Antiphospholipid Syndrome in Pregnancy

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Lecture Plan

Definitions / Classification criteria

Management of obstetric APS

Management of thromboprophylaxis in pregnancy

EULAR / BSH guidelines

RCOG recurrent miscarriage guideline

Case: Mrs EB

30-year-old Caucasian female, G3P1

Uncomplicated pregnancy 2016, SVD

Miscarriage 2018

Inter-pregnancy interval 2 years

- Same partner

Medical history: appendicectomy

No regular medications, no over-the-counter medications

34+0 weeks' gestation

Uncomplicated pregnancy

Presented with 2-day history of pain

Right upper quadrant pain, radiating to the back

Associated with nausea and vomiting

No headaches or visual disturbance

Examination and Investigations

	Day 2	Day 3	Day 4
BP (mmHg)	138/75	138/80	146/90
Proteinuria	2+		
Full blood count			
WCC (x10^9/L)	12.9	8.7	15.4
Hb (g/L)	130	126	121
Plts (x10^9/L)	156	182	127
Liver function tests			
Bili (umol/L)	9	11	5
ALT (IU/L)	155	168	131
ALP (IU/L)	85	88	90
Alb (g/L)	34	33	32
Urea and electrolytes			
Cr (umol/L)		57	
Ur (mmol/L)		3.8	
Na (mmol/L)		138	
Other			
LDH (U/L) (140-280)		395	295
CRP (mg/L)	4		
Liver screen			Negative
Bile acids (umol/L)(<10)	12		

Re-presents to ED

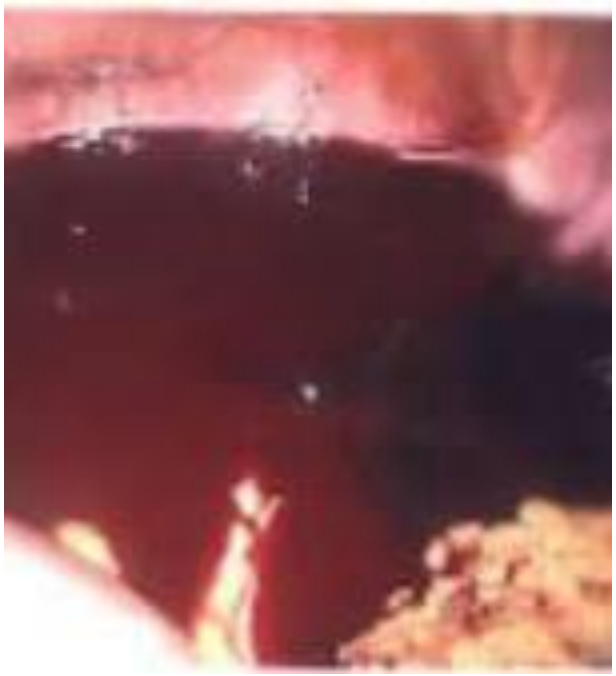
	Day 2	Day 3	Day 4	Day 5
BP (mmHg)	138/75	138/80	146/90	155/90
Full blood count				
WCC (x10^9/L)	12.9	8.7	15.4	15.6
Hb (g/L)	130	126	121	120
Plts (x10^9/L)	156	182	127	125
Liver function tests				
Bili (umol/L)	9	11	5	8
ALT (IU/L)	155	168	131	214
ALP (IU/L)	85	88	90	87
Alb (g/L)	34	33	32	32
Urea and electrolytes				
Cr (umol/L)		57		59
Ur (mmol/L)		3.8		3.7
Na (mmol/L)		138		140
Other				
LDH (U/L) (140-280)		395	295	
CRP (mg/L)	4			
Liver screen			Negative	

	Before collapse Day 5 14:00	After collapse Day 5 23:00
Full blood count		
WCC (x10^9/L)	15.6	9.5
Hb (g/L)	120	126
Plts (x10^9/L)	125	44
Liver function tests		
Bili (umol/L)	8	31
ALT (IU/L)	214	814
ALP (IU/L)	87	96
Alb (g/L)	32	33
Urea and electrolytes		
Cr (umol/L)	59	62
Ur (mmol/L)	3.7	4.0
Na (mmol/L)	140	139
Other		
LDH (U/L)		1100
CRP (mg/L)		49
Amylase (U/L)		30
PT (s) APTT (s)		17 52

Transferred to labour ward

In theatre

- Haemoperitoneum
- Colorectal surgeons called
- Blood loss 3L
  - Massive transfusion protocol initiated
- 10cm capsular tear in right lobe liver with active bleeding
- Abdomen packed
- Baby born in poor condition

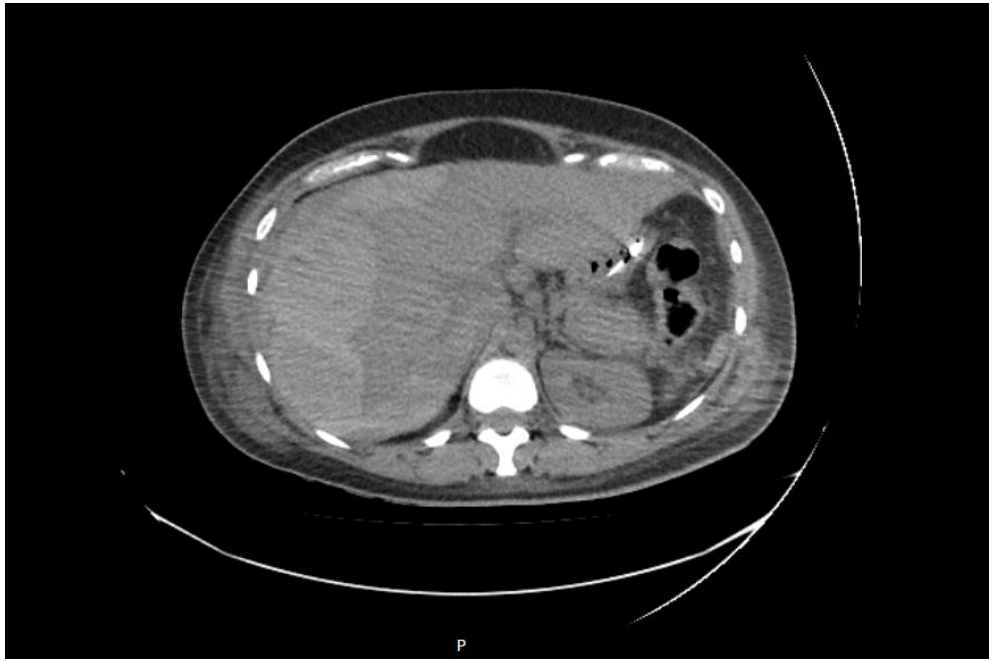


Mother transferred to ICU (27/9)

- Stabilized
- Triphasic liver CT – no active bleeding (28/9)
- Re-look and removal of packing (29/9)

Neonate transferred to tertiary centre

- Sadly died 2/7 later



Progress on ward

Monitored

Hypertension controlled

30/9	
Full blood count	
WCC (x10^9/L)	11.4
Hb (g/L)	80
Plts (x10^9/L)	96
Liver function tests	
Bili (umol/L)	8
ALT (IU/L)	624
ALP (IU/L)	87
Alb (g/L)	22
Urea and electrolytes	
Cr (umol/L)	88
Ur (mmol/L)	6.0
Na (mmol/L)	138
Other	
CRP (mg/L)	157

While on surgical ward

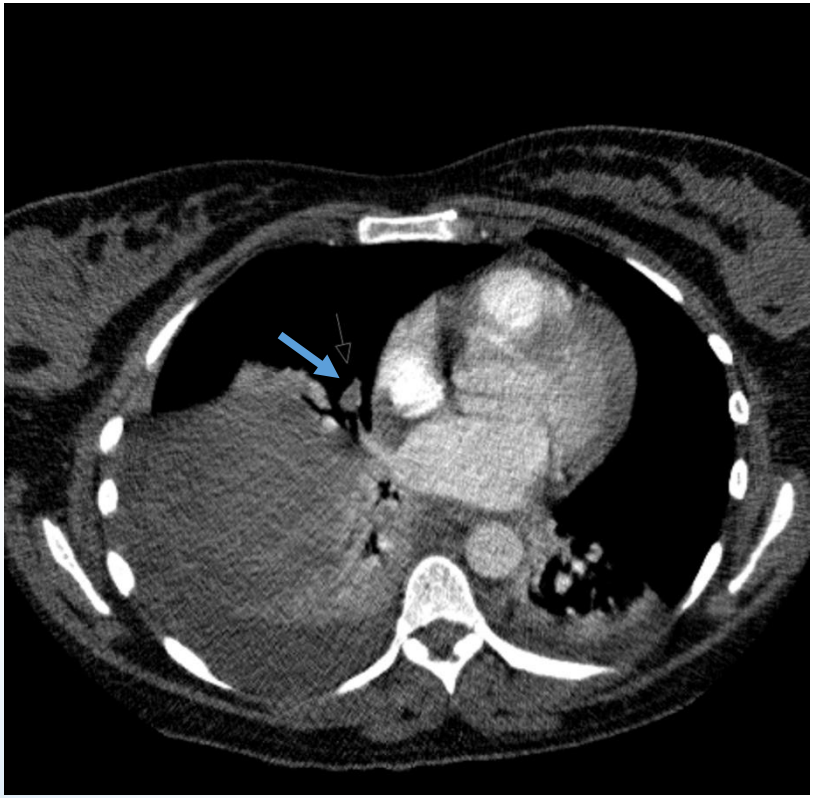
Complained of right calf tenderness

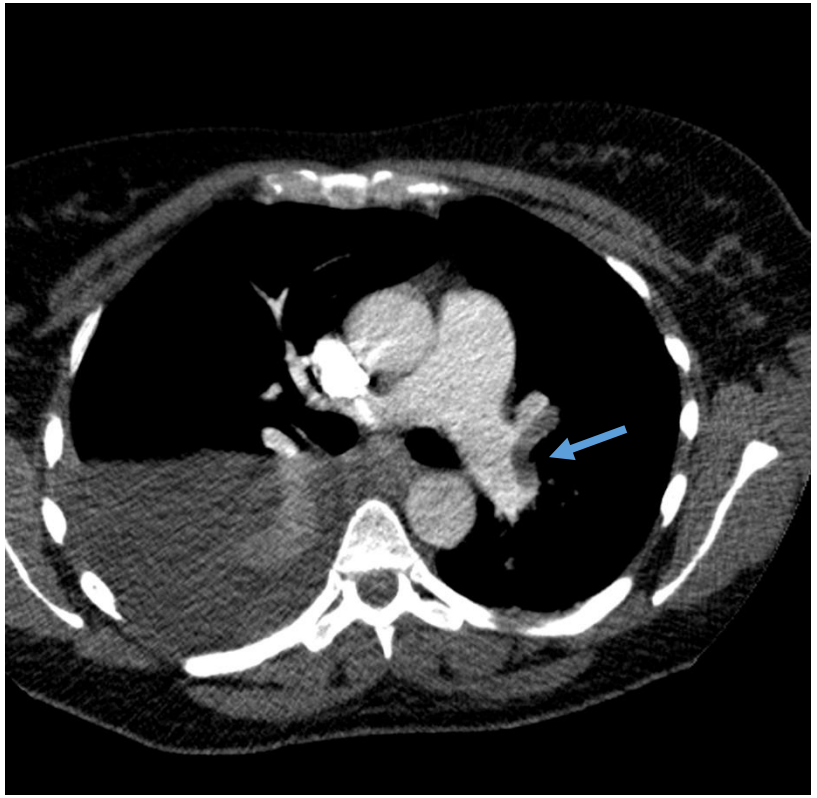
Later that day developed shortness of breath

HR 110, BP 120/84, RR 24, saturations 94% on air, apyrexial

Examination

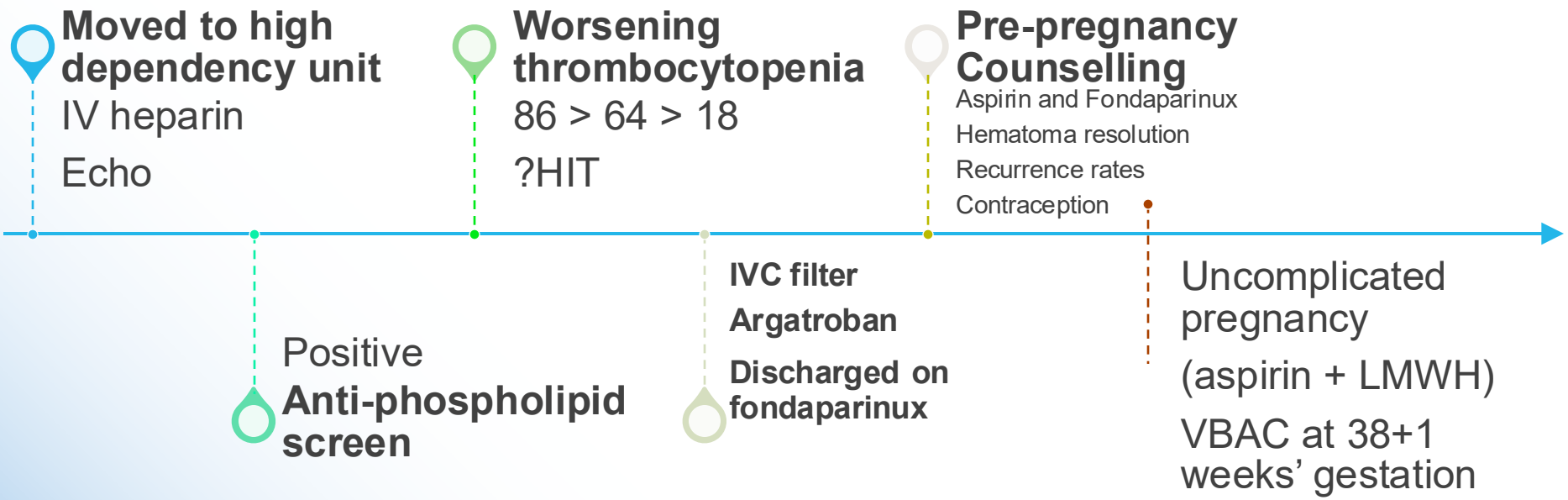
- Tender, swollen right calf
- Tachypnoea and tachycardia
- Chest clear
- Abdomen: recent surgical scar





Progress at Tertiary Unit

Summary: HELLP syndrome, ruptured liver, emCS 34+ weeks, DVT, PE



Classification Criteria for APS

CLINICAL

- Thrombosis
- Pregnancy morbidity
  - **Fetal death >10/40, morphologically normal, documented US/PM**
  - **Prem birth <35/40, morphologically normal, due to severe PET / IUGR**
  - **3 or more unexplained miscarriage <10/40, normal parental chromosomes, normal maternal anatomy and hormones**

Wilson et al 1999. Arth and Rheum 42,1309-11.

Miyakis S, et al. 2006. J Thromb Haemost 4, 295.

Classification Criteria for APS

LABORATORY

aCL IgG and/or IgM

medium/high titre (> 40 GPL or MPL)
2 or more occasions, 12 weeks apart

LA

2 or more occasions, 12 weeks apart

anti β_2 Glycoprotein 1

Titres > 99th percentile
2 or more occasions, 12 weeks apart

Wilson et al 1999. Arth and Rheum 42, 1309-11.

Miyakis 2006. JTH 4: 295.

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2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria

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on Behalf of the ACR/EULAR APS Classification Criteria Collaborators

2023 ACR/EULAR APS classification criteria

Entry Criteria[a]
At least one documented[b] clinical criterion listed below (domains 1-6)
plus
A positive antiphospholipid antibody (aPL) test
(a lupus anticoagulant test, or moderate-to-high titers of anticardiolipin or anti-β_2-glycoprotein-I antibodies [IgG or IgM])
within three years[b] of the clinical criterion

If absent, do not attempt to classify as APS - If present, apply additive criteria

Additive clinical and laboratory criteria[a]
Do not count a clinical criterion if there is an equally or more likely explanation than APS.
Within each domain, only count the highest weighted criterion towards the total score.

Clinical domains and criteria	Weight
D1. Macrovascular (Venous Thromboembolism [VTE])	
VTE with a high-risk VTE profile[c]	1
VTE without a high-risk VTE profile[c]	3
D2. Macrovascular (Arterial Thrombosis [AT])	
AT with a high-risk CVD profile[c]	2
AT without a high-risk CVD profile[c]	4
D3. Microvascular	
Suspected (one or more of the following)	2
Livedo racemosa (exam)	
Livedoid vasculopathy lesions (exam)	
Acute/chronic aPL-nephropathy (exam or lab)	
Pulmonary hemorrhage (symptoms and imaging)	
Established (one of more of the following)	5
Livedoid vasculopathy (pathology[d])	
Acute/chronic aPL-nephropathy (pathology[d])	
Pulmonary hemorrhage (BAL or pathology[d])	
Myocardial disease (imaging or pathology)	
Adrenal hemorrhage (imaging or pathology)	
D4. Obstetric	
≥3 Consecutive pre-fetal (<10w) and/or early fetal (10w 0d -15w 6d) deaths	1
Fetal death (16w 0d – 33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features	1
PEC with severe features (<34w 0d) or PI with severe features (<34w 0d) with/without fetal death	3
PEC with severe features (<34w 0d) and PI with severe features (<34w 0d) with/without fetal death	4
D5. Cardiac Valve	
Thickening	2
Vegetation	4
D6. Hematology	
Thrombocytopenia (lowest 20-130x10^9/L)	2

Laboratory (aPL) domains and criteria[e]	Weight
D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])	
Positive LAC (single – one time)	1
Positive LAC (persistent)	5
D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β_2-glycoprotein-I antibody [aβ_2GPI] ELISA [persistent])	
Moderate or high positive (IgM) (aCL and/or aβ_2GPI)	1
Moderate positive (IgG) (aCL and/or aβ_2GPI)	4
High positive (IgG) (aCL or aβ_2GPI)	5
High positive (IgG) (aCL and aβ_2GPI)	7

TOTAL SCORE
Classify as Antiphospholipid Syndrome for research purposes if there are
at least 3 points from clinical domains AND at least 3 points from laboratory domains

Entry Criteria[a]

At least one documented[b] clinical criterion listed below (domains 1-6)

plus

A positive antiphospholipid antibody (aPL) test

(a lupus anticoagulant test, or moderate-to-high titers of anticardiolipin or anti-β_2-glycoprotein-I antibodies [IgG or IgM])

within three years[b] of the clinical criterion

↓

If absent, do not attempt to classify as APS - If present, apply additive criteria

↓

Additive clinical and laboratory criteria[a]
Do not count a clinical criterion if there is an equally or more likely explanation than APS.
Within each domain, only count the highest weighted criterion towards the total score.

Clinical domains and criteria	Weight		Weight
D1. Macrovascular (Venous Thromboembolism [VTE])		**D2. Macrovascular (Arterial Thrombosis [AT])**	
VTE with a high-risk VTE profile[c]	1	AT with a high-risk CVD profile[c]	2
VTE without a high-risk VTE profile[c]	3	AT without a high-risk CVD profile[c]	4
D3. Microvascular		**D4. Obstetric**	
Suspected (one or more of the following)	2	≥3 Consecutive pre-fetal (<10w) and/or early fetal (10w 0d -15w 6d) deaths	1
Livedo racemosa (exam)			
Livedoid vasculopathy lesions (exam)			
Acute/chronic aPL-nephropathy (exam or lab)			
Pulmonary hemorrhage (symptoms and imaging)		Fetal death (16w 0d – 33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features	1
Established (one of more of the following)	5		
Livedoid vasculopathy (pathology[d])			
Acute/chronic aPL-nephropathy (pathology[d])		PEC with severe features (<34w 0d) or PI with severe features (<34w 0d) with/without fetal death	3
Pulmonary hemorrhage (BAL or pathology[d])			
Myocardial disease (imaging or pathology)		PEC with severe features (<34w 0d) and PI with severe features (<34w 0d) with/without fetal death	4
Adrenal hemorrhage (imaging or pathology)			
D5. Cardiac Valve		**D6. Hematology**	
Thickening	2	Thrombocytopenia (lowest 20-130x10^9/L)	2
Vegetation	4		

PEC = pre-eclampsia
PI = placental insufficiency

Laboratory (aPL) domains and criteria[e]	Weight
D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])	
Positive LAC (single – one time)	1
Positive LAC (persistent)	5
D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β_2-glycoprotein-I antibody [aβ_2GPI] ELISA [persistent])	
Moderate or high positive (IgM) (aCL and/or aβ_2GPI)	1
Moderate positive (IgG) (aCL and/or aβ_2GPI)	4
High positive (IgG) (aCL or aβ_2GPI)	5
High positive (IgG) (aCL and aβ_2GPI)	7

TOTAL SCORE

Classify as Antiphospholipid Syndrome for research purposes if there are at least 3 points from clinical domains AND at least 3 points from laboratory domains

Importance of stratification

Women with aPL do not all carry the same obstetric risk

Double / triple vs single aPL

IgG > IgM aCL

Med/ high titres vs low

Persistent β2GPI

Clark C. J Rheum 2015;42(2)155

Box 1 Definitions of medium-high antiphospholipid antibody (aPL) titres, and of high-risk and low-risk aPL profile

Medium-high aPL titres.

- Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma present in titres >40 IgG phospholipid (GPL) units or >40 IgM phospholipid (MPL) units, or >the 99th percentile, measured by a standardised ELISA. Antibeta2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma in titre >the 99th percentile, measured by a standardised ELISA.[1]

High-risk aPL profile.

- The presence (in 2 or more occasions at least 12 weeks apart) of lupus anticoagulant (measured according to ISTH guidelines), or of double (any combination of lupus anticoagulant, aCL antibodies or antibeta2 glycoprotein I antibodies) or triple (all three subtypes) aPL positivity, or the presence of persistently high aPL titres.

Low-risk aPL profile.

- Isolated aCL or antibeta2 glycoprotein I antibodies at low-medium titres, particularly if transiently positive.[3]

2023 ACR/EULAR APS classification criteria

Domain 4 — Obstetric

Prefetal death (preembryonic or embryonic loss): Otherwise unexplained* pregnancy loss before 10 weeks 0 days of gestation.

Fetal death: Otherwise unexplained* pregnancy loss between 10 weeks 0 days and 15 weeks 6 days gestation (early fetal death), or between 16 weeks 0 days and 34 weeks 0 days gestation.

Note: if a detailed analysis of the fetal morphology or genetic constitution is not performed or unavailable, reasonable clinical judgment should be used based on careful history and review of available medical records.

Preeclampsia with severe features (39): **Preeclampsia** defined as a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on 2 occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive or hypertensive (chronic†) patient AND new onset of one or more of the following: a) proteinuria ≥0.3 mg/mg (30 mg/mmoles) in a random urine specimen or b) dipstick protein ≥2+ if a quantitative measurement is unavailable AND one or more of the following "severe features":

Severe blood pressure elevation: Systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mm Hg on 2 occasions at least 4 hours apart while the patient is on bed rest (antihypertensive therapy may be initiated upon confirmation of severe hypertension, in which case severe blood pressure elevation criteria can be satisfied without waiting until 4 hours have elapsed).

Central nervous system dysfunction: New-onset headache unresponsive to medication and not accounted for by alternative diagnosis.

Visual disturbances.

Pulmonary edema.

Impaired liver function: Abnormally elevated blood concentrations of liver enzymes (more than twice the upper limit of normal concentrations), or severe persistent right upper quadrant or epigastric pain unresponsive to medications, not accounted by alternative diagnosis.

Renal dysfunction: Serum creatinine concentration >1.1 mg/dl or a doubling of the serum creatinine concentration in the absence of other renal disease. (88umol/l)

Thrombocytopenia: platelet count of $<100 \times 10^9$/liter.

(Continued)

2023 ACR/EULAR APS classification criteria

Placental insufficiency with severe features: Intrauterine fetal growth restriction defined as biometry indicating estimated fetal weight of less than the 10th percentile for gestational age or postnatal birth weight less than the 10th percentile for gestational age in the absence of fetal-neonatal syndromes or genetic conditions associated with growth restriction AND one or more of the following "severe features":

- **Abnormal or non-reassuring fetal surveillance test(s)** suggestive of fetal hypoxemia, e.g., a nonreactive non-stress test.
- **Abnormal Doppler flow velocimetry waveform analysis** suggestive of fetal hypoxemia, e.g., absent end-diastolic flow in the umbilical artery.
- **Severe intrauterine fetal growth restriction** suggested by fetal biometry indicating an estimated fetal or postnatal birth weight of <3rd percentile for gestational age.
- **Oligohydramnios**, e.g., an amniotic fluid index ≤5 cm, or deepest vertical pocket <2 cm.
- **Maternal vascular malperfusion on placental histology** suggested by placental thrombosis/infarction, inadequate remodeling of the uterine spiral arteries (decidual vasculopathy), decreased vasculosyncytial membranes, increased syncytial knots, or decidual inflammation (40). Note: Maternal vascular malperfusion on placental histology can be detected in the placentas of aPL-negative patients with intrauterine growth restriction and/or preeclampsia, and even in normal pregnancies; thus, these findings are not specific for APS.

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

Guidelines on the investigation and management of

TABLE 1 Comparison of the 2006 modified Sapporo and the 2023 ACR/EULAR APS classification criteria.[218]

Criteria	Revised Sapporo criteria	ACR/EULAR APS classification criteria		Comments
Clinical—thrombosis	≥1 episode of arterial, venous or small vessel thrombosis in any organ or tissue confirmed objectively (imaging/histology) Where histology used, thrombosis should be present without overt vessel wall inflammation	*Macrovascular VTE*		Although the supplementary guidance notes to the modified Sapporo criteria do suggest taking other risk factors for thrombosis into account, there is no formal downgrading in the presence of risk factors for CVD or VTE The Sapporo criteria provide no weighting to thrombotic manifestations (any thrombotic manifestation counts as towards the diagnosis equally in the appropriate clinical context) Both guidelines emphasise the need to confirm thrombosis objectively
		VTE with other high-risk VTE profile	1 point	
		VTE without other high-risk VTE profile	3 points	
		Macrovascular arterial thrombosis		
		Arterial thrombosis with high-risk CVD profile	2 points	
		Arterial thrombosis without high-risk CVD profile	4 points	
		Microvascular Thrombosis		
		Any one of:		
		Livedo racemosa, livedoid vasculopathy, aPL nephropathy, pulmonary haemorrhage		
		Suspected	2 points	
		Confirmed (e.g. histology/imaging)	5 points	
		Confirmed adrenal haemorrhage/microvascular myocardial disease	5 points	
Clinical—obstetric	≥1 unexplained death of a morphologically normal fetus at ≥10 weeks' gestation *AND/OR* ≥1 birth of a morphologically normal neonate <34 weeks' gestation due to: (i) Eclampsia or severe pre-eclampsia OR (ii) Placental insufficiency *AND/OR* ≥3 consecutive spontaneous miscarriages <10 weeks' gestation with alternative maternal/paternal factors excluded (anatomical, hormonal, chromosomal)	≥3 consecutive pre-fetal (<10 weeks gestation) and/or early fetal (10–15 weeks +6-day gestation) death	1 point	As for thrombotic manifestations, the Sapporo criteria do not provide a weighting to obstetric manifestations
		Fetal death (16–33 weeks +6-day gestation) in the absence of	1 point	
		Pre-eclampsia with severe features AND		
		Placental insufficiency with severe features		
		Pre-eclampsia with severe features (<34 w gestation) OR	3 points	
		Placental insufficiency with:		
		Severe features (<34-week gestation) with/without fetal death		
		Pre-eclampsia with severe features (<34-week gestation) AND	4 points	
		Placental insufficiency with:		
		Severe features (<34-week gestation) with/without fetal death		
Clinical—other	None counting toward diagnosis	*Cardiac Valve*		Previously termed non-criterion manifestations of APS are incorporated into the diagnostic algorithm in the ACR/EULAR guidelines. These features are mentioned in the revised Sapporo criteria, but it is suggested that they are insufficiently specific to count towards the diagnosis
		Thickening	2 points	
		Vegetation	4 points	
		Haematological		
		Thrombocytopenia	2 points	

Criteria	Revised Sapporo criteria	ACR/EULAR APS classification criteria		Comments
Laboratory	Persistently positive LA detected according to ISTH guidelines. *AND/OR* Persistently positive IgG/IgM aCL at medium or high titre by ELISA *AND/OR* Persistently positive IgG/IgM aβ2GPI by ELISA	LA detected on:		The criteria for aPL persistence (detected on 2 occasions, 12 weeks apart) has not been altered Points are assigned for transient LA positivity in ACR/EULAR, but this by itself is insufficient for the diagnosis Weighting is applied to the combination of aPL seen to account for higher risk phenotypes (e.g. triple antibody positivity)
		One occasion	1 point	
		Persistently	5 points	
		Persistently positive aCL and/or aβ2GPI:		
		Moderate or high titre IgM aCL and/or aβ2GPI	1 point	
		Moderate (40–79 U/mL) titre IgG aCL and/or β2GPI	4 points	
		High titre (≥80 U/mL) IgG aCL OR aβ2GPI	5 points	
		High titre (≥80 U/mL) IgG aCL AND aβ2GPI	7 points	
Diagnosis	APS is classified as ≥1 clinical criterion and ≥1 laboratory criterion Clinical and laboratory criteria must be detected <5 years of each other	Single highest scoring feature from each domain is summed APS is classified as ≥3 points in clinical domains and ≥3 points in laboratory domains. Clinical and laboratory criteria must be detected <3 years of each other		

Abbreviations: aCL, anticardiolipin; aPL, antiphospholipid antibody; aβ2GPI, anti-beta2-glycoprotein I; CVD, cardiovascular disease; ELISA, Enzyme-linked immunosorbent assay; ISTH, International Society on Thrombosis and Haemostasis; LA, lupus anticoagulant; VTE, venous thromboembolism.

Br J Haematol. 2024 Jul 19.

Meta-analysis

25 studies. Early < 13 weeks; late < 24 weeks

Lupus anticoagulant (LAC) was associated with late RFL (**OR 7.79**, 95% CI 2.30-26.45)

IgG anticardiolipin antibodies (aCL), (all titres), were associated with
early (OR 3.56, 95% CI 1.48-8.59)
late (OR 3.57, 95% CI 2.26-5.65).

Restricting analysis to **moderate to high titres** (**OR 4.68**, 95% CI 2.96-7.40).

IgM aCL were associated with late RFL (**OR 5.61**, 95% CI 1.26-25.03).

anti-Beta2-glycoprotein I antibodies (OR 2.12, 95% CI 0.69-6.53). No association

Opatrny L, David M, Kahn SR, Shrier I, Rey E. Association between antiphospholipid antibodies and recurrent fetal loss in women without autoimmune disease: a metaanalysis. J Rheumatol. 2006 Nov;33(11):2214-21.

Obstetric APS

- Typically placental infarction and thrombosis of placental vessels
- Deposition of platelets and prostanoid imbalance – same mechanism as in pre eclampsia
- Thrombosis within the placenta does not explain all the pregnancy complications
- aPL reduce hCG release and inhibit trophoblast invasiveness

Pathophysiology of Obstetric APS

APS is characterised by poor placentation; non-thrombotic mechanisms may be more important than placental infarction

Placental thrombosis is not the main pathogenic pathway but rather defective placentation

interplay between:

- endothelial cell stimulation
- (secondary) platelet activation
- trophoblast impairment
- Toll-like receptor-induced innate immunity activation

Spaanderman & Ghossein-Doha **2018**

Meroni. Nat Rev Rheum 2018;

Viall & Chamley Autoimmu Rev 2015

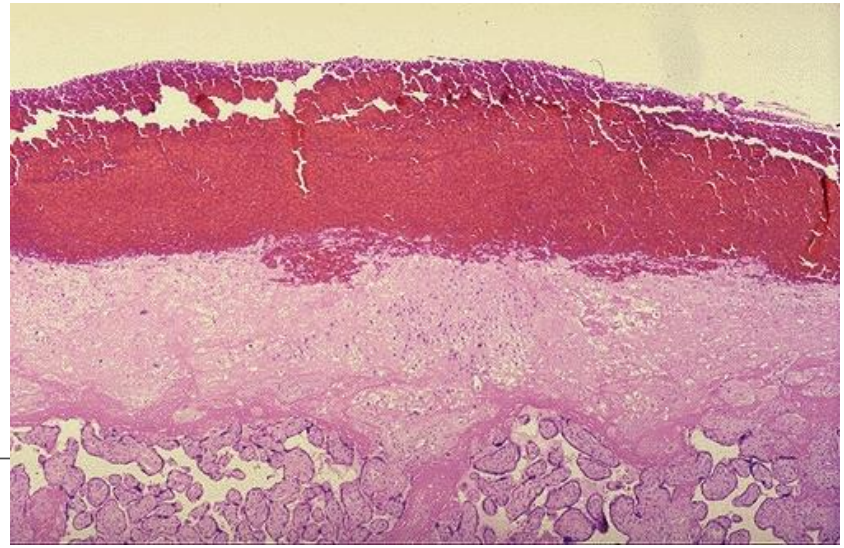
aPL mediated vasculopathy

- β2GPI is the main target Ag andβ2GPI dependent aPL are pathogenic
- Binding of Ab to trophoblasts inhibits proliferation. Poor differentiation
- Binding to decidual cells affects gene expression and initiates a proinflammatory response.
- Results in defective implantation and poor placentation
- Clinical manifestation: second trimester FGR
- aPL endocytosis → mitochondrial cytochrome C release → release of syncytial dangerous nuclear aggregates of microvesicles and exosomes.
- Anti-angiogenic effect – defective spiral artery modelling → Pre-eclampsia

Meroni. Nat Rev Rheum 2018

Fetal complications of APS

- Pregnancy loss- early and late, including 3rd trimester IUFD
- Pre-eclampsia and eclampsia / HELLP
- Intra uterine growth restriction
- Fetal hypoxemia
- Abruption



Phenotype is important

Retrospective study of 75 pregnancies in 47 women with APS

- 35 aspirin + heparin
- 36 aspirin alone
- 4 heparin alone
  - Corticosteroids in 38 pregnancies
  - Hx of vascular thrombosis in 49 pregnancies

Overall LB rate = 73%

Overall prematurity = 25%

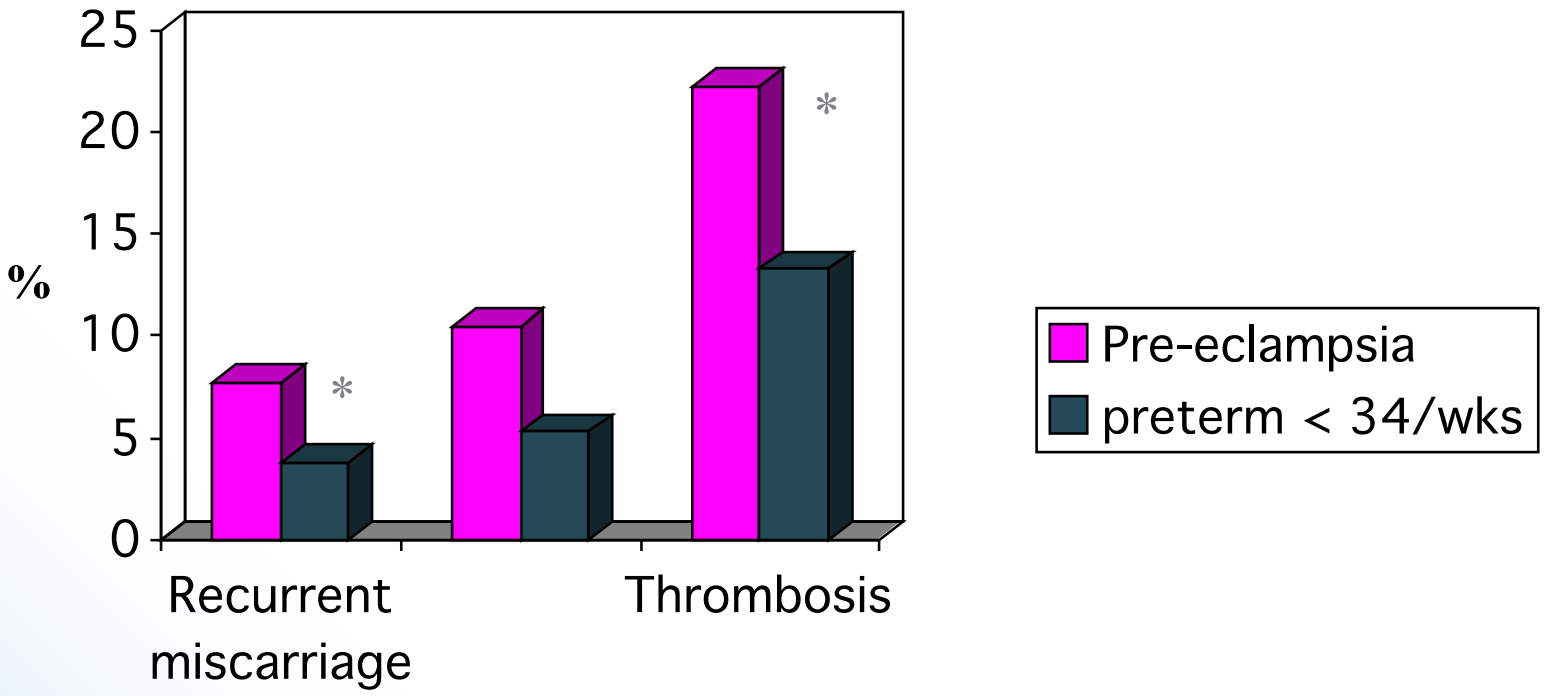
No Hx of thrombosis LB = 85%

Hx of thrombosis LB = 66%

Use of steroids correlated with PET / IUGR / severe prematurity

Huong et al. J Rheumatol 2001; 28: 2025-30

Pregnancy complications by classification of APS STH cohort (n= 90)



Bramham et al. Lupus 2010

Antiphospholipid antibodies do not a syndrome make

Stone S, Langford K, Nelson-Piercy C, et al. Lupus 2002; 11: 130-133.

Soh MC, Pasupathy D, Gray G, Nelson-Piercy C. Persistent antiphospholipid antibodies do not contribute to adverse pregnancy outcomes. J Rheumatology 2013.

	Controls (n=292	aPL (n=73)	APS (n=73)
ART (%)	6	23	12
Customized BW centile	44	51	29*
SGA (%)	11	6	27*
APS complications^	11	12 aOR^^ 1.3(0.6-2.9)	38*

^ Fetal loss>10/40, PET <34/40, SGA, IUD secondary to abruption

^^ adjusted for maternal age and comorbidities

LUPUS SCIENCE & MEDICINE™

Lupus anticoagulant is the main predictor of adverse pregnancy outcomes in aPL-positive patients: validation of PROMISSE study results

Cecile M Yelnik,[1,2] Carl A Laskin,[3] T Flint Porter,[4] D Ware Branch,[4] Jill P Buyon,[5] Marta M Guerra,[1] Michael D Lockshin,[1] Michelle Petri,[6] Joan T Merrill,[7] Lisa R Sammaritano,[1] Mimi Y Kim,[8] Jane E Salmon[1]

44 aPL-positive patients	Adverse pregnancy outcome	No adverse pregnancy outcome	P
LAC	69%	27%	0.01
APS	92%	45%	0.004
SLE	30%	39%	ns

No association between aCL aβ2GPI IgG or IgM positivity and APOs.

Yelnik et al 2016; Jan 12;3(1):e000131.

Belhocine *et al. Arthritis Research & Therapy* (2018) 20:249
https://doi.org/10.1186/s13075-018-1745-2

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Intrauterine fetal deaths related to antiphospholipid syndrome: a descriptive study of 65 women

Mériem Belhocine[1], Laetitia Coutte[1], Nicolas Martin Silva[2], Nathalie Morel[1], Gaëlle Guettrot-Imbert[1], Romain Paule[1], Claire Le Jeunne[1], Micaela Fredi[3], Michel Dreyfus[4], Jean-Charles Piette[5], Odile Souchaud-Debouverie[6], Catherine Deneux-Tharaux[7], Vassilis Tsatsaris[8], Emmanuelle Pannier[8], Véronique Le Guern[1] and Nathalie Costedoat-Chalumeau[1,9*]

Table 2 Antiphospholipid assays according to term at the intrauterine fetal death

	All patients[§] (*n* = 65)			Untreated patients[a] (*n* = 49)		
	IUFD < 18 weeks *n* = 16 (%)	IUFD ≥ 18 weeks *n* = 49 (%)	*P* value	IUFD < 18 weeks *N* = 10 (%)	IUFD ≥ 18 weeks *n* = 39 (%)	*P* value
Lupus anticoagulant	9 (56)	38 (78)	0.12	3 (30)	28 (72)	0.025
Anticardiolipin IgG	14 (88)	29 (59)	0.06	10 (100)	22 (56)	0.009
Anti-β2GP1 IgG	7(44)	24 (49)	NS	3 (30)	16 (41)	0.72
Triple- positive	6 (38)	17 (35)	NS	1 (10)	9 (23)	0.66

IUFD intrauterine fetal death, *weeks* weeks of gestation, *NS* not significant
[a]Patients who received no aspirin or low molecular weight heparin

35% had a triple-positive antibody profile

29% were diagnosed with SLE.

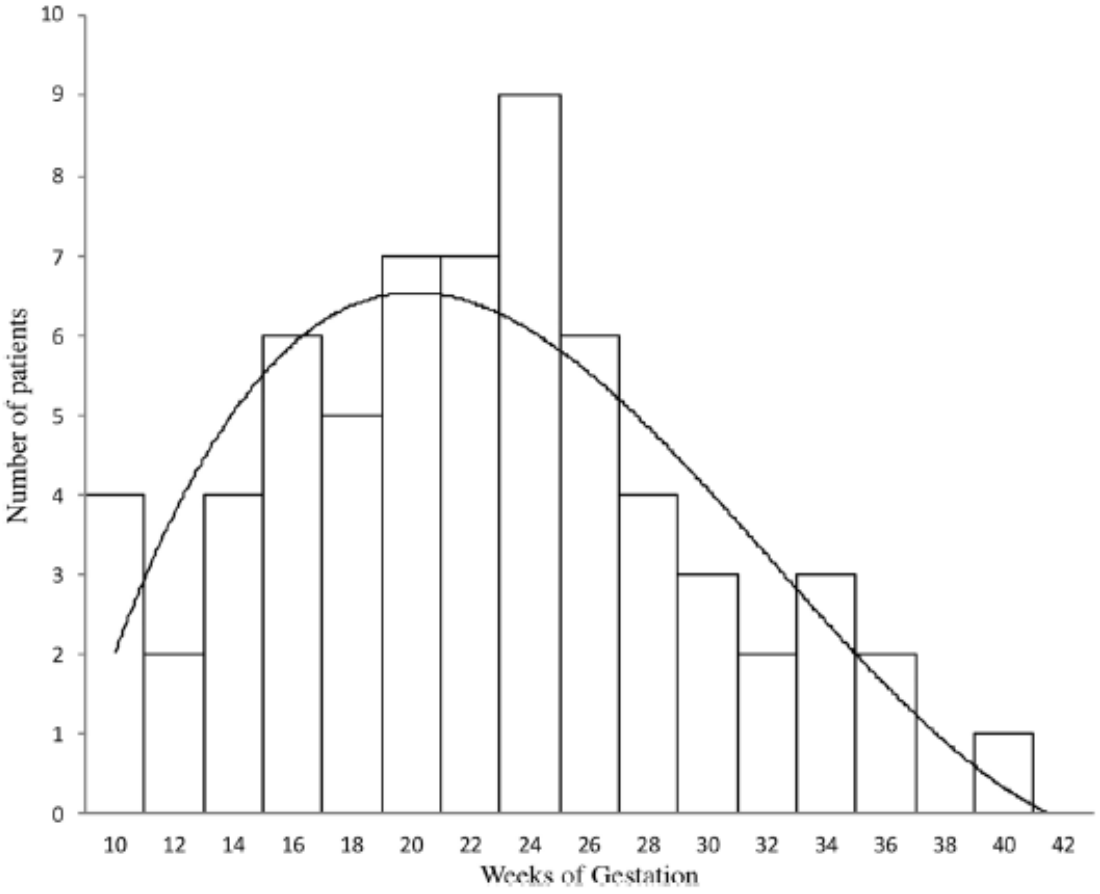
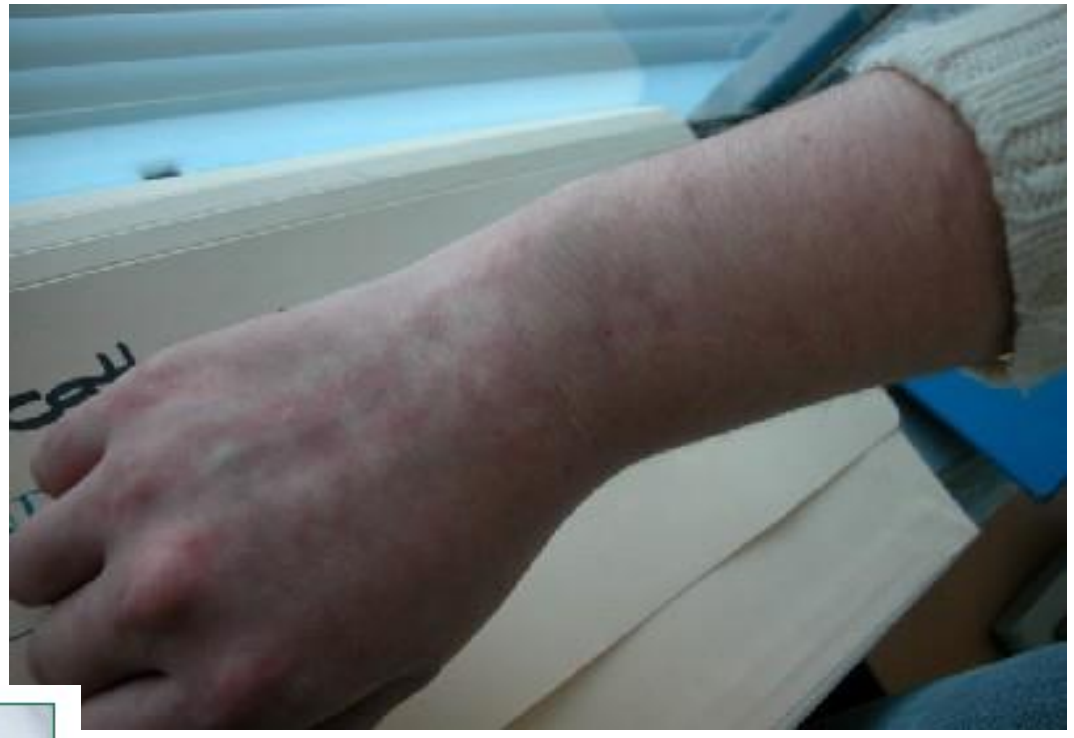


Fig. 2 Gestational term at intrauterine fetal death

IUFD occurred at median gestational age of 24 weeks (IQR 18–27)
maternal obstetric complications 16 women (25%)
preeclampsia (n = 12),
HELLP (n = 6),
and/or placental abruption (n = 5).



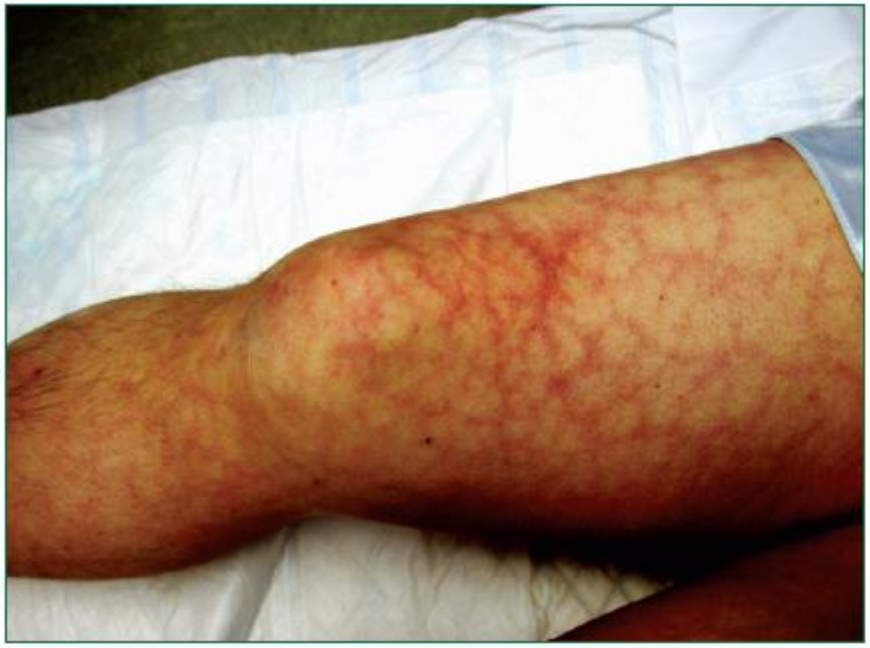


Figure 2: Livedo reticularis in a woman with antiphospholipid syndrome.

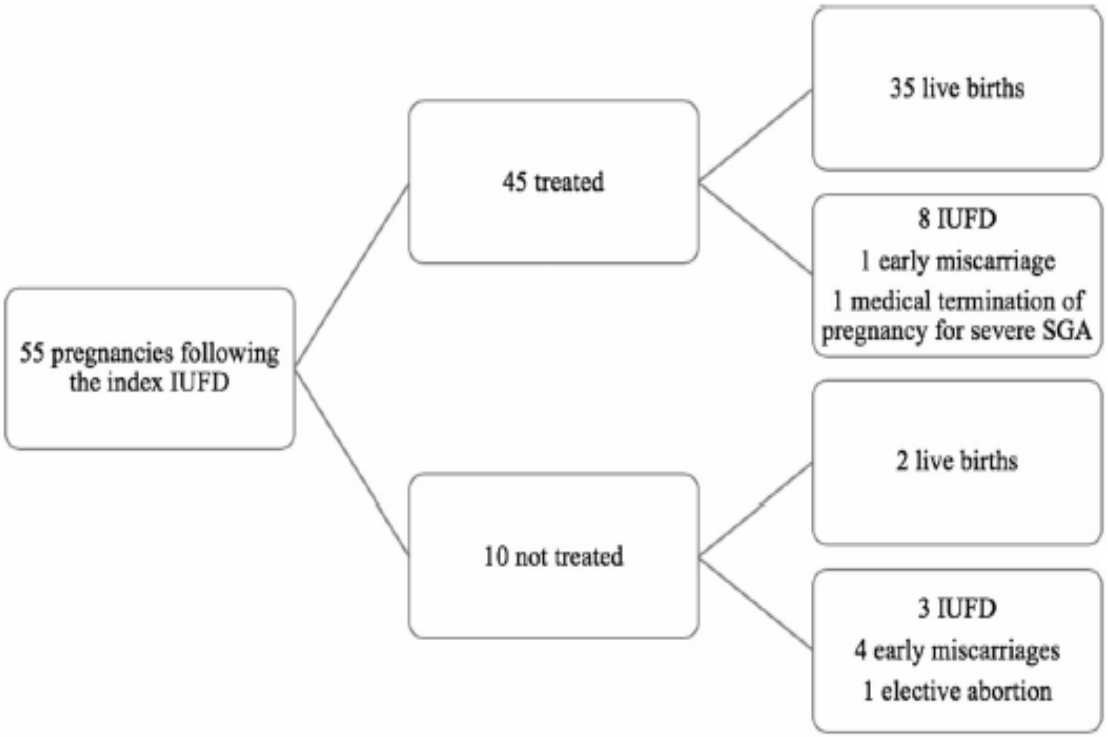


Fig. 3 Outcome of the pregnancies immediately following the index intrauterine fetal death (IUFD)

With treatment, most of the women successfully had at least one live birth.

54 women **(83%) had at least one live birth.**

EULAR recommendations for the management of antiphospholipid syndrome in adults

Maria G Tektonidou,[1] Laura Andreoli,[2] Marteen Limper,[3] Zahir Amoura,[4] Ricard Cervera,[5] Nathalie Costedoat-Chalumeau,[6] Maria Jose Cuadrado,[7] Thomas Dörner,[8] Raquel Ferrer-Oliveras,[9] Karen Hambly,[10] Munther A Khamashta,[11] Judith King,[12] Francesca Marchiori,[13] Pier Luigi Meroni,[14] Marta Mosca,[15] Vittorio Pengo,[16] Luigi Raio,[17] Guillermo Ruiz-Irastorza,[18] Yehuda Shoenfeld,[19] Ljudmila Stojanovich,[20] Elisabet Svenungsson,[21] Denis Wahl,[22] Angela Tincani,[2] Michael M Ward[23]

Tektonidou MG, et al. Ann Rheum Dis 2019;78:1296–1304.
doi:10.1136/annrheumdis-2019-215213

Obstetric APS	
8. In women with a high-risk aPL profile but no history of thrombosis or pregnancy complications (with or without SLE), treatment with LDA (75–100 mg daily) during pregnancy should be considered (5/D).	9.3 (1.5)
9. In women with a history of obstetric APS only (no prior thrombotic events), with or without SLE: A. With a history of ≥3 recurrent spontaneous miscarriages <10th week of gestation and in those with a history of fetal loss (≥10th week of gestation), combination treatment with LDA and heparin at prophylactic dosage during pregnancy is recommended (2b/B).	9.6 (0.9)
B. With a history of delivery <34 weeks of gestation due to eclampsia or severe pre-eclampsia or due to recognised features of placental insufficiency, treatment with LDA or LDA and heparin at prophylactic dosage is recommended considering the individual's risk profile (2b/B).	9.5 (0.8)
C. With clinical 'non-criteria' obstetric APS such as a the presence of two recurrent spontaneous miscarriages <10th week of gestation, or delivery ≥34 weeks of gestation due to severe pre-eclampsia or eclampsia, treatment with LDA alone or in combination with heparin might be considered based on the individual's risk profile (4/D).	8.9 (1.7)

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Mx of obstetric APS

In women with a history of obstetric APS only (no prior thrombotic events), with or without SLE:

A. With a history of ≥3 recurrent spontaneous miscarriages <10th week of gestation and in those with a history of fetal loss (≥10th week of gestation), **combination treatment with LDA and heparin at prophylactic dosage** during pregnancy is recommended (2b/B).

B. With a history of delivery <34 weeks of gestation due to eclampsia or severe pre-eclampsia or due to recognised features of placental insufficiency, treatment with **LDA or LDA and heparin at prophylactic dosage** is recommended considering the individual's risk profile (2b/B)

Recurrent Miscarriage

Green-top Guideline No. 17

Lesley Regan | Rajendra Rai | Sotirios Saravelos | Tin-Chiu Li | on behalf of the Royal College of Obstetricians and Gynaecologists

Recurrent miscarriage = 3 or more

- Women with recurrent miscarriage should be offered testing for acquired thrombophilia, particularly for lupus anticoagulant and anticardiolipin antibodies, prior to pregnancy. [Grade C]

- For women diagnosed with antiphospholipid syndrome, aspirin and heparin should be offered from a positive test until at least 34 weeks of gestation, following discussion of potential benefits versus risks. [Grade B] Aspirin and/or heparin should not be given to women with unexplained recurrent miscarriage. [Grade B]

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

Guidelines on the investigation and management of antiphospholipid syndrome

Deepa J. Arachchillage[1,2] | Sean Platton[3] | Kieron Hickey[4] | Justin Chu[5] | Matthew Pickering[2,6] | Peter Sommerville[7] | Peter MacCallum[8,9] | Karen Breen[10] | on behalf of the BSH Committee

- Women with APS should be recommended treatment with aspirin and LMWH from positive pregnancy test for the duration of the pregnancy (Grade 1B).
- Women with aPL should be recommended treatment with aspirin to reduce the risk of pre-eclampsia and fetal growth restriction (Grade 1B).
- Women with thrombotic APS who are anticoagulated with a VKA should switch to LMWH on confirmation of a positive pregnancy test (1B).
- Women with thrombotic APS who had been on a VKA, we suggest treatment dose LMWH throughout the pregnancy and post-partum period until switching back to VKA (2C).
- Women with APS who are breastfeeding and require anticoagulation should remain on either LMWH or warfarin (grade 1B).
- Prednisolone, IVIG and hydroxychloroquine treatments in women with obstetric complications despite aspirin and LMWH are suggested only on a case-by-case basis (1C).
- We suggest women with refractory obstetric APS who have poor pregnancy outcomes despite therapy should be referred to specialist centres with expertise in managing obstetric APS (2D).

Which aspirin dose?

75 mg

150 mg

Start with 75 mg, increase to 150 mg at 12 weeks

Consider bleeding risk with concomitant LMWH

many of these women will have started aspirin and LMWH at positive pregnancy test, there is a need to continue the antiplatelet and heparin therapy with consideration of increasing the dose of aspirin to 150 mg from 12 weeks' gestation.

Thromboprophylaxis in APS pregnancies

Recommendations	
D. With obstetric APS treated with prophylactic dose heparin during pregnancy, continuation of heparin at prophylactic dose for 6 weeks after delivery should be considered to reduce the risk of maternal thrombosis (4/C).	9.5 (0.9)
10. In women with 'criteria' obstetric APS with recurrent pregnancy complications despite combination treatment with LDA and heparin at prophylactic dosage, increasing heparin dose to therapeutic dose (5/D) or addition of HCQ (4/D) or low-dose prednisolone in the first trimester (4/D) may be considered. Use of intravenous immunoglobulin might be considered in highly selected cases (5/D).	8.7 (1.7)
11. In women with a history of thrombotic APS, combination treatment of LDA and heparin at therapeutic dosage during pregnancy is recommended (4/C).	9.8 (0.5)

Tektonidou MG, et al. Ann Rheum Dis 2019;78:1296–1304.
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Secondary thromboprophylaxis in APS	
4. In patients with definite APS and first venous thrombosis: A. Treatment with VKA with a target INR 2–3 is recommended (1b/B).	9.9 (0.3)
B. Rivaroxaban should not be used in patients with triple aPL positivity due to the high risk of recurrent events (1b/B). DOACs could be considered in patients not able to achieve a target INR despite good adherence to VKA or those with contraindications to VKA (eg, allergy or intolerance to VKA) (5/D).	9.1 (1.3)
C. In patients with unprovoked first venous thrombosis, anticoagulation should be continued long term (2b/B).	9.9 (0.3)
D. In patients with provoked first venous thrombosis, therapy should be continued for a duration recommended for patients without APS according to international guidelines (5/D). Longer anticoagulation could be considered in patients with high-risk aPL profile in repeated measurements or other risk factors for recurrence (5/D).	8.9 (1.4)
5. In patients with definite APS and recurrent venous thrombosis despite treatment with VKA with target INR of 2–3: A. Investigation of, and education on, adherence to VKA treatment, along with frequent INR testing, should be considered (5/D).	9.6 (0.8)
B. If the target INR of 2–3 had been achieved, addition of LDA, increase of INR target to 3–4 or change to LMWH may be considered (4–5/D).	9.4 (0.7)
6. In patients with definite APS and first arterial thrombosis: A. Treatment with VKA is recommended over treatment with LDA only (2b/C).	9.4 (0.8)
B. Treatment with VKA with INR 2–3 or INR 3–4 is recommended, considering the individual's risk of bleeding and recurrent thrombosis (1b/B). Treatment with VKA with INR 2–3 plus LDA may also be considered (4/C).	9.0 (1.3)
C. Rivaroxaban should not be used in patients with triple aPL positivity and arterial events (1b/B). Based on the current evidence, we do not recommend use of DOACs in patients with definite APS and arterial events due to the high risk of recurrent thrombosis (5/D).	9.4 (0.9)
7. In patients with recurrent arterial thrombosis despite adequate treatment with VKA, after evaluating for other potential causes, an increase of INR target to 3–4, addition of LDA or switch to LMWH can be considered (4–5/D).	9.3 (1.1)

Thromboprophylaxis in women with previous VTE and / or thrombophilia

Very high risk	Previous VTE on long-term oral anticoagulant therapy	Recommend antenatal high-dose LMWH and at least 6 weeks' postnatal LMWH or until switched back to oral anticoagulant therapy
	Antithrombin deficiency Antiphospholipid syndrome with previous VTE	*These women require specialist management by experts in haemostasis and pregnancy*
High risk	Any previous VTE (except a single VTE related to major surgery)	Recommend antenatal and 6 weeks' postnatal prophylactic LMWH
Intermediate risk	Asymptomatic high-risk thrombophilia homozygous factor V Leiden/compound heterozygote Protein C or S deficiency	Refer to local expert Consider antenatal LMWH Recommend postnatal prophylactic LMWH for 6 weeks
	Single previous VTE associated with major surgery without thrombophilia, family history or other risk factors	Consider antenatal LMWH (but not routinely recommended) Recommend LMWH from 28 weeks of gestation and 6 weeks' postnatal prophylactic LMWH
Low risk	Asymptomatic low-risk thrombophilia (prothrombin gene mutation or factor V Leiden)	Consider as a risk factor and score appropriately (see Appendix III) Recommend 10 days' if other risk factor postpartum (or 6 weeks' if significant family history) postnatal prophylactic LMWH

Thromboprophylaxis for APS in pregnancy

In women with a history of thrombotic APS, combination treatment of LDA and heparin at **therapeutic** dosage during pregnancy is recommended (4/C).

But provoked ≠ unprovoked ≠ recurrent

Three options:

- Prophylactic
- High prophylactic (ie BD)
- Treatment dose (eg. 1 mg / kg / bd enoxaparin

Suggested regimen

Thrombotic history	LMWH dose in pregnancy
Provoked x 1 (not on longterm VKA) Especially if low risk apl titre	Prophylactic throughout pregnancy and for 6 weeks post partum
Unprovoked (on longterm VKA)	High dose prophylactic or therapeutic
Recurrent VTE (on longterm VKA)	High dose prophylactic or therapeutic
Arterial thrombosis (VKA INR 3-4)	Therapeutic LMWH

Risk of VTE after obstetric APS

126 patients with obstetric APS

Median FU of 17 years

63% of women developed thrombosis after a mean time of 7.6 years (4.9 per 100 patient years), which was independently associated with multiple aPL positivity

Those who went on to have thrombosis were more frequently positive for lupus anticoagulant (alone or with other aPL) (42 versus 35, *P* = 0.004)

De Jesus BJOG 2018

Eular: Research recommendations

Obstetric APS.

- Controlled studies of the efficacy and safety of treatment with LDA and heparin versus treatment with LDA, heparin and HCQ in women with a history of recurrent obstetric complications.
- Efficacy of 150 mg daily versus 100 mg daily of aspirin.
- Safety and efficacy of statins in pregnant women with APS who develop pre-eclampsia despite treatment with LDA and heparin.

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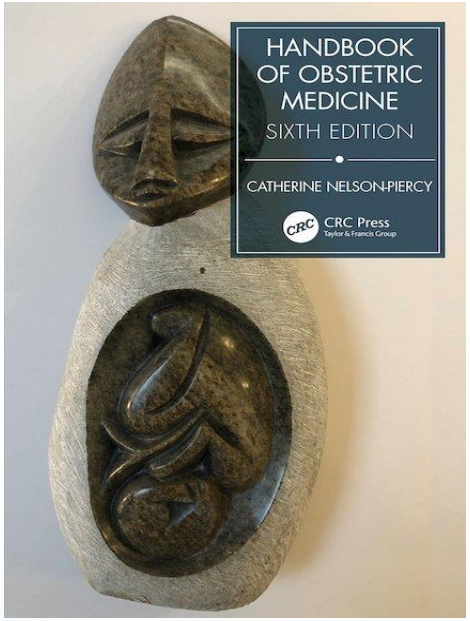
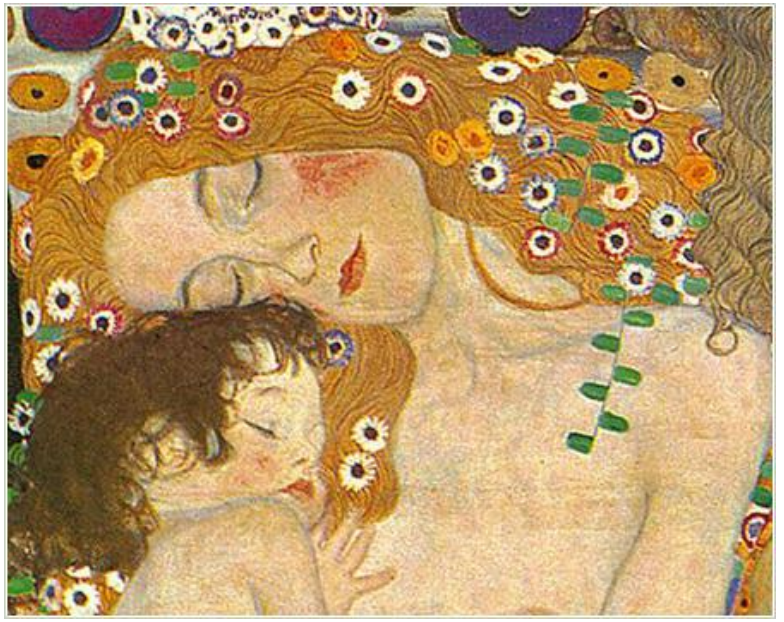
Thank you for your attention!





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