Obstetric antiphospholipid syndrome: early variations of angiogenic factors are associated with adverse outcomes

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Table S 1. The baseline clinical and biological characteristics of the APS women who initiated a new pregnancy during the 18 months individual observational period after obstetric APS diagnosis

BASELINE CHARACTERISTICS:	
N	513
Age, years	29 (4) [18-41]
>35 years, n (%)	15 (2.9%)
Body mass index, kg/m^2	26.0 (4.6) [15.3-37.0]
>30 kg/m^2	60 (11.7%)
<18.5 kg/m^2	5 (1%)
Ethnicity:	
Caucasians	489 (95.3%)
From Europe	418 (81.5%)
From North Africa	67 (13.1%)
Black Africans	22 (4.2%)
Asians	6 (1.2%)
MEDICAL HISTORY:	
Positive history in a first-degree relative:	
Venous thromboembolism	12 (2.3%)
Atherothrombosis	53 (10.3%)
Recurrent abortions	14 (2.7%)
Fetal loss	6 (1.2%)
Previous pregnancy loss (PL) subtypes:	
embryonic PL < 10 WG	204 (39.8%)

fetal PL ≥ 10 WG	309 (60.2%)
primary PL secondary PL	341 (66.5%) 172 (33.5%)
Inflammatory disease:	32 (6.2%)
Current tobacco users:	50 (9.7%)
Diabetes mellitus:	6 (1.2%)
Hypertension:	17 (3.3%)
Hyperlipidemia:	
hypercholesterolemia	31 (6.0%)
hypertriglyceridemia	27 (5.3%)
Interval inclusion/new pregnancy, days:	143 (33) [91-378]
ANTIPHOSPHOLIPID ANTIBODIES:	
Lupus anticoagulant (LA)	
Positive for LA	319 (61.7%)
Anticardiolipin IgG	
Positive for aCL-G	244 (47.2%)
aCL-G titer, $\mu g.ml^{-1}$	0.70 (1.37) [0.05-7.1]
Anticardiolipin IgM	
Positive for aCL-M	369 (71.9%)
aCL-M titer, $\mu g.ml^{-1}$	1.60 (1.55) [0.05-18.1]
Anti-β2-glycoprotein I IgG	
Positive for aβ2GP1-G	114 (22.1%)

aβ2GP1-G titer, µg/ml	0.57 (0.55) [0.03-6.9]
Anti-β2-glycoprotein I IgM	
Positive for aβ2GP1-M	209 (40.7%)
aβ2GP1-M titer, $\mu g.ml^{-1}$	0.72 (0.85) [0.05-19.4]
Categories of positive aPlAb	
I	383 (74.7%)
IIa	31 (6%)
IIb	98 (19.1%)
IIc	0
LA + aCL + aβ2GP1	149 (28.8%)
CONSTITUTIONAL THROMBOPHILIAS:	
F5 rs6025 or *F2* rs1799963	17 (3.3%)

Quantitative data are given as median (interquartile range) [minimum-maximum] values, qualitative data as number (percentage) values.

Type I, more than one aPlAb present; type IIa, LA present alone; type IIb, aCL-Ab present alone; type IIc, aβ2GP1-Ab present alone. Triple positivity: association of a positive LA test, a positive aCL-Ab test and a positive aβ2GP1-Ab test.

Table S2. Risk factors of severe PMCs, of pregnancy loss/neonatal death in APS women.

The 20 cases with pregnancy loss before 10 weeks and no karyotype were excluded from the analyses, an abnormal karyotype being systematically used as a confounder in the models. All babies born alive without any clinical abnormality evoking a chromosomal defect were assumed to have a normal karyotype.

Univariate analysis: results are restricted to putative predictors with p-value <0.20. Multivariate analysis: final models include only main effects with P<0.05, adjusted for variables with p<0.20.

LA: positive for lupus anticoagulant, aCL-G: positive for anticardiolipin IgG; aCL-M: positive for anticardiolipin IgM; aβ2GP1-G: positive for anti-β2-glycoprotein I IgG; aβ2GP1-M: positive anti-β2-glycoprotein I IgM.

*: Multivariate model 1 does not include the [(Δ PlGF/ ΔsFlt1) . 10^2] variable.

**: Multivariate model 2 does not include the [Δ PlGF . 10^{-1}] and the [ΔsFlt1 . 10^{-3}] variables.

Outcomes, models	**Variables**	**OR ($_{95\%}$CI)**	**P**
A-Severe PMCs (N= 59)			
Univariate			
	Age	1.077 (0.995-1.167)	0.0673
	Fetal death	1.935 (1.057-3.544)	0.0324
	aCL-M	1.646 (0.836-3.243)	0.149
	ΔPlGF . 10^{-1}	0.301 (0.161-0.561)	0.0002
	ΔsFlt1 . 10^{-3}	2.482 (1.458-4.225)	0.0008

	(ΔPlGF/ΔsFlt1) . 10^2 1st quartile Q1 (0.75; 1.39) 2nd quartile Q2 (1.40-1.77) 3rd quartile Q3 (1.78-2.32) 4th quartile Q4 (2.33-63.1)	 1 0.325 (0.160-0.659) 0.148 (0.061-0.355) 0.106 (0.039-0.285)	 0.0018 < 0.0001 < 0.0001
Multivariate 1* *(adjusted for age and abnormal karyotype)*			
	ΔPlGF . 10^{-1}	0.082 (0.041-0.188)	< 0.0001
	ΔsFlt1 . 10^{-3}	8.629 (4.420-17.2)	< 0.0001
	Fetal death	2.309 (1.298-5.034)	0.0092
Multivariate 2** *(adjusted for abnormal karyotype)*			
	(ΔPlGF/ΔsFlt1) . 10^2 1st quartile Q1 (0.75; 1.39) 2nd quartile Q2 (1.40-1.77) 3rd quartile Q3 (1.78-2.32) 4th quartile Q4 (2.33-63.1)	 1 0.282 (0.135-0.599) 0.140 (0.053-0.330) 0.081 (0.028-0.226)	 0.0009 < 0.0001 < 0.0001
	Fetal death	2.235 (1.60-4.328)	0.0165
	Age	1.099 (1.008-1.200)	0.0322
B-Pregnancy loss and neonatal death			
Abortion (N=93)			

Univariate			
	Hypertriglyceridemia	0.372 (0.089-1.589)	0.182
	aβ2GP1-M	0.521 (0.318-0.863)	0.0132
	Abnormal karyotype	483 (64-3633)	< 0.0001
Multivariate *(adjusted for hypertriglyceridemia and* aβ2GP1-M*)*			
	Abnormal karyotype	491 (64-3745)	< 0.0001
Fetal death (N=37)			
Univariate			
	Fetal death	2.103 (1.158-3.793)	0.0153
	Familial thromboembolism	2.778 (0.683-11.4)	0.167
	Familial atherothrombosis	1.748 (0.818-3.752)	0.149
	Abnormal karyotype	18.7 (1.656-212)	0.0179
	ΔPlGF . 10^{-1}	0.289 (0.139-0.604)	0.0010
	ΔsFlt1 . 10^{-3}	2.364 (1.254-4.455)	0.0078
	(ΔPlGF/ ΔsFlt1) . 10^{2} 1st quartile Q1 (0.75; 1.39) 2nd quartile Q2 (1.40-1.77) 3rd quartile Q3 (1.78-2.32) 4th quartile Q4 (2.33-63.1)	 1 0.279 (0.114-0.683) 0.230 (0.094-0.561) 0.053 (0.012-0.234)	 0.0052 0.0012 0.0001
Multivariate			

(adjusted for familial atherothrombosis)			
	(ΔPlGF/ΔsFlt1) . 10^2 1st quartile Q1 (0.75; 1.39) 2nd quartile Q2 (1.40-1.77) 3rd quartile Q3 (1.78-2.32) 4th quartile Q4 (2.33-63.1)	 1 0.268 (0.106-0.671) 0.216 (0.087-0.539) 0.047 (0.011-0.218)	 0.0048 0.0009 0.0001
	Fetal death	2.897 (1.200-6.356)	0.0200
-	Abnormal karyotype	18.3 (1.58-213)	0.0200
Stillbirths (N=29)			
Univariate			
	Familial thromboembolism	4.074 (0.784-21.2)	0.0948
	Familial atherothrombosis	2.050 (0.730-5.733)	0.173
	ΔPlGF . 10^{-1}	0.271 (0.120-0.616)	0.0018
	ΔsFlt1 . 10^{-3}	1.674 (0.826-3.394)	0.153
	(ΔPlGF/ΔFlt1) . 10^2 1st quartile Q1 (0.75; 1.39) 2nd quartile Q2 (1.40-1.77) 3rd quartile Q3 (1.78-2.32) 4th quartile Q4 (2.33-63.1)	 1 0.497 (0.196-1.261) 0.182 (0.056-0.593) 0.167 (0.051-0.542)	 0.141 0.0047 0.0029
Multivariate *(adjusted for abnormal karyotype)*			

	(ΔPlGF/ΔsFlt1) . 10^2 1st quartile Q1 (0.75; 1.39) 2nd quartile Q2 (1.40-1.77) 3rd quartile Q3 (1.78-2.32) 4th quartile Q4 (2.33-63.1)	 1 0.453 (0.174-1.174) 0.177 (0.053-0.579) 0.161 (0.049-0.528)	 0.0990 0.0048 0.0039
	Familial thromboembolism	2.705 (1.219-5.305)	0.0159
	Familial atherothrombosis	1.218 (1.037-1.275)	0.0388
Neonatal death (N=18)			
Univariate			
	Primary pregnancy loss	2.602 (0.738-9.173)	0.137
	Age	1.099 (0.960-1.259)	0.172
	Tobacco	3.784 (1.265-11.3)	0.0173
	LA	2.351 (0.757-7.295)	0.139
	aβ2GP1-M	2.121 50.802-5.606)	0.129
	Triple positivity	2.574 (0.991-6.685)	0.0521
	F5 rs6025 or *F2* rs1799963	4.075 (0.823-20.2)	0.0851
	ΔPlGF . 10^{-1}	0.316 (0.114-0.870)	0.0258
	ΔsFlt1 . 10^{-3}	2.814 (1.168-6.784)	0.0212
	(ΔPlGF/ΔsFlt1) . 10^2 1st quartile Q1 (0.75; 1.39) 2nd quartile Q2 (1.40-1.77) 3rd quartile Q3 (1.78-2.32)	 1 0.120 (0.026-0.565) 0.149 (0.040-0.558)	 0.0073 0.0047

	4th quartile Q4 (2.33-63.1)	0.091 (0.019-0.425)	0.0023
Multivariate *(adjusted for F5 rs6025 or F2 rs1799963 and for abnormal karyotype)*			
	(ΔPlGF/ΔsFlt1) . 10^2		
	1st quartile Q1 (0.75; 1.39)	1	
	2nd quartile Q2 (1.40-1.77)	0.103 (0.022-0.491)	0.0045
	3rd quartile Q3 (1.78-2.32)	0.144 (0.037-0.555)	0.0048
	4th quartile Q4 (2.33-63.1)	0.082 (0.017-0.390)	0.0017
	Tobacco	3.788 (1.180-12.2)	0.0252
	Triple positivity	2.838 (1.046-7.704)	0.0406

Figure S1. Patient flow diagram.