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; 2; 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 preeclampsia, 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; intravenous 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 significantly 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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Appendix A. Supplementary data

Supplementary data (Figure S1, Table S1) associated with this article can be found in the online version at …

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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)
Intrauterine growth restriction, n (%)	5/68 (7)	1/31 (3)
Prematurity, n (%)	2/68 (3)**	4/31 (13)
Live births in untreated pregnancy, n (%)	7/48 (14.5)	3/14 (21)
Preeclampsia, 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)*	10/31 (32)
Live births in treated pregnancies, n (%)	15/20 (75)	8/17 (58)

***p<0.05; **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