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Letter to the Editor

Obstetrical morbidity related to anti-SSA antibodies: Data from a French monocentric retrospective study

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Anti-SSA/Ro autoantibodies can be found in several connective-tissue diseases. Their impact on obstetrical outcomes other than congenital heart block is controversial, and was mainly explored in women with connective-tissue diseases [1–3]. However, anti-SSA positivity in women with recurrent unexplained adverse obstetrical events has not been assessed. Here, we report a French monocentric study of women with unexplained adverse obstetrical outcomes and the prevalence and impact of anti-SSA/Ro antibodies on the obstetrical outcome.

We retrospectively included all patients consulting for obstetrical morbidity (early recurrent miscarriage, intrauterine death; intra-uterine growth restriction; preeclampsia, eclampsia prematurity) in the absence of known etiology from 2011 to 2015 (244 women, median age 34 years [IQR 21-53]) and recorded 869 pathological pregnancies over the 12,250 followed in this center [Appendix A, Figure S1; See the supplementary material associated with this article online]. All patients underwent testing for anti-nuclear antibodies, anti-SSA/Ro and anti-SSB/La antibodies, antiphosholipid and antithyroid antibodies at pre-conception visit.

A total of 27/244 women (11%) had anti-SSA antibodies (4 had both anti-SSA and anti-SSB antibodies); among them, diagnosis of primary Sjogren's syndrome (pSS) was made in 8 cases and 19 were asymptomatic anti-SSA antibodies carriers. In the anti-SSA carrying subgroup, median age was 29.5 [IQR 17-40] years, with a mean number of 3.66 pregnancies/ woman. Eighty three of the 99 pregnancies (84%) had an adverse outcome: 65 fetal losses, 15 pre-eclampsia, 7 IUGR, 7 prematurity, 2 congenital heart blocks. Women with pSS ($n=8$; 31 pregnancies) and asymptomatic anti-SSA carriage ($n=19$; 68 pregnancies) had similar rates of fetal death and miscarriage, but were more often treated (55% vs 30%) (Appendix A, Table 1). Treatment was initiated during pregnancy for 38/99 pregnancies in women with anti-SSA antibodies and consisted in low-dose aspirin ($n=34$), low-molecular-weight heparin (LMWH, $n=21$), hydroxychloroquine ($n=18$), low-dose steroids ($n=18$) and other agents ($n=5$; intra-venous immunoglobulins, rituximab, eculizumab). Among asymptomatic anti-SSA carriers, treatment decreased fetal losses from 85% to 25% (OR 0.06 [95% CI 0.01; 0.39]; $P=0.003$). A similar effect was found in women with confirmed Sjogren's syndrome (OR 0.22 [95% CI 0.06; 0.83]; $P=0.02$). Low-dose aspirin and hydroxychloroquine were signifi-

Table 1
Adverse obstetrical outcomes in women with isolated anti-SSA antibodies and primary Sjögren's syndrome.

Characteristics	Isolated anti-SSA antibodies $n=19$ (68 pregnancies)	Primary Sjögren's syndrome $n=8$ (31 pregnancies)
Miscarriages, *n* (%)	35/68 (51.5)	15/31 (49)
Fetal loss, *n* (%)	44/68 (65)	20/31(64)
Intra-uterine growth restriction, *n* (%)	5/68 (7)	1/31 (3)
Prematurity, *n* (%)	2/68 (3)[b]	4/31 (13)
Live births in untreated pregnancy, *n* (%)	7/48 (14.5)	3/14 (21)
Pre-eclampsia, *n* (%)	12/68 (17.6)	3/31 (10)
Treated during pregnancy, *n* (%)	20/68 (30)	17/31 (55)
Aspirin, *n* (%)	19/68 (28)	14/31 (45)
Hydroxychloroquine, *n* (%)	10/68 (15)	8/31 (26)
LWMH, *n* (%)	10/68 (15)	10/31 (32)
Prednisone, *n* (%)	4/68 (6)[a]	10/31 (32)
Live births in treated pregnancies, *n* (%)	15/20 (75)	8/17 (58)

[a] $P<0.05$.
[b] $P=0.07$.

Table 2
Factors associated with pregnancy loss and obstetrical complications.

	Fetal loss or obstetrical complication ($n=83$)	No fetal loss/obstetrical complication ($n=16$)	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
Age (years, at pregnancy)	29.5 ± 5.9	29.5 ± 5.3	0.91 (0.83; 1.00)	0.05	1.13 (1.03; 1.24)	0.009
Untreated pregnancies, *n* (%)	1.64 ± 1.60	1.44 ± 1.36	0.72 (0.54; 0.95)	0.02	1.68 (1.01; 2.79)	0.04
Sjögren syndrome, *n* (%)	26 (32)	5 (31)	0.57 (0.14; 2.32)	0.43		
Placental intervillitis, *n* (%)	16 (22)	1 (7)	3.73 (0.46; 30.4)	0.21		
Treatment, *n* (%)	25 (30)	13 (81)	0.09 (0.03; 0.27)	<0.0001		
Aspirin, *n* (%)	22 (27)	12 (75)	0.10 (0.03; 0.28)	<0.0001	0.05 (0.01; 0.37)	0.003
LMWH, *n* (%)	5 (31)	16 (19)	0.29 (0.11; 0.81)	0.018	2.92 (0.52; 16.3)	0.2
Prednisone, *n* (%)	3 (19)	11 (13)	0.39 (0.13; 1.11)	0.07		
Hydroxychloroquine, *n* (%)	8 (10)	10 (63)	0.05 (0.01; 0.18)	<0.0001	0.15 (0.02; 0.98)	0.04

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cantly associated with a favorable obstetrical outcome and reduced fetal loss: OR 0.05 [95% CI 0.01; 0.37] ($P = 0.003$) and 0.15 [0.02; 0.98] ($P = 0.04$) (Table 2). Considering various adverse obstetrical complications separately, no factor was significantly associated on univariate analysis (data not shown). Among women with unexplained obstetrical morbidity, 139 (27.2%) treated pregnancies (low-dose aspirin and LMWH combination) resulted in 101 (72%) live births, whereas 371 untreated pregnancies led to 128 live births (34.6%). The prevalence of asymptomatic anti-SSA carriage in women with adverse obstetrical events history was elevated compared to general population (11% versus 0.2% [4]), but there were no significant differences in the obstetrical phenotype when compared to the obstetrical APS and to the unexplained adverse obstetrical events subgroups (Table S1).

Treatment with low-dose aspirin and hydroxychloroquine strongly improved the obstetrical outcome in anti-SSA antibodies carriers. Hydroxychloroquine has been shown to be safe [5], to prevent anti-SSA antibodies cardiac foetotoxicity [6] and its efficacy could be raised for anti-SSA antibodies-related obstetrical complications.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2018.11.005.

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