EXTENDED REPORT

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European registry of babies born to mothers with antiphospholipid syndrome

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ABSTRACT

Objectives This study aimed to describe the long-term outcome and immunological status of children born to mothers with antiphospholipid syndrome, to determine the factors responsible for childhood abnormalities, and to correlate the child's immunological profile with their mothers.

Methods A prospective follow-up of a European multicentre cohort was conducted. The follow-up consisted of clinical examination, growth data, neurodevelopmental milestones and antiphospholipid antibodies (APL) screening. Children were examined at 3, 9, 24 months and 5 years.

Results 134 children were analysed (female sex in 65 cases, birth weight 3000±500 g, height 48±3 cm). Sixteen per cent had a preterm birth (<37 weeks; n=22), and 14% weighted less than 2500 g at birth (n=19). Neonatal complications were noted in 18 cases (13%), with five infections (4%). During the 5-year follow-up, no thrombosis or systemic lupus erythematosus (SLE) was noted. Four children displayed behavioural abnormalities, which consisted of autism, hyperactive behaviour, feeding disorder with language delay and axial hypotony with psychomotor delay. At birth lupus anticoagulant was present in four (4%), anticardiolipin antibodies (ACL) IgG in 18 (16%), anti-β_2 glycoprotein-I (anti-β2GPI) IgG/M in 16 (15%) and three (3%), respectively. ACL IgG and anti-β2GPI disappeared at 6 months in nine (17%) and nine (18%), whereas APL persisted in 10% of children. ACL and anti-β2GPI IgG were correlated with the same mother's antibodies before 6 months of age ($p<0.05$).

Conclusion Despite the presence of APL in children, thrombosis or SLE were not observed. The presence of neurodevelopmental abnormalities seems to be more important in these children, and could justify long-term follow-up.

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Antiphospholipid syndrome (APS) is an autoimmune disorder characterised by thrombosis and/or pregnancy morbidity, associated with antiphospholipid antibodies (APL).[1 2] During pregnancy in mothers with autoimmune disorders, the mother's antibodies could influence fetal development. In mothers with anti-Sjögren's syndrome A antibodies, cardiac impairment and in particular auriculoventricular block could be present. In children born to mothers with APS, thrombosis is rare, and only a few cases are reported, mostly associated with other prothrombotic factors.[3] APL could be present in 30% of offspring of mothers with APS. The disappearance of anticardiolipin antibodies (ACL) at 12 months could account for the passive transplacental transfer of APL.[4]

Interest has recently grown in the long-term behaviour and neuropsychological outcome of offspring of mothers with autoimmune disorders. Instead of a normal intellectual quotient, offspring from mothers with systemic lupus erythematosus (SLE) could have more frequent dyslexia and learning disabilities, which were found to be related to anti-Sjögren's syndrome A or APL antibodies.[5 6] In children from mothers with APS, learning disabilities without other neurodevelopmental abnormalities were present in 15–20% of cases in two retrospective reports.[7 8]

In the European multicentre prospective registry, we aimed to describe the long-term outcome and immunological status of children born to mothers with APS, to determine the factors responsible for childhood abnormalities, and to correlate the child's immunological profile with their mothers.

PATIENTS AND METHODS

Registry

A prospective multicentre registry of a cohort of children born to mothers with APS was initiated in 2003 by the European forum of antiphospholipid antibodies until May 2010.[9] All consecutive newborns (or fetuses after 22 weeks or weight >500 g) were included. All women included in this study had thrombotic and/or obstetric APS according to Sapporo criteria.[2] Seven European obstetric centres were participating in this longitudinal study in order to follow the children from birth up to 5 years of age. Each participating team included an internist, a rheumatologist, an immunologist, an obstetrician, a paediatrician and a haematologist.

Physicians were asked to transmit a standardised task form including data on the mothers and children. All data were stored at the Jean Verdier Hospital. All data concerning mothers and children were reviewed by AM, EL and MCB.

Maternal age, clinical APS features, associated autoimmune diseases, course and outcome of pregnancy, treatments before and during pregnancy, immunological status, Doppler data and delivery mode during pregnancy were recorded. Immunological status was assessed at the diagnosis of APS, before pregnancy, every trimester during pregnancy and in postpartum.

Neonatal outcome was assessed on the basis of the following parameters: weeks of gestational age at delivery, birth weight, birth height, cranial perimeter at birth, 1 and 5-min Apgar scores, neonatal lupus, thrombosis and other neonatal complications.

The follow-up consisted in clinical examination, growth data, neurodevelopmental milestones, medical events and hospitalisation. Children have been examined at 3, 9, 24 months and 5 years. Immunological status was assessed at birth, 1/3, 9/12, 18/24 months and 5 years, and consisted of an APL screening.

Neonates and childhood complications were defined as the presence of one of the following features in the babies of this study among: less than 37 weeks term, birth weight, birth height or the cranial perimeter at birth being less than the 10th percentile or greater than the 97th percentile, Apgar score less than 8, neonatal complications, or neuropsychological developmental abnormalities during follow-up. Different factors were analysed to predict the neonates' complications: the mother's previous APS characteristics, number and type of previous obstetric events, associated SLE, type and number of APL, treatments before and during pregnancy, Doppler data, as well as delivery mode and term. For children, the weight, height, cranial perimeter and child's APL during follow-up were also analyzed.

APL assays

All women were tested for the presence of lupus anticoagulant (LA), IgG/IgM ACL and IgG/IgM anti-β_2 glycoprotein-I (β_2GPI) antibodies (Cardiolisa, BMD, Marne-La-Valle, France; and Instrumental Laboratories, San Diego, California, USA, respectively). LA was detected using diluted Russell's viper venom and diluted activated partial thromboplastin time as screening tests. ACL IgG/M and anti-β_2GPI antibodies IgG/M positivity was defined as value above the 99th percentile (medium titre). Triple positivity was defined by the association of a positive LA test, a positive ACL (IgG and/or IgM) and a positive anti-β_2GPI (IgG and/or IgM).

Children were tested for APL similarly to the mothers and the same cut-offs were applied to children.

This study was approved by the University Hospital of Jean Verdier Institutional Review Board and the Comité de Protection des Personnes soumises à la Recherche Biomédicale (CCPPRB, Aulnay Sous Bois, 2003). Written informed consent was obtained from all patients.

Statistical analysis

All quantitative data are expressed as means with SD, whereas qualitative data were expressed as frequencies with percentages. The Fisher's exact test or χ^2 was used to compare qualitative variables, while the non-parametric Mann–Whitney U test or Student's t test was used for continuous variables, as a function of their distributions.

Univariate analysis (Cox proportional hazard regression models) ($p<0.15$) and a multivariate analysis (also from Cox's regression model) with stepwise selection was carried out to identify significant predictors of neonates and childhood complications (as defined above) ($p<0.05$). The analysis was first applied to all patients, and then only to mothers with primary APS. Statistical analysis was performed using SAS (version 9.1), and significance was defined as $p<0.05$.

RESULTS

Mothers' characteristics

One hundred and thirty-three women with APS (Sapporo) (mean age 36±5 years) were included (table 1). Patients with obstetric APS have had previous recurrent spontaneous abortion (more than three) in 48 cases, intrauterine death in 58 cases, preeclampsia before 34 weeks and/or abrutio placenta in 30 cases. Anticoagulant treatment was started at 13±8 weeks of pregnancy. APL in mothers before and during pregnancy is shown table 2. ACL IgG levels decreased significantly during pregnancy (table 2). During pregnancy, APL were present in 80 (69%) of previous APL-positive patients: LA in 19 (33%), ACL IgG/M in 49/12 cases (63%/16%), anti-β2GPI IgG/M in 32/25 cases (42%/33%), respectively.

Abnormal Doppler data during pregnancy were noted in 50 cases (45%), with the presence of notch in 22 cases (46%). Spontaneous vaginal delivery occurred in 37 cases (28%), labour was induced in 30% and caesarean section was performed in 56 cases (42%).

Pregnancy and neonatal outcome

One hundred and thirty-four children born to mothers with APS were analysed (female sex in 65 cases, birth weight 3000±500 g, height 48±3 cm, cranial perimeter 34±2 cm, and Apgar 1–3 min 10/10). The gestational term was 38±2 weeks. Sixteen per cent

Table 1 Mothers' characteristics, pregnancy outcome and treatments

Mothers' characteristics	N=133
Age (years)	36±5
BMI (kg/m^2)	25±5
Primary APS	108 (81%)
Purely thrombotic APS	37 (28%)
SLE	18 (14%)
Laboratory data	
Lupus anticoagulant	33 (25%)
Anticardiolipin IgG/M	66 (50%)/16 (12%)
Anti-β_2 glycoprotein-I antibodies G/M	32 (25%)/25 (19%)
Double/triple positivity	20 (15%)/10 (8%)
Treatment before pregnancy	
Corticosteroids	21 (16%)
Hydroxychloroquine	15 (11%)
Aspirin	26 (19%)
Treatment during pregnancy	
Aspirin and low-molecular weight heparin	118 (90%)
Corticosteroids	25 (19%)
Hydroxychloroquine	15 (11%)
Actual pregnancy outcome	
Gestational hypertension/diabetes mellitus	12 (9%)/14 (11%)
Intrauterine growth restriction	12 (9%)
Preeclampsy/hellp syndrome	3 (2%)
Thrombosis	3 (2%)

Values are means with SD and numbers with frequencies.
APS, primary antiphospholipid syndrome; BMI, body mass index; SLE, systemic lupus erythematosus.

had a preterm birth (<37 weeks; n=22) and 14 per cent weighted less than 2500 g at birth (n=19). Neonatal thrombocytopaenia was present in two cases. There were no cases of neonatal lupus or thrombosis. Neonatal complications were noted in 18 cases (13%), mostly related to prematurity, and among them five cases (4%) had infections. The presence of LA during pregnancy in mothers and of long-term antithrombotic treatment was more frequent in small for gestational age neonates and neonates with other complications (p<0.05). The presence of maternal SLE and lower dosage of low molecular weight heparin (4500±1900 UI vs 5400±3200 UI) tended to be more frequent in these children (p=0.06). At birth, ACL anti-β2GPI IgG were the more frequent APL (table 3).

Follow-up

Children's characteristics

During the 5-year follow-up, no thrombosis or SLE was noted. Four children displayed behavioural abnormalities between 3 months and 3 years of age (tables 4 and 5). All of these children were born to mothers with primary obstetric APS. During these four pregnancies, gestational diabetes occurred in two cases and intrauterine growth restriction in one case, all of them were treated and only one of the neonates had a birth weight less than 2000 g. Genetic and metabolic screening was normal in all these children. Among children with abnormal neurodevelopment, only one had persistent ACL IgG antibodies.

Children's immunological data

Immunological data during follow-up are summarised in table 3. After 6 months, ACL IgG were still present in nine cases (20%) and anti-β_2GPI IgG in 15 cases (33%) (table 3). APL persisted in 10% of children, whereas de novo anti-β_2GPI IgG appeared in 16% (table 6). ACL IgG and anti-β_2GPI IgG antibodies in children were correlated with the same mother's isotypes before 6 months of age (p<0.05). While using APL cut-off at the 95th percentile in offspring, ACL IgG were detected in 22 (20%) cases at birth (vs 18 (16%) at the 99th percentile) and 14 cases (30%) at 9 months (vs 20%) (table 3).

Predictors of neonatal and complications in children

In univariate analysis, the presence of neonatal complications in all patients was associated with the mother's SLE, an antiaggregant used before the pregnancy, LA, abnormal Doppler data during pregnancy and caesarean delivery, whereas mothers with recurrent spontaneous abortions were associated with better neonatal outcomes (table 7). In multivariate analysis only the presence of LA during pregnancy was associated with neonatal complications with OR 3.9 (1.2 to 12.4). At 3, 9 and 24 months, because of missing data, no variable could predict an outcome in multivariate analysis.

In patients with primary APS, when different factors were analysed in order to predict children's complications (as defined in 'Patients and methods'), the presence of anti-β_2GPI IgG antibodies in children was the only significant variable with OR 0.4 (0.15 to 0.9) at 3 and 9 months. At 24 months, no variable reached sufficient power to be significant in multivariate analysis, even the presence of anti-β_2GPI IgG antibodies in children and of ACL IgM in mothers were associated with better outcome, unlike caesarean delivery in univariate analysis.

DISCUSSION

In this large prospective European study, we aimed to assess the outcome of offspring of mothers with APS. Instead of the persistent high rate of prematurity and small for gestational age neonates in treated pregnancies, the outcome of children born to mothers with APS remains without specific features, such as thrombosis or SLE during the 5-year follow-up. On the contrary, several cases of neurodevelopmental abnormalities were more frequently present than in the general population.[10] Moreover, APS-exposed children frequently have APL, by passive transplacental transfer, as by de novo synthesis.

Table 2 Antiphospholipid antibodies in mothers before and during pregnancy

	At diagnosis (n=133)	1st Trimester (n=87)	2nd Trimester (n=46)	3rd Trimester (n=46)
Lupus anticoagulant	33 (25%)	16 (18%)	6 (13%)	6 (13%)
Anticardiolipin IgG	66 (50%)	34 (39%)	23 (50%)	11 (24%)
Anticardiolipin IgG (UGPL)	48±105*	30±54	24±43	31±97
Anticardiolipin IgM	16 (12%)	9 (10%)	1 (2%)	2 (4%)
Anticardiolipin IgM (UMPL)	7±12	5±5	6±8	6±12
Anti-β2GPI IgG	32 (25%)	22 (25%)	10 (22%)	5 (11%)
Anti-β2GPI IgG (UGPL)	8±18	7±11	6±7	11±28
Anti-β2GPI IgM	25 (19%)	19 (22%)	10 (22%)	4 (10%)
Anti-β2GPI IgM (UMPL)	4±8	7±11	6±7	3±4

Values are means with SD. Anti-β2GPI, anti-β_2 glycoprotein-I antibodies.
*p<0.05 from baseline at diagnosis to 1st, 2nd and 3rd trimester of pregnancy.
anti-β_2GPI, anti-β_2 glycoprotein-I; IgG, immunoglobulin G.

Table 3 Antiphospholipid antibodies in offspring of antiphospholipid syndrome mothers at birth and during follow-up

	Umbilical cord (n=40)	First week (n=110)	3 Months (n=46)	9 Months (n=46)	24 Months (n=27)
Lupus anticoagulant	0	4 (4%)	1 (2%)	1 (2%)	0
Anticardiolipin IgG (99e)	7 (18%)	18 (16%)	6 (13%)	9 (20%)	5 (19%)
Anticardiolipin IgM	0	0	0	0	1 (4%)
Anti-β2GPI IgG	5 (13%)	16 (15%)	14 (30%)	15 (33%)	1 (4%)
Anti-β2GPI IgM	0	3 (3%)	0	0	1 (4%)
Anticardiolipin IgG (95e)	11 (28%)	22 (20%)	10 (22%)	14 (30%)	8 (30%)

Anti-β2GPI, anti-β_2 glycoprotein-I antibodies; IgG, immunoglobulin G.

Previous studies have already highlighted the presence of premature births and small for gestational age neonates even in mothers with APS who are treated.[3 11] Complications during pregnancy were rare in our patients, as less than 10% of patients presented with thrombosis, hypertension or pre-eclampsia. Despite this fact, premature birth was present in 17% of our study and was similar to previous studies, as was the rate of premature neonatal-related complications.

Evidence of neurodevelopmental difficulties, learning disabilities and language delay have been described in children of mothers with autoimmune disorders.[7 8] The language delay was more frequent in offspring of SLE mothers, and was associated with the presence of APL.[6] Little is known about children born to mothers with APS, but language delay was noted.[7 8] In experimental models, prolonged exposure to APL was shown to induce hyperactive behaviour and neurological dysfunctions in mice.[12] Otherwise it has been shown that APL can bind to the cells of the central nervous system.[13] Several studies have previously demonstrated that the prevalence of autoimmune disorders, such as type 1 diabetes, psoriasis, SLE rheumatoid arthritis, is elevated in mothers of individuals diagnosed with autism spectrum disorders.[14] Even though most children show normal neuropsychological development, several cases of neurodevelopmental abnormalities were also noted in our study from APS-exposed children. The prevalence of neurodevelopmental abnormalities depends on the geographical area and other socioeconomic conditions, but is usually near 1% and was more than twice that in our study. We observed three other cases of autism with persistent APL in children born to mothers with APS. (N Abisror *et al*, unpublished data). The presence of autism was recently found to be more prominent in children born prematurely, weighting less than 2000 g, as in one of our babies with behavioural abnormalities.[15] Because of the high rate of prematurity and small for gestational age neonates in children of APS mothers, this could constitute an additional factor of neurodevelopmental abnormalities in APS-exposed children.

The presence of APL in offspring of mothers with APS was previously reported in children.[4] ACL disappeared at 3 months in children from APS mothers, similar to another report with a 12-month follow-up.[4, 16] In our study, APL correlated with mothers' APL before 6 months and mostly disappeared after 6 months, which helps the argument for passive transplacental transfer. Nevertheless, 20% of the children studied have persistent APL at 24 months and 16% have de-novo production of anti-β2GPI antibodies. We had previously determined that the cut-off in healthy children was lower, when compared with mothers, and 11% low-titre APL was noted in healthy children.[17 18] When compared with healthy children, APL titres are higher in APS-exposed children, but less than in patients with APS.[4 19] APS exposure could constitute an additional immunological trigger, like vaccinations or infections in children, and explain the higher rate of APL in these children.

Table 4 Offspring's general characteristics, neurodevelopment and follow-up during 5 years

	At birth (n=130)	3 Months (n=110)	9 Months (n=105)	24 Months (n=64)	5 Years (n=27)
Weight (kg)	3±0.5	5.7±1.1	8.8±1.5	12±2	19±5
Weight <2 SD	–	3 (3%)	4 (4%)	0	0
Height (cm)	48±3	58±21	71±5	84±7	111±10
Height <2 SD	–	9 (9%)	9 (9%)	0	0
Cranial perimeter (cm)	34±2	40±2	45±2	48±2	50±2
Cranial perimeter <2 SD	–	0	2 (2%)	0	–
Infections	5 (4%)	6 (5%)	10 (10%)	11 (17%)	–
Atopy	–	8 (7%)	8 (7%)	7 (11%)	1 (4%)
Lupus	0	0	0	0	0
Thrombosis	0	0	0	0	0
Neurodevelopmental abnormality	–	1 (1%)	1 (1%)	3 (5%)	2 (7%)
Neurodevelopmental abnormality description	–	Axial hypotony	Axial hypotony, psychomotor delay	Autism; hyperactive behaviour; feeding disorders, language delay, growth failure	Autism; hyperactive behaviour

Each column represents the number of evaluated children at the check point.

Table 5 Characteristics of children with neurodevelopmental abnormalities

Case	Mother's age	APS features	Pregnancy outcome	Pregnancy treatment	Gestational age (weeks)	Sex	Birth weight (g)	Clinical features	APL
1	32	Obstetrical (IUGR/IUD)	Gestational diabetes	LWMH	38	M	2790	Autism	Negative
2	23	Obstetrical (RFL)	–	LWMH	36	M	2500	Hyperactive behaviour	Negative at birth; ACL IgG 12 U at 2 years
3	44	Obstetrical (RFL)	Gestational diabetes	LWMH-aspirin	37	F	2900	Feeding disorders, language delay, growth failure	Negative at birth; transient anti-β2GPI IgG 3–9 months
4	33	Obstetrical (IUGR/IUD)	IUGR	LWMH	37	F	1570	Axial hypotony, psychomotor delay	Negative

ACL, anticardiolipin antibodies; anti-β2GPI, anti-β_2 glycoprotein-I antibodies; APL, antiphospholipid antibodies; APS, antiphospholipid syndrome; F, female; IUD, intrauterine fetal death; IUGR, intrauterine growth restriction; LWMH, low-weight molecular heparin; M, male; RFL, recurrent fetal loss.

Table 6 APL evolution in children during follow-up with at least 1 dosage before and after 6 months

	Non-persistent APL	Persistent APL	De novo APL
Lupus anticoagulant (n=24)	1 (4%)	1 (4%)	1 (4%)
Anticardiolipin IgG (n=54)	9 (17%)	5 (9%)	5 (9%)
Anticardiolipin IgM (n=53)	–	–	1 (2%)
Anti-β_2GPI IgG (n=49)	9 (18%)	4 (8%)	8 (16%)
Anti-β_2GPI IgM (n=48)	1 (2%)	–	1 (2%)

This table represents APL in children who have at least two APL determinations before and after 6 months in order to discriminate the passive transplacental transfer from APL synthesis de novo, as well as to represent the persistent APL.
Anti-β_2GPI; anti-β_2 glycoprotein-I antibodies; APL, antiphospholipid antibodies.

Despite the high rate of premature birth and the presence of APL in close to 20% of the children studied, no specific complication was noted during the follow-up. Similar to previous data, there was no thrombosis in APS-exposed children in our study, and other associated prothrombotic factors seem to explain the few reported cases.[3] The presence of APL against domain I of β2GPI was mostly found in patients with APS, whereas anti-domain IV/V APL in healthy children and those from mothers with autoimmune disorders was predominant and could be an 'innocent' profile, reflecting more an immunological stimulation, rather than underlying immunological disease.[19] The long-term consequences of asymptomatic, 'innocent' or low-titre APL remain to be determined.

Several biases could limit the conclusions of this study. Despite its prospective design, only 20% of neonates were still assessed at the 5-year follow-up. Systematic psychomotor and cognitive checking was not done in all of the children and could mask the presence of more subtle abnormalities. The absence of a control group limits the definite conclusion about the risk of neurodevelopmental troubles in APS-exposed children. The role of vaccinations and infections, as well as age-dependent APL levels, could better explain APL evolution in children, but prospective studies are needed to confirm the impact of these factors on APL. Antibodies against domain I of β2GPI were not available at the beginning of this study and the profile of persistent APL could not be assessed.

CONCLUSION

In this study, despite the presence of APL in children born to mothers with APS, we did not observe thrombosis or SLE. The presence of neurodevelopmental abnormalities seems to be more important in these children, and could justify long-term follow-up. Further studies are necessary to assess the prevalence of neurodevelopmental abnormalities and to analyse the β2GPI domain specificity in children with persistent APL, as well as the significance of persistent APL in these children.

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Table 7 Factors to explain neonates' complications

Characteristics	Univariate OR (95% CI)	Multivariate OR (95% CI)
SLE	2.8 (0.9 to 8.7)	
Anticoagulants before pregnancy	2.2 (1.01 to 4.8)	
Recurrent miscarriage	0.8 (0.6 to 1.002)	
Doppler notch	2.1 (0.8 to 5)	
Mother's lupus anticoagulant	3.9 (1.2 to 12)	3.9 (1.2 to 12.4)
Caesarean delivery	1.8 (0.9 to 3.6)	

Neonates' complications were defined as the presence of one of the following features among: less than 37 weeks term, birth weight, birth height or the cranial perimeter at birth being less than the 10th percentile or greater than the 97th percentile, Apgar score less than 8, neonatal complications, or neuropsychological developmental abnormalities during follow-up. Factors analysed to predict the neonates' complications: the mother's previous antiphospholipid syndrome characteristics, number and type of previous obstetric events, associated SLE, type and number of antiphospholipid antibodies, treatments before and during pregnancy, Doppler data, as well as delivery mode and term.
SLE, systemic lupus erythematosus.

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