paris, France;

(9) C. Deligny, MD, CHU Fort de France, Martinique, France;

(10) E. Hachulla, MD, PhD, Univ. Lille, Inserm, CHU Lille, Service de Médecine Interne et Immunologie Clinique, Centre de référence des maladies autoimmunes systémiques rares du Nord et Nord-Ouest de France (CeRAINO), U1286 - INFINITE - Institute for Translational Research in Inflammation, F-59000 Lille, France

(11) B. Romefort, MD, Cardiopédiatrie, CHU de Nantes, France.

(12) N. Costedoat-Chalumeau, MD, PhD, AP-HP, Hôpital Cochin, Centre de référence maladies auto-immunes et systémiques rares d'Ile de France, Paris, France; Université Paris Descartes-Sorbonne Paris Cité, Paris, France ; INSERM U 1153, Center for Epidemiology and Statistics Sorbonne Paris Cité (CRESS), Paris, France.

Group of collaborators (to be added in Pubmed): Pascal CATHEBRAS, Laurence COHEN, Elisabeth DIOT, Pierre DUHAUT, Yves DULAC, Olivier FAIN, Laurent FERMONT, Loïc GUILLEVIN, Quentin HAUET, François HEITZ, Anne-Sophie KORGANOW, Hugues LUCRON, Jean-René LUSSON, Jacques NINET, Nicolas PANGAUD, Jean-Luc PELLEGRIN, Jean Loup PENNAFORTE, Jacques POUCHOT, Viviane QUEYREL-MORANNE, Françoise SARROT-REYNAULD, Nicolas SCHLEINITZ, Pascal SEVE, Bertrand STOS, Arnaud THEULIN, Guy VAKSMANN, Denis VITAL-DURAND.

Address for correspondence: Nathalie Costedoat-Chalumeau, Hôpital Cochin, 75014, Paris, France. Fax number: +33158413246. Phone number: +33687508123

nathalie.costedoat@aphp.fr

Total word count (text): 2418

FUNDING SOURCES: No specific funding was received from any bodies in the public, commercial, or not-for-profit sectors to carry out the work described in this article.

DISCLOSURES: the authors declare no conflicts of interest.

Keywords: Congenital heart block, neonatal lupus erythematosus syndrome, maternal diseases, anti-SSA/Ro antibodies, pregnancy, systemic lupus erythematosus.

ABSTRACT (250 words):

Objective. Transplacental passage of maternal anti-SSA and -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 one pregnancy with CHB. Before this diagnosis, only 52 (24%) mothers had been diagnosed with an autoimmune disease, mainly systemic lupus erythematosus (SLE) (n=26, 12%) and Sjögren's 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 SLE patients 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 ($p<0.0001$), dry syndrome ($p=0.01$), and parotid swelling ($p=0.05$).

Conclusion. One quarter of the patients had an autoimmune disease diagnosis at the fetal CHB diagnosis. Nearly half 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 rarely required.

Neonatal lupus (NLS) syndrome 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 around 1% in anti-SSA–positive women: 1/154 (0.65%) in the prospective study by Buyon et al[3], 1/99 (1%) in a study by Costedoat-Chalumeau et al[4], and 2/100 (2%) in a study by Brucato et al[5].

Mothers with anti-SSA and anti-SSB antibodies can have diseases, or be asymptomatic or pauci-symptomatic when NLE 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 old 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 NLE 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 four years for asymptomatic mothers[6].

Given that the outcome of the mothers of children with cutaneous or cardiac NLE 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.

PATIENTS AND METHODS

Patients. As described previously, the French NLE 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 NLE 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 more than one 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, dry eyes or dry mouth, parotid enlargement and/or rash. We were interested in any systemic autoimmune diseases or rheumatic diseases. By systemic autoimmune diseases 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 SLE[15], the revised European criteria for 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, but not fulfilling the criteria for any defined systemic autoimmune disease, with positive antinuclear antibodies[18].

We excluded patients who declined to participate and to answer the questionnaires and 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 ± standard deviations (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 two-tailed, and differences with a p value less than 0.05 were considered statistically significant. The statistical analysis was performed with SPSS 10 software.

RESULTS

Patient characteristics. By September, 2019, the French registry included 280 pregnancies complicated by CHB, corresponding to 255 individual women with at least one 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 finally 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).

Their mean age at delivery of the infant with CHB was 30.6 ± 5 years (range: 18 to 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 liveborn 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, while 52 (24%) were already seeing a doctor for at least one systemic autoimmune disease: SLE (n=26; 12%), SS (n=16; 7%), UCTD (n=7; 3%), and/or another autoimmune disease (n=5; 2%) including rheumatoid arthritis, systemic sclerosis, and autoimmune hepatitis (Figure 1).

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

At delivery, the remaining 157 women who had not met classification criteria for any systemic autoimmune disease 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 Raynaud's phenomenon (n=14, 22%).

Long-term outcomes of the 157 mothers with no initial systemic autoimmune disease. After a median follow-up of 11 years [range: 21 days to 54 years], 77 mothers (49%) had developed a systemic autoimmune disease after a median delay of 2 years [range 1 month to 38 years] (Table 2 and Figure 1). The leading diagnosis was SS (n=54, 34%), followed by SLE (n=24, 15%), UCTD (n=7; 4%) and/or rheumatoid arthritis (n=5; 3%). Thirty-two women developed a systemic autoimmune disease among 93 with no symptoms initially (34.4%) versus 45 among 64 with at least one initial symptom (70.3%) ($p<0.001$). The estimated median time to progression for symptomatic and asymptomatic mothers was respectively 12 and 72 months ($p=0.019$) (Figure 3). Symptoms associated with rapid onset of diseases were parotid swelling ($p=0.025$) and erythema ($p=0.033$).

The estimated disease-free survival probability at 5 years was 69.4% and at 10 years 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 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 distribution of time from delivery to disease progression are shown in Figure 4.

Systemic autoimmune disease 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 systemic autoimmune disease were arthralgia and myalgia (p<0.0001), dry syndrome (p=0.01), and parotid swelling (p=0.05) (Table 1).

Long-term outcomes for the entire population (215 mothers). Finally, at the end of follow-up, 135 mothers had a systemic autoimmune disease: 72 SS (33%), 54 SLE (25%), 14 UCTD (6%), and 10 other autoimmune diseases, including 7 RA (Figure 2). Three patients had lupus glomerulonephritis (class V in 2 and class IV in one), one associated with "neurolupus" and requiring cyclophosphamide pulses. The others reported only cutaneous and articular manifestations.

Among the 215 mothers, 36 (17%) had been treated at some point with hydroxychloroquine, 33 (16%) with steroids, and 6 (3%) with immunosuppressive drugs (methotrexate n=4, cyclophosphamide n=1, 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 disease during the index pregnancy). This finding is important for making recommendation 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 recent systematic review of the literature on underlying maternal autoimmune diseases. It included 856 mothers of children with CHB: more 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 years), 77 of the 157 (49%) mothers with no initial diagnosis of systemic autoimmune disease had developed such a disease. The review by Brito-Zeron et al. includes no data on this point[1]. Our results are consistent with the two largest studies on this topic, one from the USA including 229 mothers of children with NL[6] and the other from Finland, covering 83 mothers of children with autoimmune CHB[12]; respectively, 25 of 51 (49%) and 10 of 23 (43.5%) mothers asymptomatic at enrolment remained asymptomatic after a mean follow-up of 4.1 years (range 0.5 to 9) and 9.6 years (range 0 to 21) 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 two of the following symptoms: arthralgia, oral or nasal ulcers, photosensitivity, lymphopenia, Raynaud's phenomenon, dry eyes or dry mouth, or parotid swelling[6].

Our analysis of the 215 women included in our registry showed that 135 had a systemic autoimmune disease at last follow-up: 72 had SS (33%), and 54 had SLE (25%). Maternal disease was severe in only three women (lupus nephritis and/or neurolupus) and required immunosuppressive drugs, mainly methotrexate, in six. None had died from a systemic autoimmune disease. The literature on the diagnoses of diseases 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%) while 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 enrolment, and 24 additional mothers had developed SLE at the end of follow-up. Only 4 had developed lupus nephritis (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 SS[6] compared with 12.7% and 28% respectively in our study. Of note, the influence of ethnicity on the phenotypic expression of systemic autoimmune diseases has previously been described, with less favorable outcomes in non-white population, 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 systemic autoimmune disease (32/63 (51%) vs 45/93 (48%), p=0.77). By 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=0.011)[6]. We found that arthralgia and myalgia (p<0.0001), dry mouth and/or eye syndrome (p=0.01), and parotid swelling (p=0.05) best predicted the development of a systemic autoimmune disease (Table 1). 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 systemic autoimmune disease. It is therefore possible that we missed some diagnoses. Most symptomatic patients had mild connective tissue diseases, and their classification as SLE, SS, and especially UCTD might have changed if they had undergone thorough investigations at each time point. 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, while they defined a group called pauci-CTD[6]. It is also difficult to compare various studies from the literature, since some included isolated cutaneous NLE[6] while others included patients negative for anti-SSA or anti-SSB antibodies[9]. To overcome this issue, we chose to describe a homogeneous and well-defined group, i.e., high-degree CHB only and positive for anti-SSA antibodies. We recognize that this prevented us from analyzing non-CHB NLE cases, but these will be the subject of future studies. In addition, we cannot exclude an immortal person time bias due to inclusion of follow-up time preceding enrolment 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 hydroxychloroquine 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 impact of anti-SSA52 and anti-SSA60 antibodies.

In conclusion, one quarter of the women had a diagnosis of systemic autoimmune disease at diagnosis of fetal CHB. Nearly half the mothers with no initial diagnosis progressed toward a systemic autoimmune disease during follow-up, most developing only mild symptoms. SS was more frequent than SLE. Severe diseases such as lupus nephritis were rarely seen, and immunosuppressive drugs 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, associated with minor salivary gland biopsy when required.

ACKNOWLEDGMENTS: We acknowledge the doctors participating in the ‘’Neonatal Lupus Group’’, the “Société Nationale Française de Médecine Interne” and the families for their kind collaboration.

REFERENCES

1. Brito-Zeron P, Izmirly PM, Ramos-Casals M, Buyon JP, Khamashta MA. The clinical spectrum of autoimmune congenital heart block. Nat Rev Rheumatol 2015;11:301-12.
2. Morel N, Georgin-Lavialle S, Levesque K, et al. [Neonatal lupus syndrome: Literature review]. Rev Med Interne 2015;36:159-66.
3. 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.
4. Costedoat-Chalumeau N, Amoura Z, Lupoglazoff JM, et al. Outcome of pregnancies in patients with anti-SSA/Ro antibodies: a study of 165 pregnancies, with special focus on electrocardiographic variations in the children and comparison with a control group. Arthritis Rheum 2004;50:3187-94.
5. Brucato A, Frassi M, Franceschini F, et al. Risk of congenital complete heart block in newborns of mothers with anti-Ro/SSA antibodies detected by counterimmunoelectrophoresis: a prospective study of 100 women. Arthritis Rheum 2001;44:1832-5.
6. Rivera TL, Izmirly PM, Birnbaum BK, et al. Disease progression in mothers of children enrolled in the Research Registry for Neonatal Lupus. Ann Rheum Dis 2009;68:828-35.
7. Levesque K, Morel N, Maltret A, et al. Description of 214 cases of autoimmune congenital heart block: Results of the French neonatal lupus syndrome. Autoimmun Rev 2015;14:1154-60.
8. Waltuck J, Buyon JP. Autoantibody-associated congenital heart block: outcome in mothers and children. Ann Intern Med 1994;120:544-51.
9. Press J, Uziel Y, Laxer RM, Luy L, Hamilton RM, Silverman ED. Long-term outcome of mothers of children with complete congenital heart block. Am J Med 1996;100:328-32.
10. Julkunen H, Kurki P, Kaaja R, et al. Isolated congenital heart block. Long-term outcome of mothers and characterization of the immune response to SS-A/Ro and to SS-B/La. Arthritis Rheum 1993;36:1588-98.
11. Brucato A, Ferraro G, Gasparini M, De Juli E, Franceschini F. Long-term outcome for the mothers of infants with isolated congenital complete heart block: comment on the article by Julkunen et al. Arthritis Rheum 1994;37:1261.
12. Julkunen H, Eronen M. Long-term outcome of mothers of children with isolated heart block in Finland. Arthritis Rheum 2001;44:647-52.
13. Lawrence S, Luy L, Laxer R, Krafchik B, Silverman E. The health of mothers of children with cutaneous neonatal lupus erythematosus differs from that of mothers of children with congenital heart block. Am J Med 2000;108:705-9.
14. Morel N, Levesque K, Maltret A, et al. Incidence, risk factors, and mortality of neonatal and late-onset dilated cardiomyopathy associated with cardiac neonatal lupus. Int J Cardiol 2017;248:263-269.
15. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
16. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-8.

17. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
18. Mosca M, Neri R, Bombardieri S. Undifferentiated connective tissue diseases (UCTD): a review of the literature and a proposal for preliminary classification criteria. Clin Exp Rheumatol 1999;17:615-20.
19. Costedoat-Chalumeau N, Morel N, Fischer-Betz R, et al. Routine repeated echocardiographic monitoring of fetuses exposed to maternal anti-SSA antibodies: time to question the dogma. The Lancet Rheumatology 2019;1:E187-E193.
20. Uribe AG, Alarcon GS, Sanchez ML, et al. Systemic lupus erythematosus in three ethnic groups. XVIII. Factors predictive of poor compliance with study visits. Arthritis Rheum 2004;51:258-63.
21. Maldini C, Seror R, Fain O, et al. Epidemiology of primary Sjogren's syndrome in a French multiracial/multiethnic area. Arthritis Care Res (Hoboken) 2014;66:454-63.
22. Brito-Zeron P, Acar-Denizli N, Ng WF, et al. Epidemiological profile and north-south gradient driving baseline systemic involvement of primary Sjogren's syndrome. Rheumatology (Oxford) 2020;59:2350-2359.
23. McCue CM, Mantakas ME, Tingelstad JB, Ruddy S. Congenital heart block in newborns of mothers with connective tissue disease. Circulation 1977;56:82-90.
24. Brito-Zeron P, Pasoto SG, Robles-Marhuenda A, et al. Autoimmune congenital heart block and primary Sjogren's syndrome: characterisation and outcomes of 49 cases. Clin Exp Rheumatol 2020;38 Suppl 126:95-102.

Table 1: Symptom frequencies among the 157 mothers with no diagnosis of autoimmune disease at delivery, by subsequent development of systemic autoimmune disease.

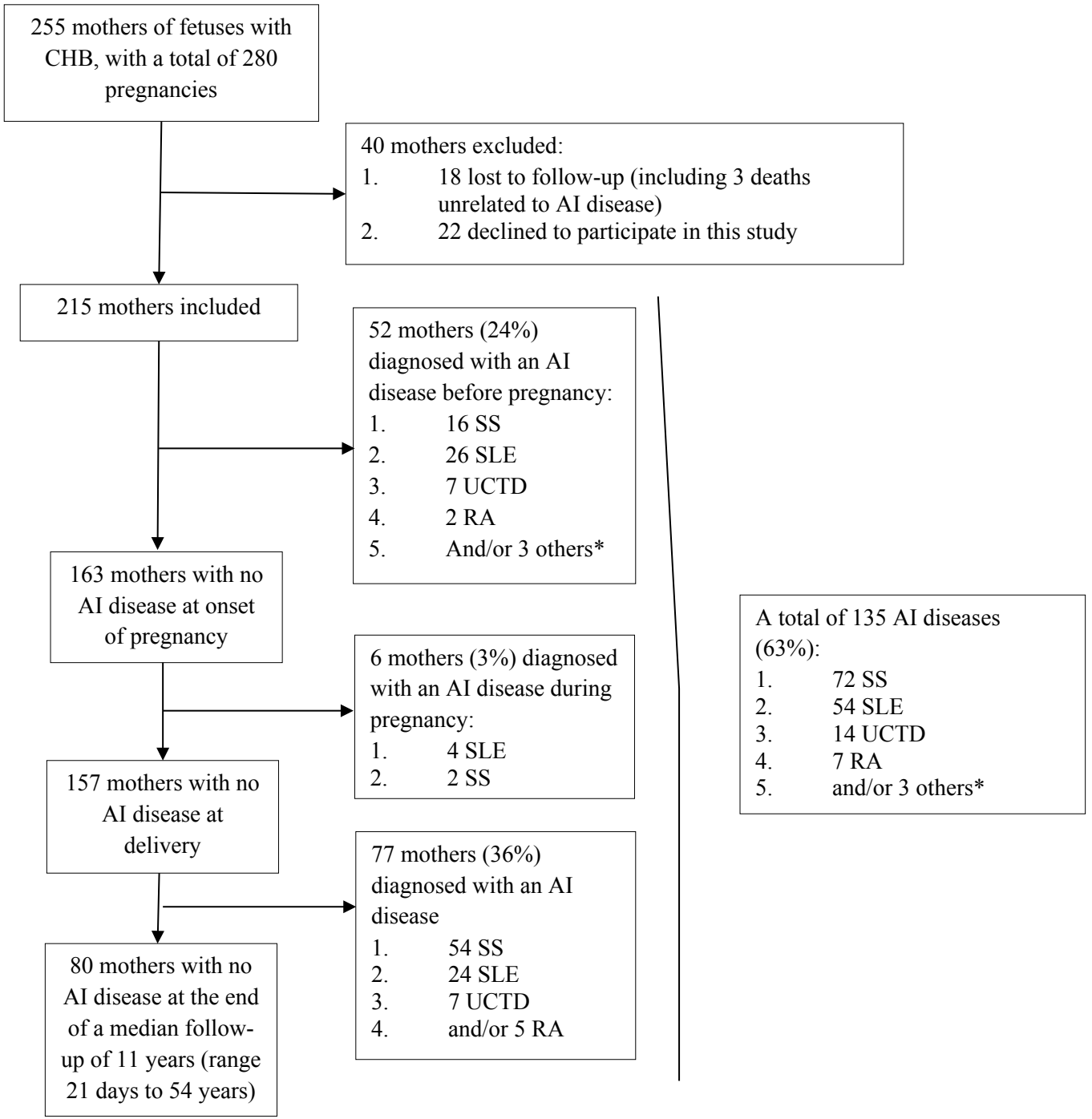
Maternal symptoms at delivery	Development of a systemic autoimmune disease		P value
	No, n=80 (%)	Yes, n=77 (%)	
No symptom	61 (76%)	32 (42%)	**<0.0001**
Arthralgia, myalgia	10 (12.5%)	32 (42%)	**<0.0001**
Dry syndrome (mouth and/or eye)	9 (11%)	27 (35%)	**0.001**
Raynaud's phenomenon	6 (7.5%)	8 (10%)	0.52
Parotid swelling	7 (9%)	15 (19%)	**0.05**
Cutaneous rash	6 (7.5%)	12 (16%)	0.11
SSB/La positivity	48 (60%)	45 (58%)	0.84

Table 2: Estimated median time to progression to systemic autoimmune diseases for mothers with no systemic autoimmune disease at delivery.

Progression to systemic autoimmune disease after delivery	Number 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]

Legends: SLE: systemic lupus erythematosus, SS: Sjögren's syndrome, RA: rheumatoid arthritis, UCTD: undifferentiated connective tissue disease.

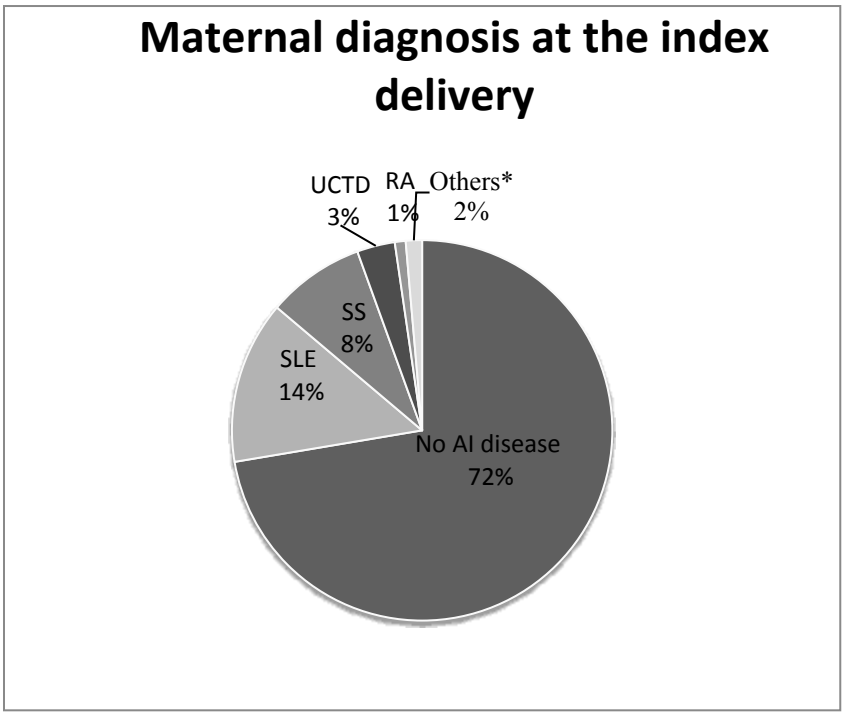
Figure 1: Flow chart

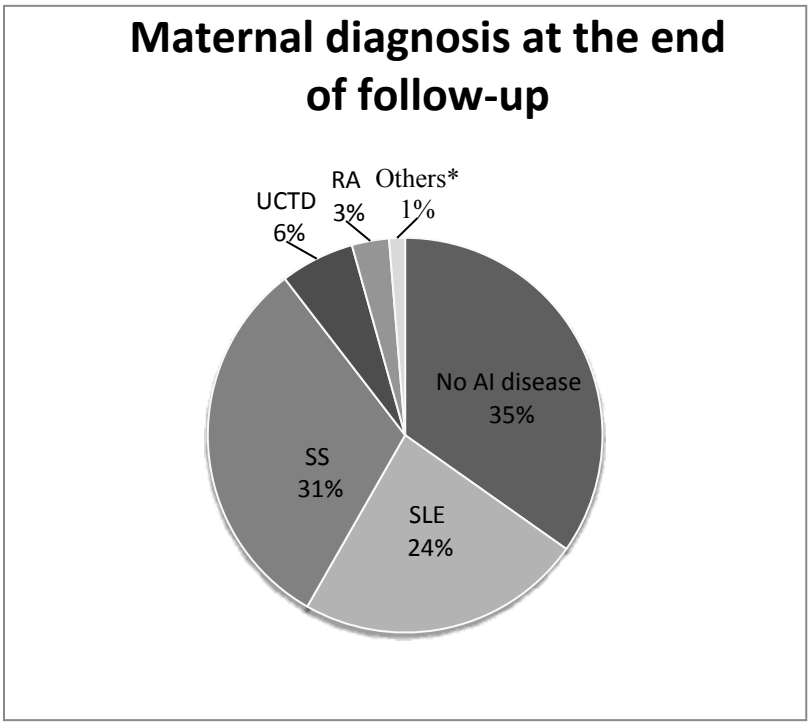


Legend: CHB: congenital heart block, AI: autoimmune, SLE: systemic lupus erythematosus, SS: Sjögren's syndrome, RA: rheumatoid arthritis, UCTD: undifferentiated connective tissue disease.

*****Others included rheumatoid arthritis, systemic sclerosis and autoimmune hepatitis.

Figure 2: Maternal diagnosis at the index delivery and at the end of follow-up (n=215).

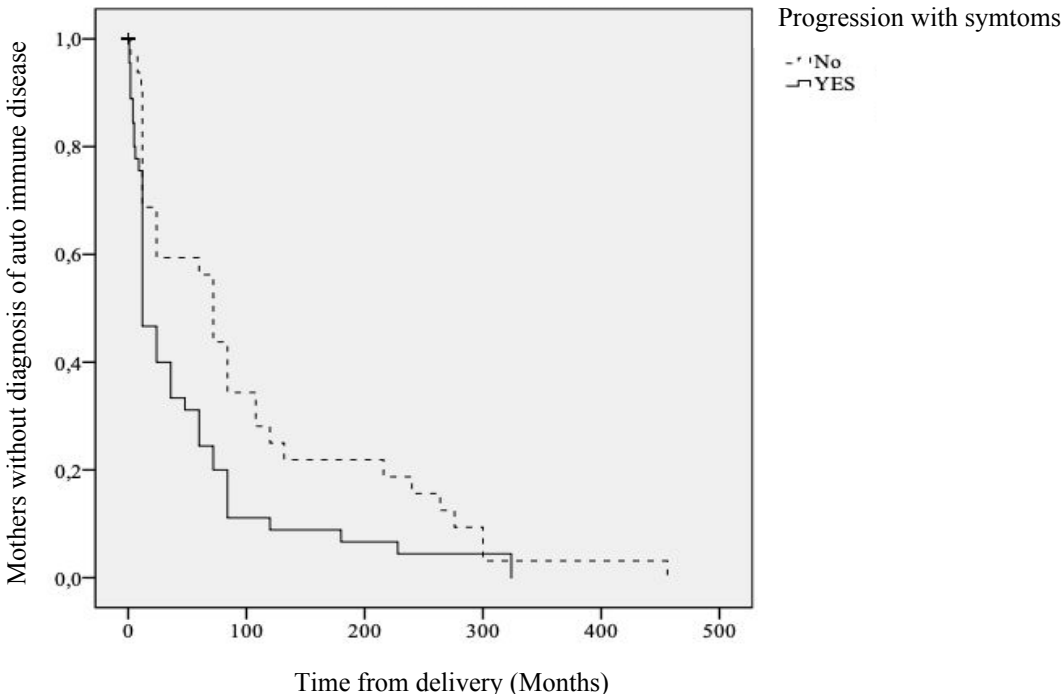




Legend: AI: autoimmune, SLE: systemic lupus erythematosus, SS: Sjögren's syndrome, RA: rheumatoid arthritis, UCTD: undifferentiated connective tissue disease.

*Others included rheumatoid arthritis, systemic sclerosis and autoimmune hepatitis.

Figure 3: Estimates of distribution of time to disease progression by symptoms.

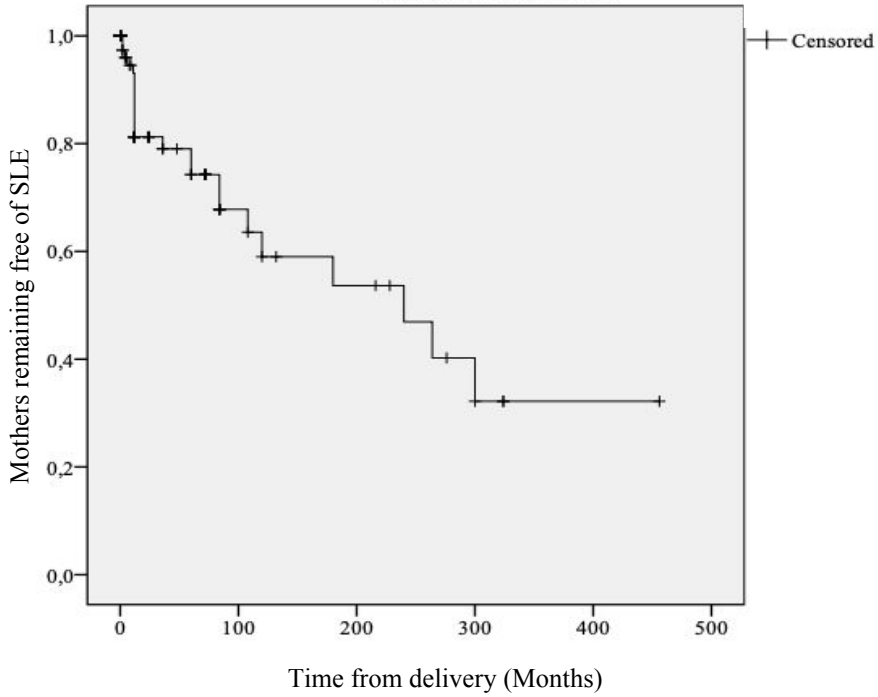


Number of symptomatic mothers				
64	6	4	2	
Number of asymptomatic mothers				
93	11	7	3	1

Legend: 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.

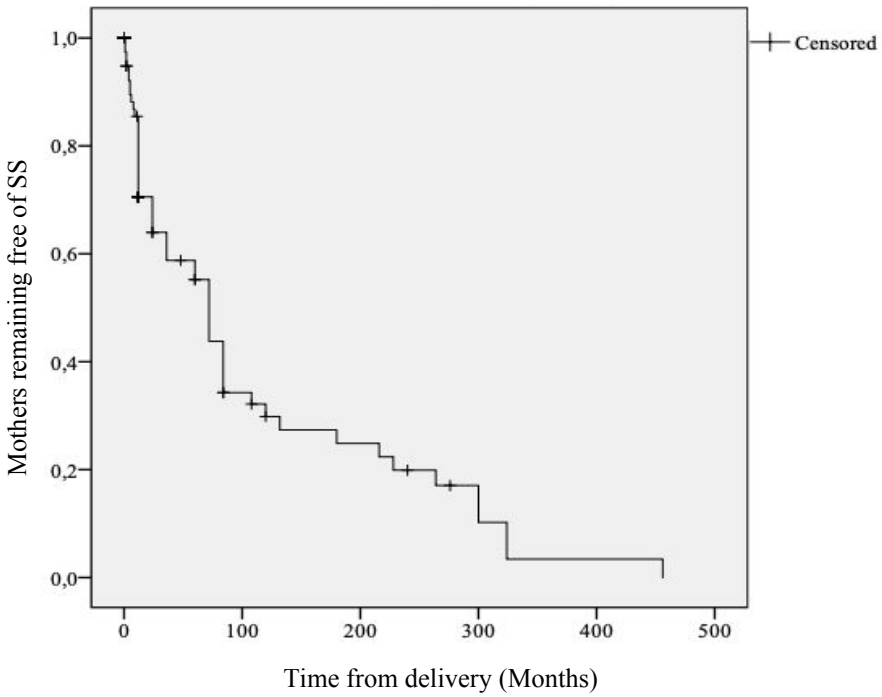
A



Number of mothers exposed

157	17	10	5	1

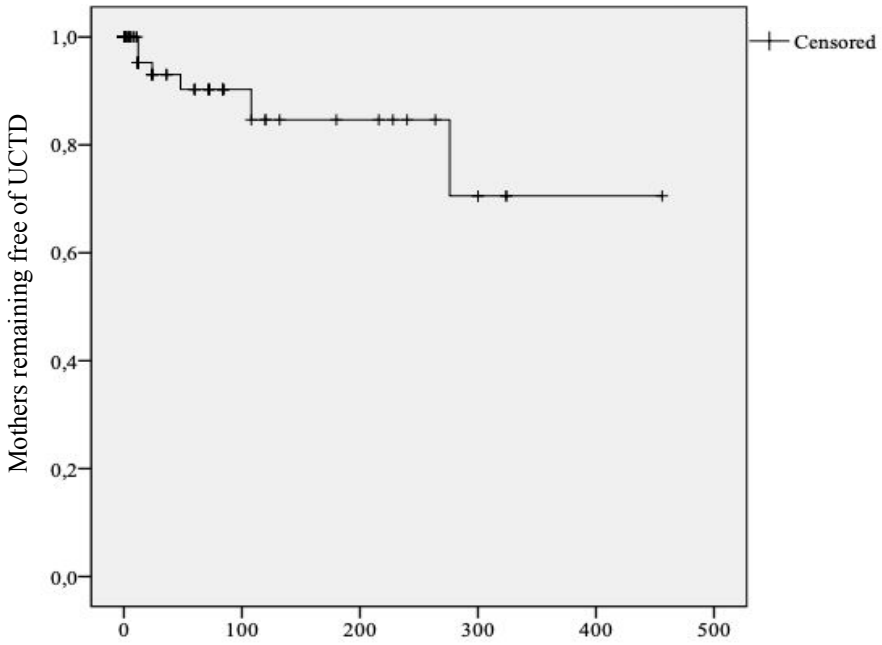
B



Number of mothers exposed

157	17	10	5	1

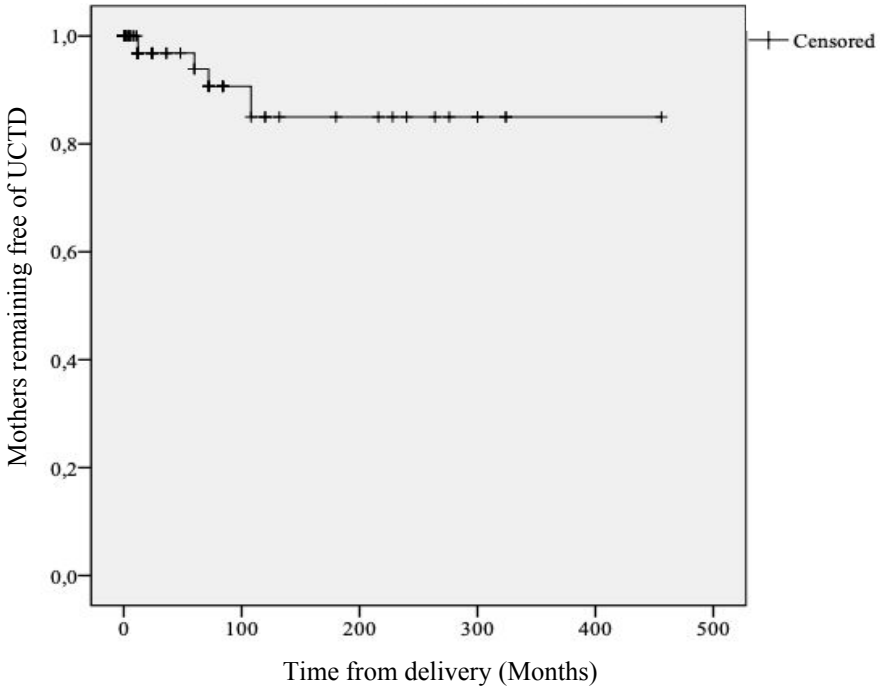
C



Number of mothers exposed

157	17	10	5	1

D



Number of mothers exposed

157	17	10	5	1

Legend: 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).

SLE: Systemic lupus erythematosus, SS: Sjögren's syndrome, UCTD: Undifferentiated connective tissue disease, RA: Rheumatic arthritis.