OBSTETRICAL OUTCOME AND TREATMENTS DURING PREGNANCY IN SERONEGATIVE PRIMARY APS

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Conflicts of interest

PI TOCITAKA (tocilizumab TAKAYASU arteritis), ROCHE CHUGAI

PI AZA SAID (azacytidine for autoimmune diseases in MDS/CMML)

Antiphospholipid syndrome

≥1 clinical criteria

- Thrombosis:
  - ✓ ≥1 arterial and/or venous thrombosis
- Obstetrical morbidity:
  - ✓ ≥ 1IUD after 10 wg
  - ✓ ≥3 early miscarriages without other etiologies
  - ✓ Prématurity <34SA from placental insufficiency

≥1 biological criteria

- LA
  (>12 weeks)
- aCL IgG/IgM
  (>12 weeks)
  (>40GPL/MPL ou >99ème percentile) (ELISA)
- aβ2GPI IgG/IgM
  (>12 weeks)
  (>99ème percentile) (ELISA)

≥1 clincal criteria

- Thrombosis:
- ✓ ≥1 arterial and/or venous thrombosis

- Obstetrical morbidity:
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- ✓ Prématurity <34SA from placental insufficiency

No detectable antiphospholipid antibodies

- LA
- AC IgG/IgM
- Aβ IgG/IgM

Seronegative APS ?

SAPL séronégatif

Variable	SN-APS (n=67)	SP-APS (n=87)	p value
Age	45.7 (9.3)	46.1 (11.1)	0.82
Age first pregnancy event	25.9 (5.7)	27.8 (6.8)	0.11
Age first thrombotic event	33.8 (11.5)	36.7 (12.7)	0.26
Sex			
Female	66 (98.5%)	80 (91.9%)	0.13
Race			
Caucasian	64 (95.5%)	71 (81.%)	0.34
Primary vs secondary APS			<0.001
Primary APS	56 (83.5%)	53 (60.9%)	
SLE-APS	11 (16.4%)	34 (39.1%)	
Clinical manifestations			
Venous thrombosis	27 (40.2%)	40 (45.9%)	0.51
Arterial thrombosis	23 (34.3%)	30 (34.4%)	0.98
Pregnancy morbidity*	55/64 (85.9%)	54/69 (78.2%)	0.26

Variable	SN-APS (n=67)	SP-APS (n=87)	p value
Immune diseases			
CTD	16 (23.8%)	38 (43.6%)	0.01
SLE	11 (16.4%)	34 (39.0%)	<0.001
Sjögren's syndrome	2 (2.9%)	12 (13.8%)	0.02
Non-CTD immune disease	12 (17.9%)	26 (29.8%)	0.09
Thyroiditis	7 (10.4%)	18 (20.6%)	0.12
Haemolytic anaemia	0	3 (3.4%)	0.25
Immunological profile			
ANA	15 (22.3%)	47 (54.0%)	<0.001
DNA(ds)	0	12 (13.7%)	<0.001
ENA	6 (8.9%)	14 (16.0%)	0.23
Sm	1 (1.5%)	1 (1.1%)	0.85
Ro	3 (4.4%)	11 (12.6%)	0.09
La	1 (1.5%)	4 (4.5%)	0.38
RNP	3 (4.4%)	2 (2.9%)	0.65
Rheumatoid factor	19 (28.3%)	19 (21.8%)	0.45

- Non criteria APL ?

Rodriguez-Garcia JL ARD 2012

Various non conventionnal APL

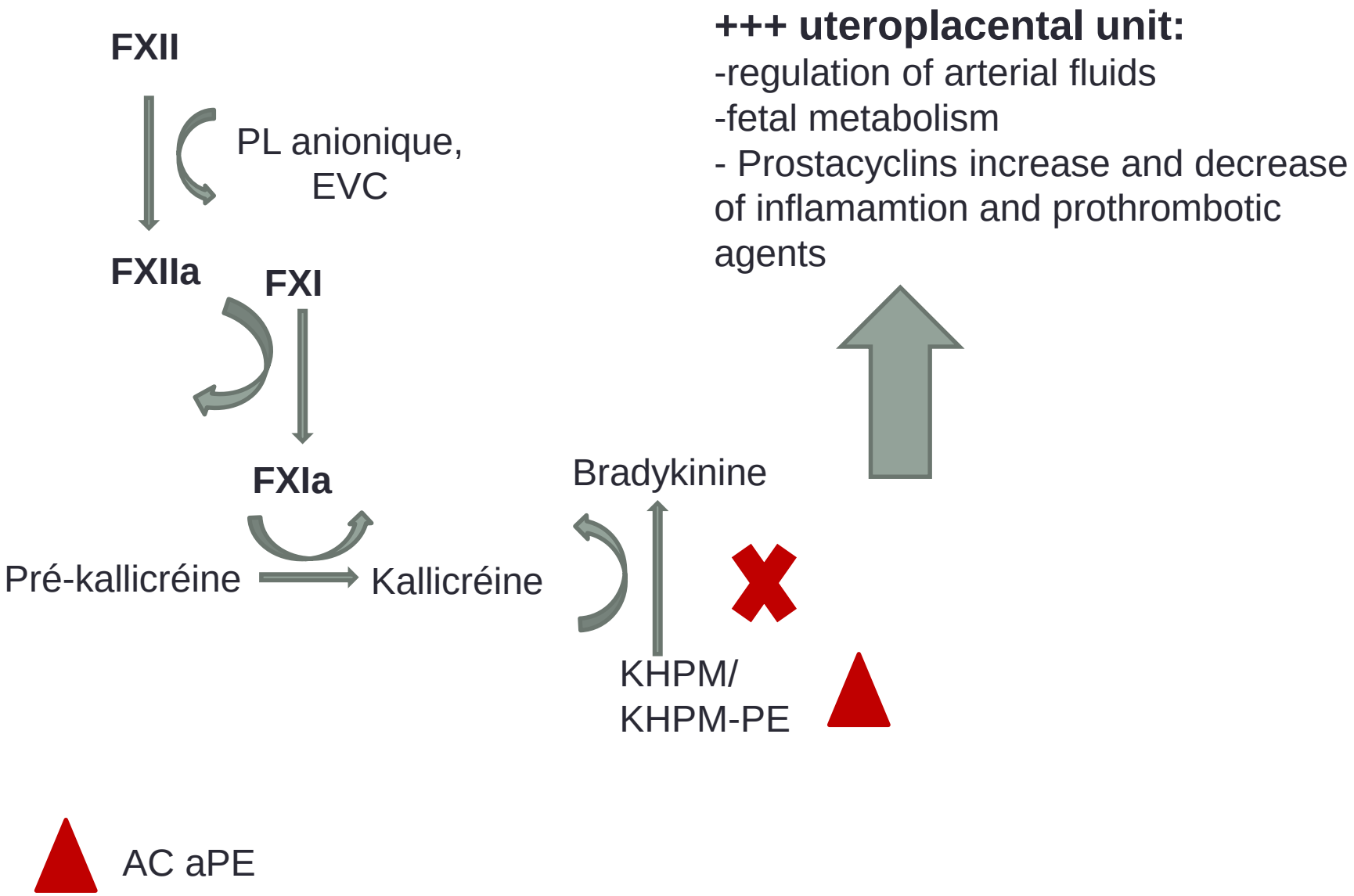
aPLs

- LA
- aCL
- aβ2GPI

Non conventionnal aPLs

- Ac anti-vimentine
- **aPE**
- **aA5**
- aPTs: aPT ; **aPS/PT**

Phosphatidylethanolamine (PE): Hypothèse de l'action Ac aPE



Annexin V and AC aAV

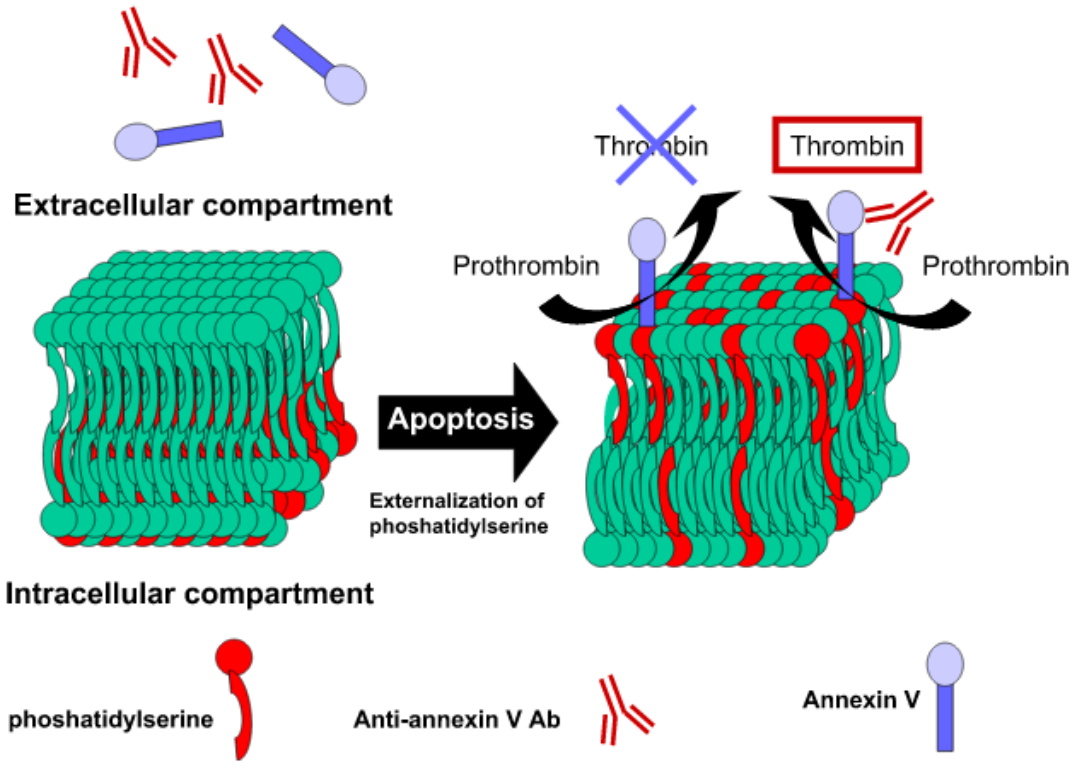


Fig. 1. Physiological function of annexin V and suspected role of anti-annexin V antibodies.

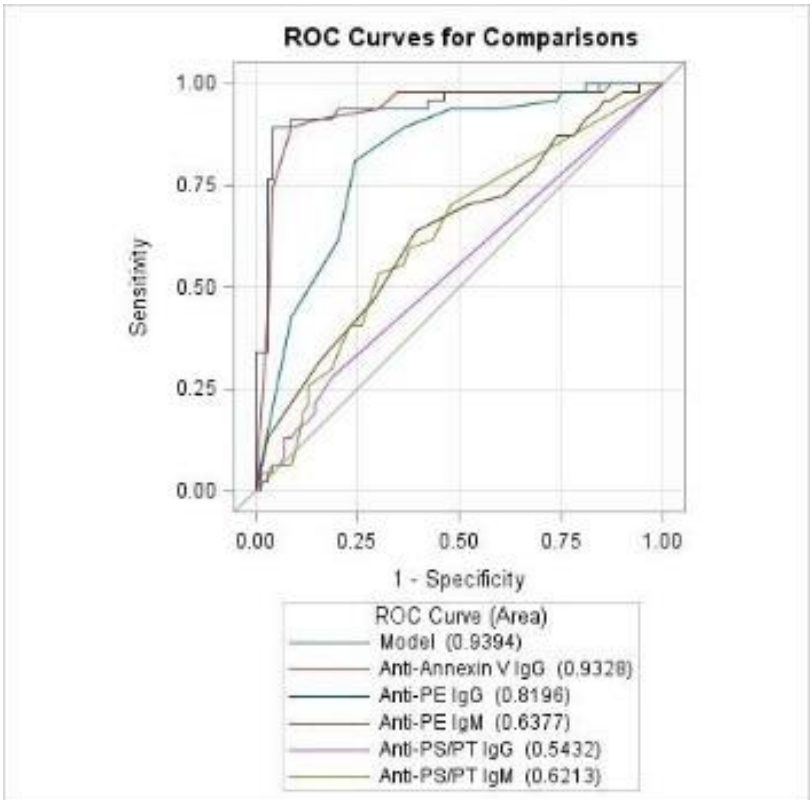
Placenta+++: µvillosities of syncytiotrophoblastes

→Anticoagulant activity during pregnancy

Seuil des APL NC

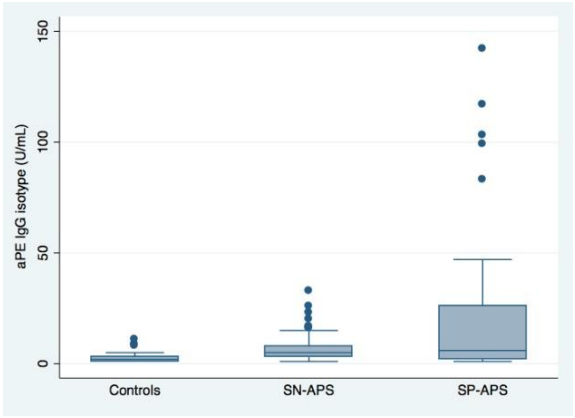
- N=96 Clinical APS without conventional APL :
  - Miscarriages = 44 (46%), IUD = 38 (40%) cases, prematurity<34 wg=25 (27%) cas, PE / HELLP = 25 (26%) / thrombosis 14 (15%)

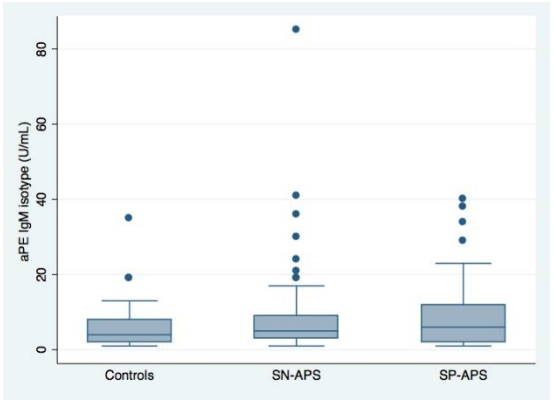
APL	Cut-off U/ml	Sensibility	Specificity	AUC	Odds Ratio Estimates*	95% CI	
Anti-Annexin V IgG	6	98%	60%	0.93	0.48	0.34	0.63
Anti-PE IgG	6	94%	46%	0.82	0.85	0.65	1.08
Anti-PE IgM	6	72%	39%	0.64	0.97	0.87	1.07
Anti-PS/PT IgG	15	9%	93%	0.54	1.01	0.92	1.09
Anti-PS/PT IgM	13	40%	74%	0.62	1.03	0.94	1.14

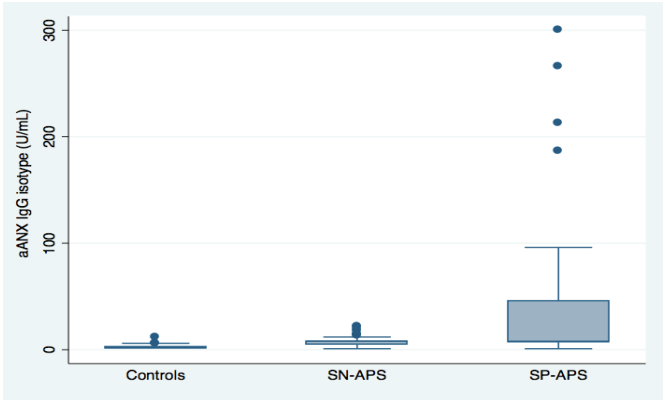


* OR for an increase of 1 unit of the Non-conventional APL variable

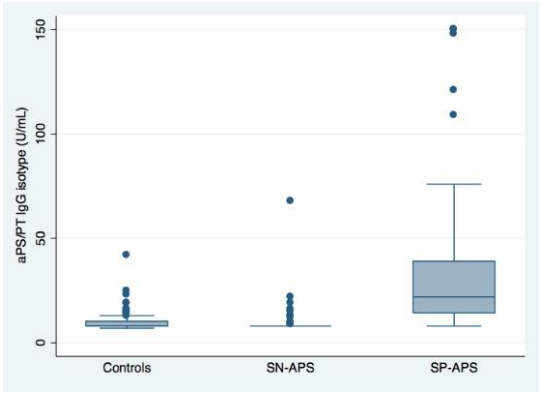
Non criteria APL

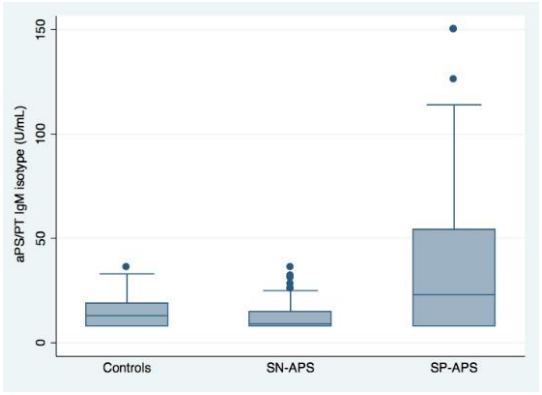






IgG aPE and IgG aAN5 increased in **SN-APS et SP-APS group versus controls** (p<0,0001)





IgG aPS/PT and IgM aPS/PT increased in **SP-APS vs controls** (p<0,0001)

Caractéristiques des SAPL NC et SAPL vrai

	Non-conventional APS (N = 65)	Confirmed APS (N = 83)
Obstetrical history		
Age (years)	32 ± 5 (*n* = 64)	40 ± 9* (*n* = 78)
Normal pregnancies	39/64 (60%)	30/46 (65%)
Number of normal pregnancies	1.0 ± 1.0	1.2 ± 1.4
Recurrent miscarriages	28/65 (43%)	18/45 (38%)
Intrauterine fetal deaths	29/65 (45%)	19/47 (40%)
Prematurity < 34 wg	14/64 (22%)	11/41 (27%)
Preeclampsia/HELLP	12/65 (18%)/3/65 (5%)	8/46 (17%)/1/18 (6%)
Live-born babies	1.4 ± 1.0 (*n* = 64)	1.6 ± 0.9 (*n* = 16)
Thrombosis history	10/65 (15%)	12/48 (25%)
Thrombosis number	0.2 ± 0.4	0.3 ± 0.5
Anti-Annexin V IgG	57/65 (88%)	38/52 (73%) (*p* = 0.057)
Anti-PE IgG	39/61 (60%)	26/50 (52%)
Anti-PE IgM	8/61 (12%)	4/50 (8%)
Anti-PS/PT IgG	2/56 (3%)	31/49 (63%)*
Anti-PS/PT IgM	3/56 (5%)	18/49 (37%)*
Anti-domain I β2 GPI	2/49 (3%)	12/24 (50%)*
Anti-β2 GPI IgA	0	9/22 (41%)*
Pregnancies treatment	*N* = 261	*N* = 81
Treated pregnancies	67 (26%)	33 (41%)*
Aspirin /LMWH alone	35 (13%)	11 (14%)
Aspirin-LMWH	19 (7%)	19 (24%)*
Prednisone	12 (5%)	3 (4%)
Hydroxychloroquine	7 (3%)	3 (4%)
Neonates characteristics (last pregnancy)	*N* = 64	*N* = 18
Birth weight (g)	3823 ± 4238 (*n* = 26)	3064 ± 722 (*n* = 9)
SGA (< 10e percentile)	10/27 (37%)	12/18 (67%)
Apgar 10/IU admission	26/28 (93%)/1 (3%)	10/10 (100%)/1 (9%)

Mekinian A, Semin Arthritis 2016

Pregnancies treatment

474 pregnancies:

- Foetal losses > 64% in non-APL group, 74% in APS

- 136/474 (29%) treated during pregnancy (aspirin/ aspirin-LMWH):
  > **fotal losses 26% vs 72%** if untreated (p<0,05)

Pregnancies treatment	SN-APS N=261	APS N=81	NON –APL N=132
Treated pregnancies	67 (26%)	33 (41%)*	36 (27%)
Aspirin /LMWH alone	35 (13%)	11 (14%)	14 (11%)
Aspirin-LMWH	19 (7%)	19 (24%)*	17 (13%)***
Prednisone	12 (5%)	3 (4%)	5 (4%)
Hydroxychloroquine	7 (3%)	3 (4%)	2 (2%)

OR at **1.9 [95% CI; 1.1 to 3.5]** for non-APL group
versus **5.3 [95% CI; 3.5 to 8.1],** p=0.0025

Obstetrical outcome and treatments during pregnancy in seronegative primary APS

Prospective and retrospective multicentre open-labelled study.

Inclusion criteria:

- Thrombotic arterial and/or venous; and /or obstetrical primary clinical seronegative APS (Sydney criteria)

- Presence of at least one non-conventional APL (among IgA ACL, IgA antiB2GPI, anti-Vimentin G/M, anti-AnnexinV G/M, anti-PE G/M, anti-PSPT G/M)

- Mother's consent to participate

Exclusion criteria:

- Confirmed APS with conventional APS
- Associated SLE or SLE like (SLE features and or positive antinuclear autoantibodies)
- Other systemic connective tissue disease (Sjogren's syndrome, systemic sclerosis, myositis)

Case control studies

- Each case age matched with 3 cases of confirmed APS

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Thank you

Data to analyse

- Type, site and number of previous thrombosis and obstetrical features

- Non conventional Antiphospholipides antibodies (anti-annexine V, anti-PS/PT, antiphosphatidylethanolamine antibodies and others)

- Associated thrombotic factors (obesity, tabacco use, diabetes, arterial hypertension)

- Mother's treatments, aspirin, heparin type and amount and steroids and hydroxychloroquine use during pregnancy

- Adverse pregnancy outcome (miscarriage, intrauterine death, IUGR, PE, HELLP syndrome, prematurity, arterial hypertension and thrombosis recurrence), time to previous thrombosis

- In the case of several pregnancies 2 first ones will be included

Traitements des GIU par groupes

Parameter	%Pregnancy losses	OR [95% CI]	p-value
Group			
APS (referent)	158/261: 61%		
Non-conventional APS	48/81: 59%	0.93 [0.56 to 1.55]	NS
Non-APL group	75/132: 57%	0.87 [0.57 to 1.34]	
Pregnancy Treatment			
Treated	36/136: 26%	0.14 [0.09 to 0.22]	Not included
Untreated	245/338: 72%		
Type of Pregnancy Treatment			
None (referent)	245/338: 72%		
Aspirin or LMWH alone	22/60: 37%	0.23 [0.13 to 0.40]	
Aspirin and LMWH	9/55: 16%	0.08 [0.04 to 0.17]	
Other	5/21:24%	0.13 [0.04 to 0.36]	<0.0001
Type of Pregnancy Treatment by Group			0.0125
APS untreated (referent)	146/194: 75%	3.35 [1.84 to 6.07]	<0.0001
APS treated	10/33: 30%		
• **Aspirin or LMWH alone**	7/34: 21%		
• **Aspirin and LMWH**	3/18: 17%		
• **Other**	2/13: 15%		
Non-conventional APS untreated (referent)	38/48: 79%	6.91 [3.89 to 12.27]	<0.0001
Non-conventional APS treated	12/65: 18%		
• **Aspirin or LMWH alone**	6/11: 55%		
• **Aspirin and LMWH**	3/19: 16%		
• **Other**	1/3: 33%		
Non-APL group untreated (referent)	61/96: 64%	1.95 [1.08 to 3.51]	0.04
Non-APL group treated	14/34: 41%		
• **Aspirin or LMWH alone**	9/14: 64%		
• **Aspirin and LMWH**	3/16: 19%		
• **Other**	2/4:50%		

Analyse multivariée, traitement pdt GIU et moins GIU compliquées antérieures associés avec une grossesse vivante

Conclusion

- **Prévalence APL non-conventionnels**
  - ✓ SAPL clinique sans APL conventionnels
  - ✓ Importance d'une étiologie dysimmunitaire / thrombotique
  - ✓ AAV et Anti-PE, mais pas anti-PS/PT, IgA ou antidomaine IV/V
  - ✓ Effet du traitement sur le pronostic obstétrical 6.91 [3.89 to 12.27] ?
- **Limites étude**
  - ✓ Faible effectif, groupe contrôle SAPL clinique sélectionnés
  - ✓ Absence du contrôle pour persistance des APL
  - ✓ Absence démonstration effet pathogène APL non conventionnels
  - ✓ Type de traitement suffisant ?