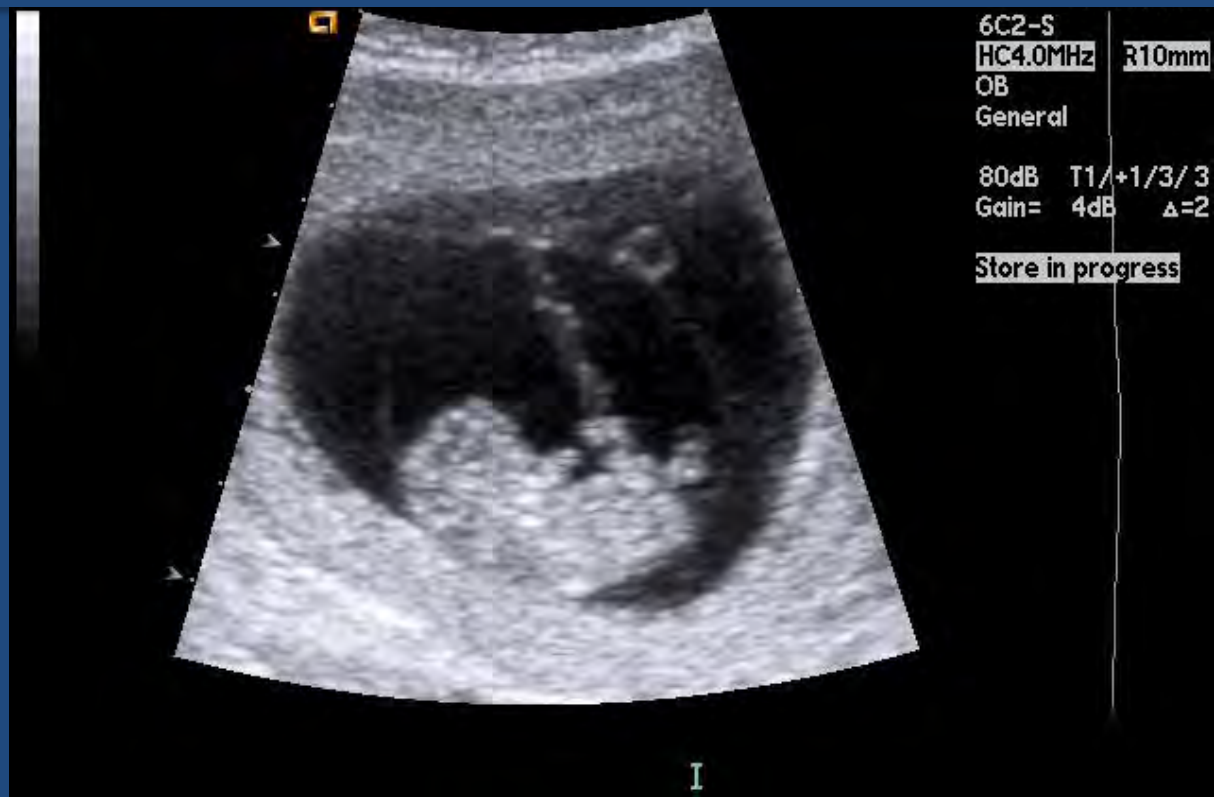
Antiphospholipid Syndrome: Who Should Be Tested?

Ware Branch, MD



Antiphospholipid Syndrome
2006 International Criteria

- **Clinical Criteria**
  - **Thrombosis (venous or arterial)**
    - **Confirmed by objective validated criteria**
    - **Includes small vessel thrombosis but not superficial thrombosis**

Antiphospholipid Syndrome
2006 International Criteria

- **Clinical Criteria**
  - **Obstetric criteria**
    - **Early pregnancy:**
      - **Three or more consecutive miscarriages < 10 weeks gestation**
    - **Late 1st – 3rd trimester:**
      - **Fetal death (at or beyond 10 weeks)**
      - **Delivery < 34 weeks gestation for eclampsia, severe preeclampsia, or placental insufficiency**

Antiphospholipid Syndrome: Who Should Be Tested?

- Thrombosis – arterial or venous
- Recurrent early miscarriage
- Fetal death
- Early delivery for gestational hypertensive disease or placental insufficiency

Antiphospholipid Syndrome
2006 International Criteria

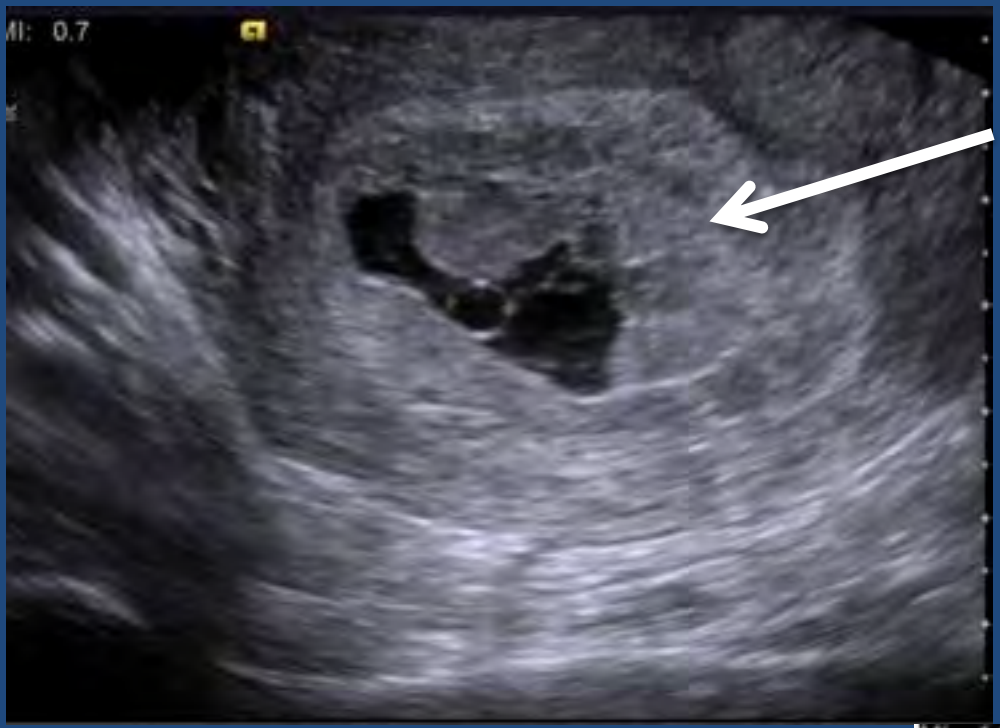
- **Laboratory Criteria**
  - Lupus anticoagulant
  - Anticardiolipin antibodies (IgG or IgM >40 or > 99th percentile)
  - Anti-β_2-glycoprotein I antibodies (IgG or IgM > 99th percentile)
  - *Positive on 2 or more occasions at least 12 weeks apart*

Antiphospholipid Syndrome

- **Clinical Criteria**
  - **Thrombosis (venous or arterial)**
    - **Strongest risk factor is LA**
      - **Case-control study of VTE < 70 yrs old**
        - **» 3.1% with VTE had LA vs 0.9% of controls**
      - **Case-control study of stroke in women < 50 yrs old**
        - **» 17% with stroke had LA vs 0.7% of controls**

Obstetric Criteria for Antiphospholipid Syndrome

- **Early pregnancy criterion**
  - **Three or more consecutive miscarriages < 10 weeks gestation (recurrent early miscarriage)**
    - **Other "causes" should be excluded**
  - **REM relatively common (about 1 in 200 women)**
  - **Persistently "positive" aPL in 5% - 15% (?)**

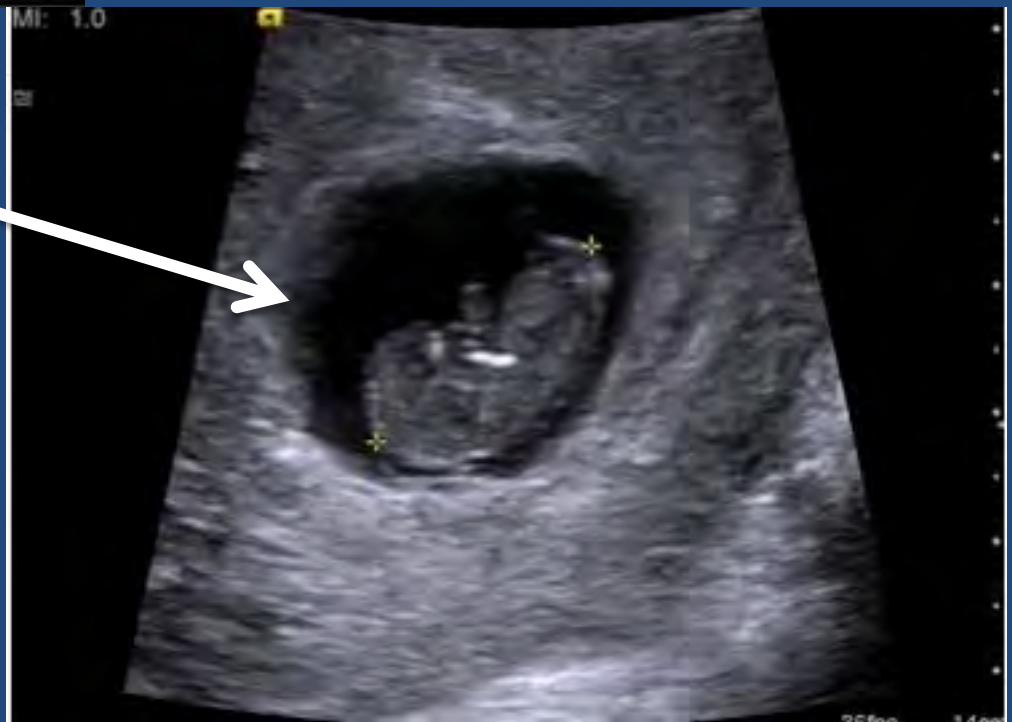


Pre-embryonic demise (anembryonic pregnancy)

- Amniotic sac and yolk sac seen
- No visible embryo
- Pregnancy failure < 6 weeks

Embryonic demise

- Amniotic sac and yolk sac seen
- Visible embryo with no cardiac activity
- CRL c/w 8 weeks 6 days



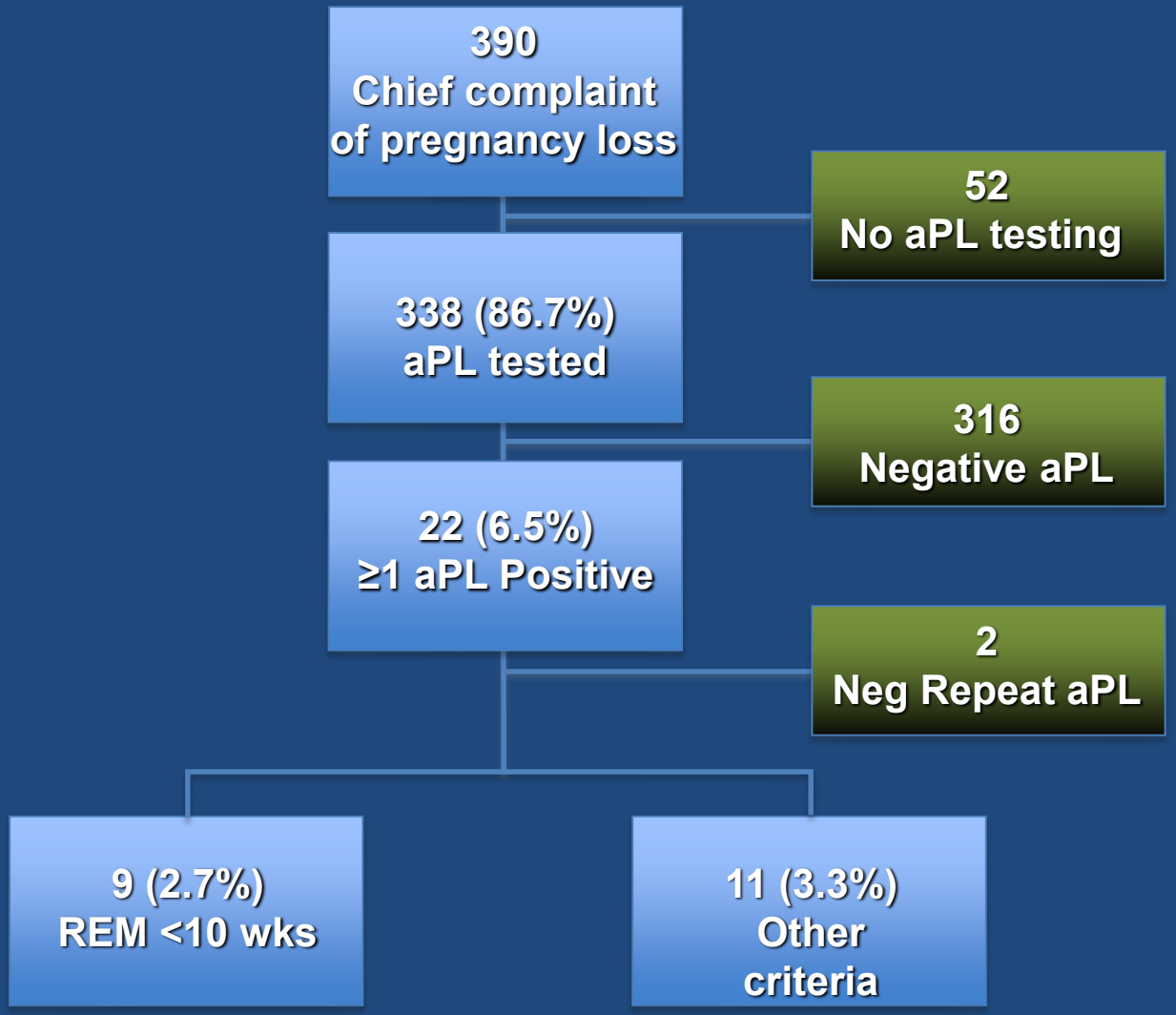
Pre-embryonic and Embryonic losses (<10 weeks gestation)

- Karyotype abnormalities occur in
  - 50% of sporadic early abortuses
  - 25%-60% of recurrent abortuses

Type	Approximate proportion of abnormal karyotypes
Aneuploidy	
Autosomal trisomy	52%
Autosomal monosomy	<1%
45, X	19%
Triploidy	16%
Tetraploidy	6%
Other	7%

Antiphospholipid Antibodies and Pregnancy Loss

University of Utah and Intermountain Healthcare



Patient Demographics

	≥2 REM n=9	SLE and/or VTE n=8	IUFD (>10 wks) N=3
Maternal age (mean±S.D.)	30.1±6.6	29.9±4.8	34.7±2.5
Lupus anticoagulant	0	1	0
Anticardiolipin Ab IgG	2	0	0
Anticardiolipin Ab IgM	2	0	0
Anti-β2 glycoprotein 1 IgG	2	0	0
Anti-β2 glycoprotein 1 IgM	2	0	1
Multiple antibodies	1	7 (all with LAC)	2

* 6/9 REM patients, 6/8 SLE/VTE patients, and 2/3 IUFD patients had repeat testing

Subsequent Adverse Outcomes

		Subsequent Adverse Pregnancy Outcome		
Clinical History	No. (%)	Yes	No	p-value*
REM (≥2)	9 (2.7)	0	6	Ref.
EM and other APS criteria	11(3.3)	5	2	0.021
-SLE and/or VTE	8 (2.4)	4	1	0.015
-IUFD	3 (0.9)	1	1	0.250

*Fisher's exact test

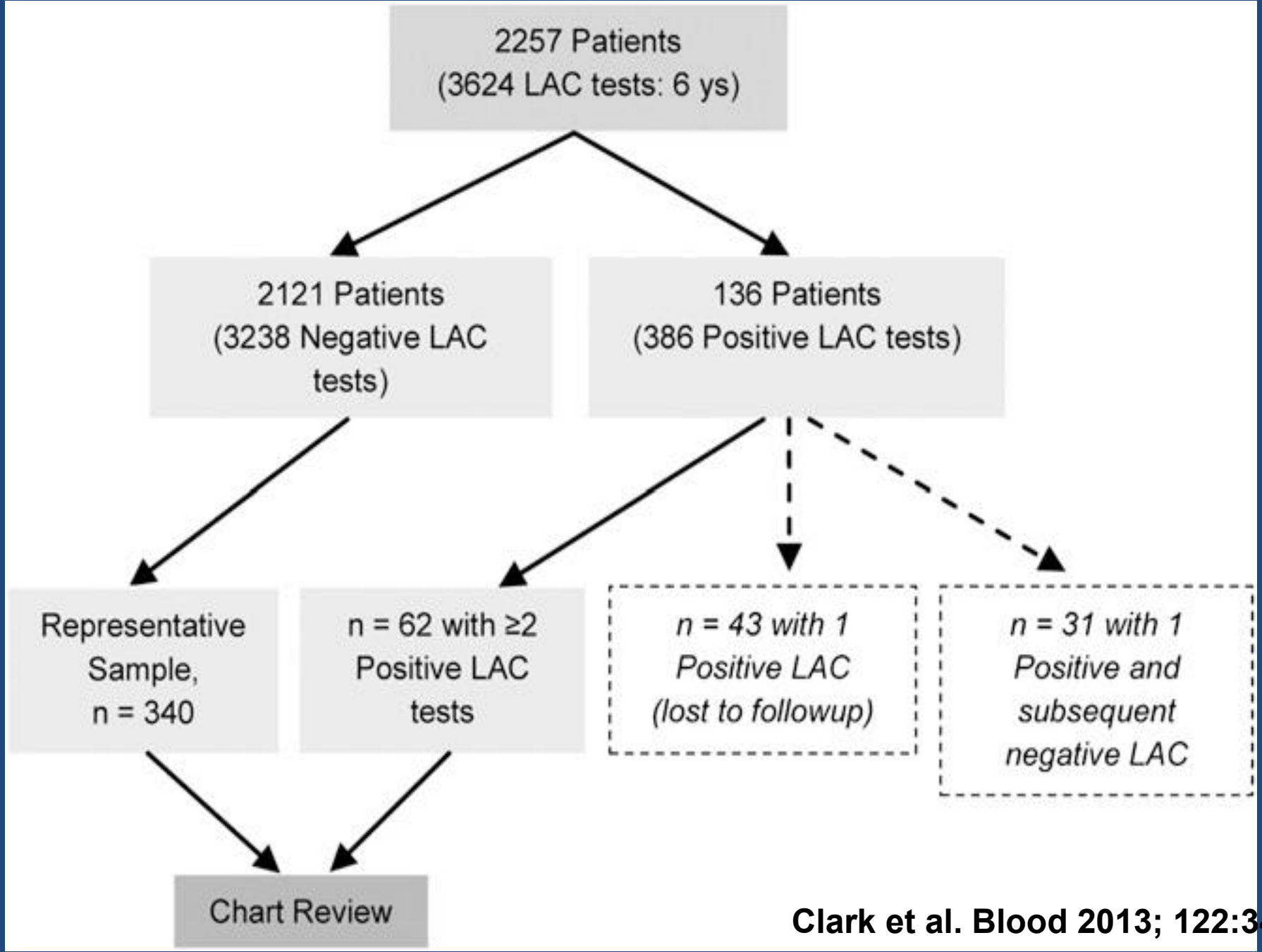
Subsequent Adverse Pregnancy Outcome was defined as one or more of the following:

- Early miscarriage (<10 weeks gestation)
- Fetal demise (≥10 weeks gestation)
- Delivery <34 weeks for either preeclampsia or placental insufficiency
- Venous thromboembolism

LA in Women with Recurrent Miscarriage, SLE, & APS

- Laboratory database study
  - All patients who tested positive for LAC at least twice between January 2005 and February 2011
    - From a tertiary clinic that sees 250 new patients annually with recurrent pregnancy loss, in addition to hundreds of patients with SLE and/or APS
- Random selection of LAC-negative patients for comparison
- LA testing: dPT, DRVVT, PTT-LA, and KCT

Clark et al, Blood 2013; 122:341



Clark et al. Blood 2013; 122:341

LA in Women with Recurrent Miscarriage, SLE, & APS

Distribution of diagnoses among LA positive and LA negative patients			
Diagnosis	LA Negative, N=340	LA Positive, N=62	P (95% CI)
SLE	66 (19.4%)	13 (21%)	NS
Primary APS	0	24 (38.7%)	<0.001 (0.322-0.452)
SLE/APS	3 (0.9%)	13 (21%)	<0.001 (0.147-0.255)
REM	238 (70.0)	5 (8.0%)	<0.001 (0.489-0.755)
Other	33 (9.7%)	7 (11.3)	NS

Clark et al, Blood 2013; 122:341

Obstetric APS
More Controversies than Certainties?

- At least 2 experienced centers find very few women with REM and repeatedly positive LA or medium-to-high-titer aPL
  - Patient selection/population?
  - Laboratory issues?
  - What about lower immunoassay titers?

Recurrent Pregnancy in Women with Antiphospholipid Antibodies

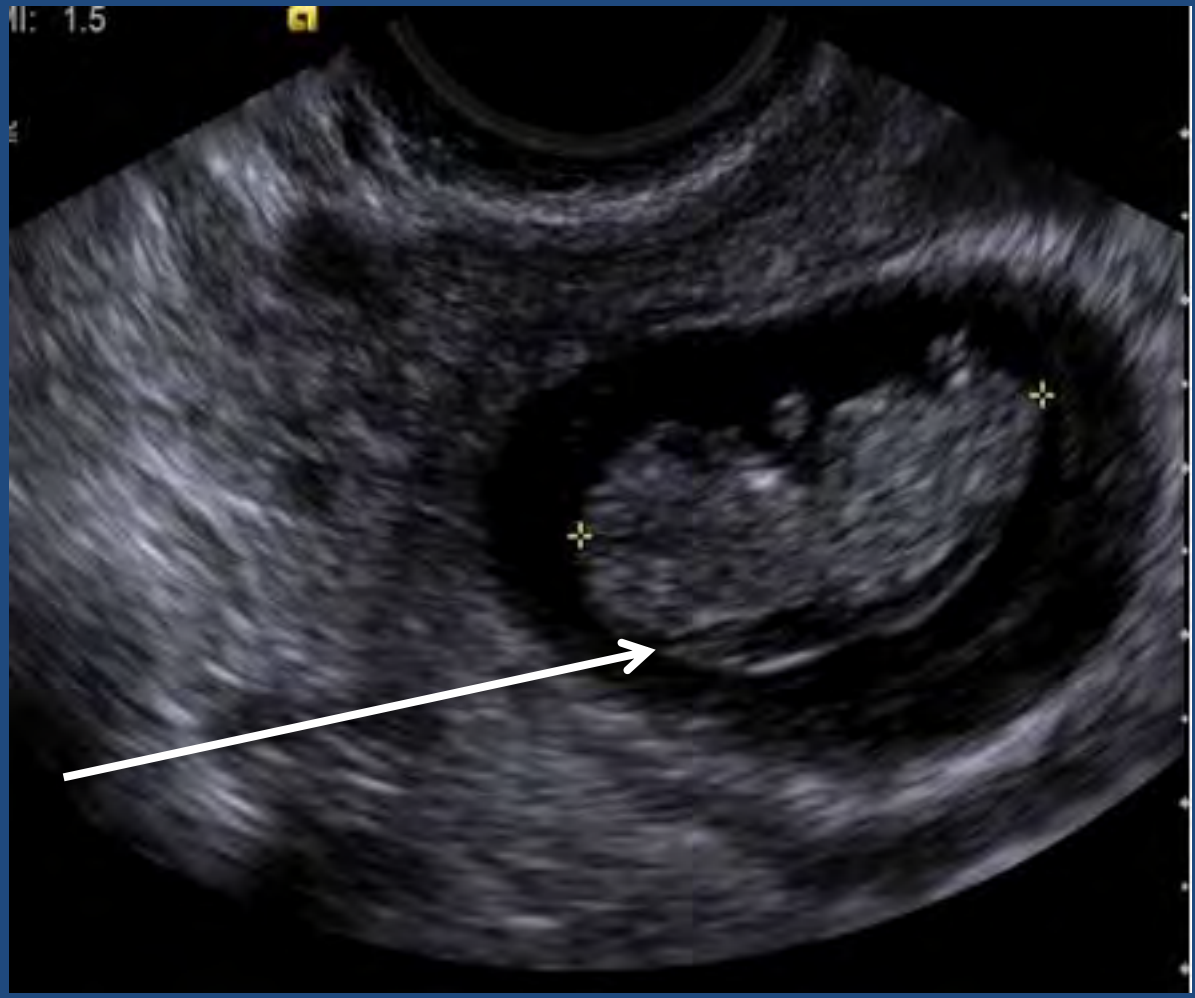
- Secondary analysis of the EAGeR trial comparing pre-conception LDA vs placebo in women with prior pregnancy loss
  - Pre-conception aPL testing in 868 women
    - 576 became pregnant, 433 (76%) had live births, and 137 (24%) had pregnancy loss

Recurrent Pregnancy in Women with Antiphospholipid Antibodies

- 21% positive for any aPL had pregnancy loss vs 24% negative for aPL (aOR 0.79 (0.31-1.65)
- Of 137 women with pregnancy loss
  - 6 (4.4%) were positive for any aPL
    - all IgM isotypes

Fetal death

- Amniotic sac and yolk sac seen
- Visible fetus with no cardiac activity
- CRL c/w 10 weeks 2 days
- Posterior sonolucency c/w cystic hygroma



Stillbirth Collaborative Research Network (SCRN)

- Population-based case-control study of stillbirths and term livebirths
  - 59 hospitals in 5 states
  - 582 stillbirths (≥ 20 weeks)
  - 1,547 livebirths
- Stored maternal sera assayed for IgG and IgM anticardiolipin (aCL) and anti-β_2-glycoprotein 1 (aβ_2GP1)
  - Positive defined as ≥ 20

Silver et al, Obstet Gynecol 2013

Stillbirth Collaborative Research Network

- Maternal history
  - Of 56 mothers with stillbirth and at least one positive test for aPL antibodies:
    - 1 (1.8%) had a history of thrombosis
    - None had SLE or other frank autoimmune disease
    - 22 (39.3%) had NO history of prior pregnancy loss, thrombosis, SLE, SGA fetus, or preeclampsia

Silver et al, Obstet Gynecol, submitted

Abnormal aPL in Non-Anomalous Stillbirths and Term Livebirths

Antibody	Stillbirths	Livebirths	Adjusted OR (95% CI)
Weighted sample size (N)	387	1,063	
IgG aCL	4.8%	1.0%	4.16 (1.84, 9.40)
IgM aCL	5.0%	3.0%	1.68 (0.88, 3.21)
IgG anti-β_2-GP1	1.8%	0.6%	2.88 (0.99, 8.35)
IgM anti-β_2-GP1	3.1%	1.9%	1.31 (0.59, 2.89)
≥ 1 antibody	11.3%	5.9%	1.93 (1.24, 2.99)

Silver et al, Obstet Gynecol 2013

Stillbirth Collaborative Research Network

- Of the 53 non-anomalous stillbirth pregnancies associated with a positive aPL result:
  - 7 (14%) had APS as the probable cause of stillbirth based on INCODE criteria

Silver et al, Obstet Gynecol 2013

Obstetric Criteria for Antiphospholipid Syndrome

- **Delivery < 34 weeks gestation due to eclampsia, severe preeclampsia, or placental insufficiency**
  - **HELLP syndrome a manifestation of severe preeclampsia**

Obstetric Criteria for Antiphospholipid Syndrome

- **Delivery < 34 weeks gestation due placental insufficiency – *the obstetrician's judgment call***
  - **Abnormal or non-reassuring fetal surveillance test(s), e.g. a non-reactive NST**
  - **Abnormal Doppler flow velocimetry waveform analysis**
  - **Oligohydramnios, e.g. an amniotic fluid index of 5 cm or less**
  - **Birth weight less than the 10th percentile for the gestational age**

PREPI
(PREeclampsia and Placental Insufficiency)

- Objective: To prospectively collect aPL and determine the relationship between aPL and severe preeclampsia (PE) or placental insufficiency (PI)
- Cases (111): Women delivered for severe PE or PI prior to 36 weeks
- Controls (77): Women without PE or PI, matched for age, gestational age at time of collection, and parity
- Assays: lupus anticoagulant, anti-cardiolipin (aCL) antibodies (igM and IgG), and anti-β2-glycoprotein-I antibodies (aβ2-g-I) (IgM and IgG)
  - ≥40 units used as test positive for aCL and aβ2-g-I
  - Return visit in 12 weeks if positive

PREPI Results

- Any aPL positive in 9% of cases and 1% of controls, OR 7.1 (95% CI 0.97-313.5)
  - Of positive aPL cases: 7/10 LA, 5/10 aCL, 2/10 aβ2-g-I
  - PE cases: 8/60 aPL positive
  - PI cases: 2/10 positive
- If using ≥20 units as definition of positive aCL or aβ2-g-I:
  - 13/111 (12%) of cases positive and 1/73 (1%) of controls, OR 9.6 (95% CI 1.4-411.4)

PREPI Results

Table 1. Positive aPL in cases and controls.

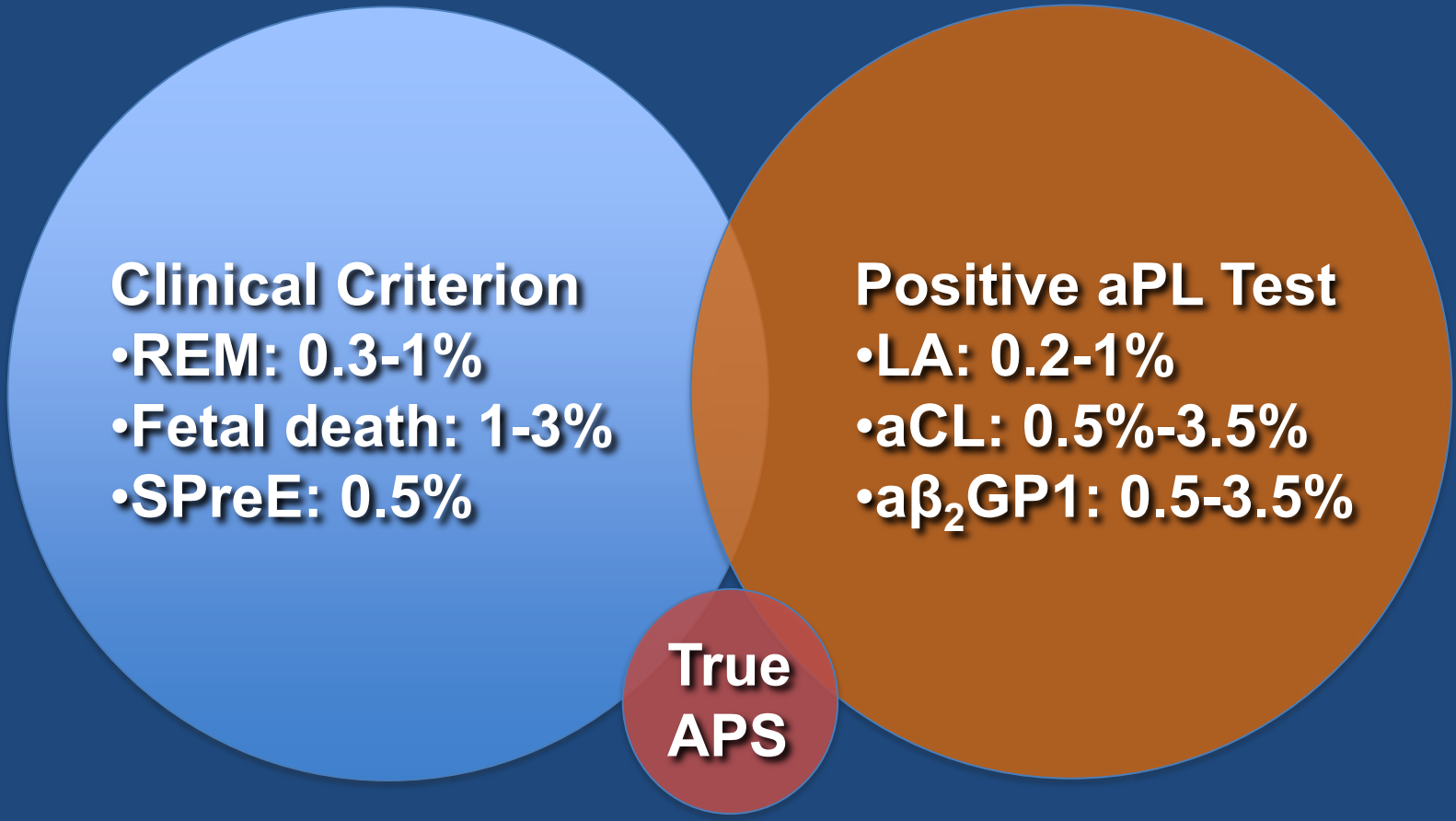
	Cases			Controls (n=77)	OR
	Preeclampsia (n=60)	Placental Insufficiency (n=51)	Combined (n=111)		
Any aPL positive	8	2	10	1	7.1 (0.97-313.5)
LA positive	5	2	7	1	4.8 (0.60-221.35)
aCL positive	4	1	5	0	--
aβ2-g-I positive	1	1	2	0	--

PREPI results

- Of 10 cases with one positive sample, 4 have had repeat testing (all consistent)
  - 2 were only positive on retesting of stored initial sample
  - 2 have been unable to be reached
  - 2 were not due yet at time of data collection

Obstetric APS

More Controversies than Certainties?



Antiphospholipid Syndrome
2006 International Criteria

- **Other Features associated with APS**
  - **Heart valve disease**
  - **Livedo reticularis**
  - **Nephropathy**
  - **Neurological manifestations**
  - ***Immune Thrombocytopenia***
  - ***False positive STS***
  - ***Warm anti-erythrocyte antibodies***

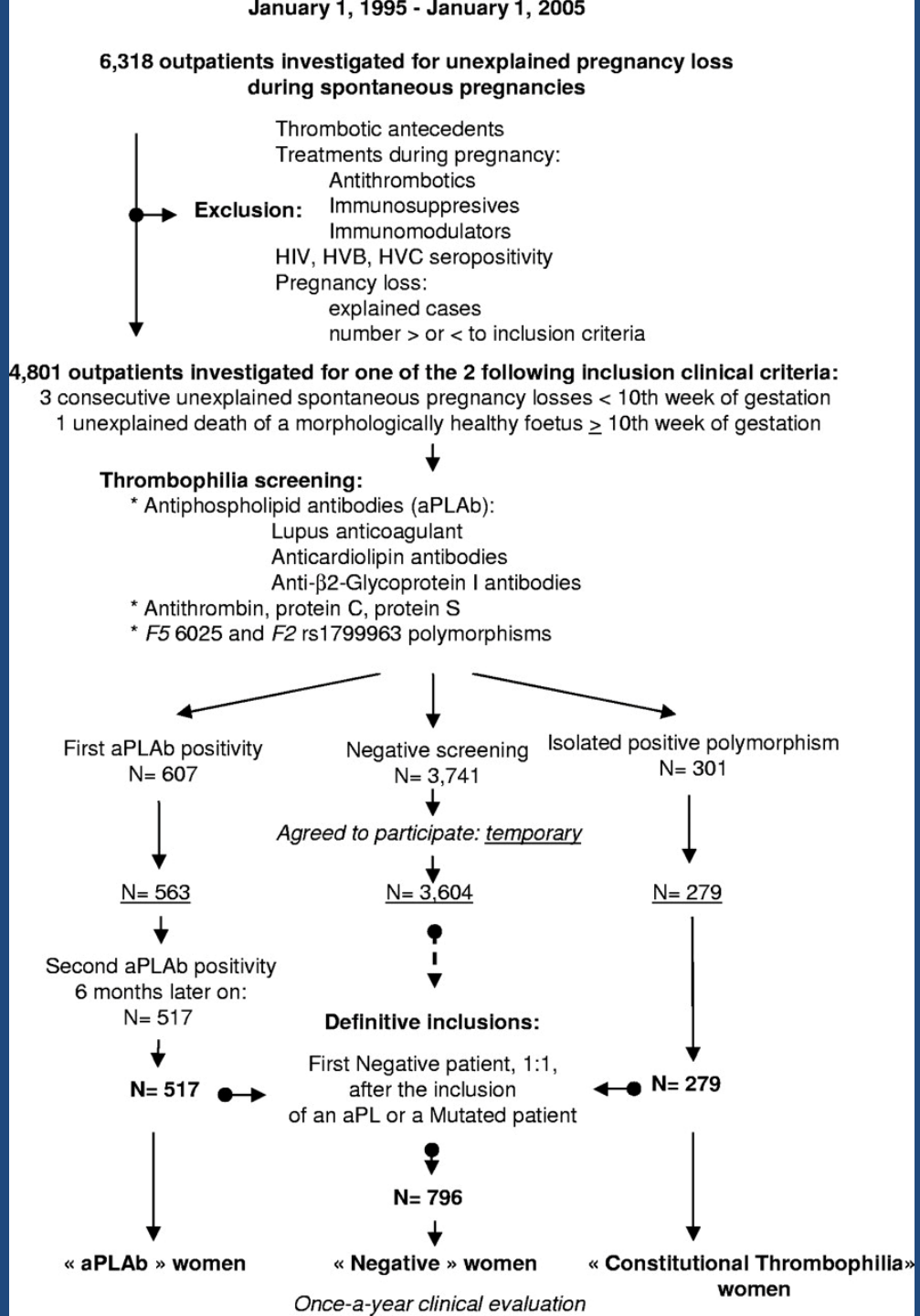
Why Identify and Treat Women with APS?

- To decrease the likelihood of maternal adverse outcome
  - Thrombosis, including thrombotic stroke
  - Adverse consequences of severe preeclampsia
- To decrease the likelihood of adverse fetal outcome?
  - Early miscarriage?
  - Fetal death?
  - Complications of prematurity?

Antiphospholipid Syndrome
Obstetric → Thrombotic?

- 10 year observational study of 1,592 women without prior thrombosis who had
  - 3 consecutive SABs prior to 10 weeks, or
  - 1 FD at or beyond 10 weeks
  - Tested for persistently + aPL
    - + aPL subjects advised to take LDA
    - Estrogen contraceptives avoided
    - Subsequent pregnancies treated with LMWH
  - Constitutional thrombophilia = FVL or PT mutation
    - Women with AT, PC, PS deficiencies, abn fibrinogen, or JAK2 V617F mutation excluded

Gris et al, Blood 2012; 119:2624-32


January 1, 1995 - January 1, 2005
6,318 outpatients investigated for unexplained pregnancy loss during spontaneous pregnancies
Exclusion:
Thrombotic antecedents
Treatments during pregnancy:
Antithrombotics
Immunosuppresives
Immunomodulators
HIV, HVB, HVC seropositivity
Pregnancy loss:
explained cases
number > or < to inclusion criteria
4,801 outpatients investigated for one of the 2 following inclusion clinical criteria:
3 consecutive unexplained spontaneous pregnancy losses < 10th week of gestation
1 unexplained death of a morphologically healthy foetus ≥ 10th week of gestation
Thrombophilia screening:
* Antiphospholipid antibodies (aPLAb):
Lupus anticoagulant
Anticardiolipin antibodies
Anti-β2-Glycoprotein I antibodies
* Antithrombin, protein C, protein S
* F5 6025 and F2 rs1799963 polymorphisms
First aPLAb positivity
N= 607
Negative screening
N= 3,741
Isolated positive polymorphism
N= 301
Agreed to participate: temporary
N= 563
N= 3,604
N= 279
Second aPLAb positivity
6 months later on:
N= 517
Definitive inclusions:
N= 517
First Negative patient, 1:1,
after the inclusion
of an aPL or a Mutated patient
N= 279
N= 796
« aPLAb » women
« Negative » women
« Constitutional Thrombophilia» women
Once-a-year clinical evaluation

Outcome	Group	N (%)	Annualized Rates (range)	Adj Hazards Ratio
DVT	Negative	33 (4.2%)	0.43% (0.30-0.61)	Ref
	Constitutional thrombophilia	15 (5.4%)	0.57% (0.32-0.93)	1.33 (0.73-2.46)
	aPL	68 (13.2%)	1.46% (1.15-1.82)	1.85 (1.50-2.28)
PE	Negative	9 (1.13%)	0.12 (0.05-0.22)	Ref
	Constitutional thrombophilia	3 (1.08%)	0.11 (0.02-0.33)	0.98 (0.26-3.61)
	aPL	20 (3.87%)	0.43 (0.26-0.66)	1.93 (1.30-2.87)
Stroke	Negative	3 (0.38%)	0.04 (0.01-0.12)	Ref
	Constitutional thrombophilia	1 (0.36%)	0.04 (0.01-0.21)	0.97 (0.10-9.26)
	aPL	8 (1.55%)	0.17 (0.07-0.34)	2.10 (1.08-4.08)

Predictors of Pregnancy Outcome: Biomarkers in APS and SLE
PROMISSE Study (J. Salmon, PI)

- Prospective observational study of APS, SLE, and controls
  - On target to enroll 700 pregnancies <12 weeks for SLE and controls and <18 weeks for aPL positive patients
  - Serial evaluations, including rheumatologic, and blood draws
  - Exclusions
    - Prednisone > 20 mg/day
    - Urine protein ≥ 1000 mg/24 hrs or urP/Cr ratio ≥ 1000 mg/g Cr
    - Serum Cr > 1.2
    - Diabetes
    - BP ≥ 140/90
    - Multiple gestation

Predictors of Pregnancy Outcome: Biomarkers in APS and SLE

PROMISSE Study (J. Salmon, PI)

Group	N	Neonatal death	Fetal death	FGR	Preterm birth	Pre-eclampsia (preterm or term)
APS	85	0	9%	6%	9.5%	9.5%
SLE and aPL	40	2.5%	15%	17.5%	22.5%	15%
SLE, no aPL	262	1%	3%	3%	7.5%	9.5%
SLE or APS	387	1%	5.5%	5%	9.5%	10%
Controls	149	0	0.5%	1.5%	1.5%	2%

PROMISSE Study Outcomes in Women with APS or SLE and LAC

Outcome	N	Percent of Total Pregnancies	Mean GA of Outcome (Range)
Fetal death	79	20.3%	21.6 (13-38.1)
Preeclampsia requiring delivery <34 weeks	14	17.7%	27.8 (20.3-32.2)
Placental insufficiency requiring delivery <34 weeks	6	7.6%	25.3 (21.1-30.2)
One or more outcome	31	39.2%	24.8