Recurrent Abortions –
what is the evidence for antiplatelets / anticoagulants?

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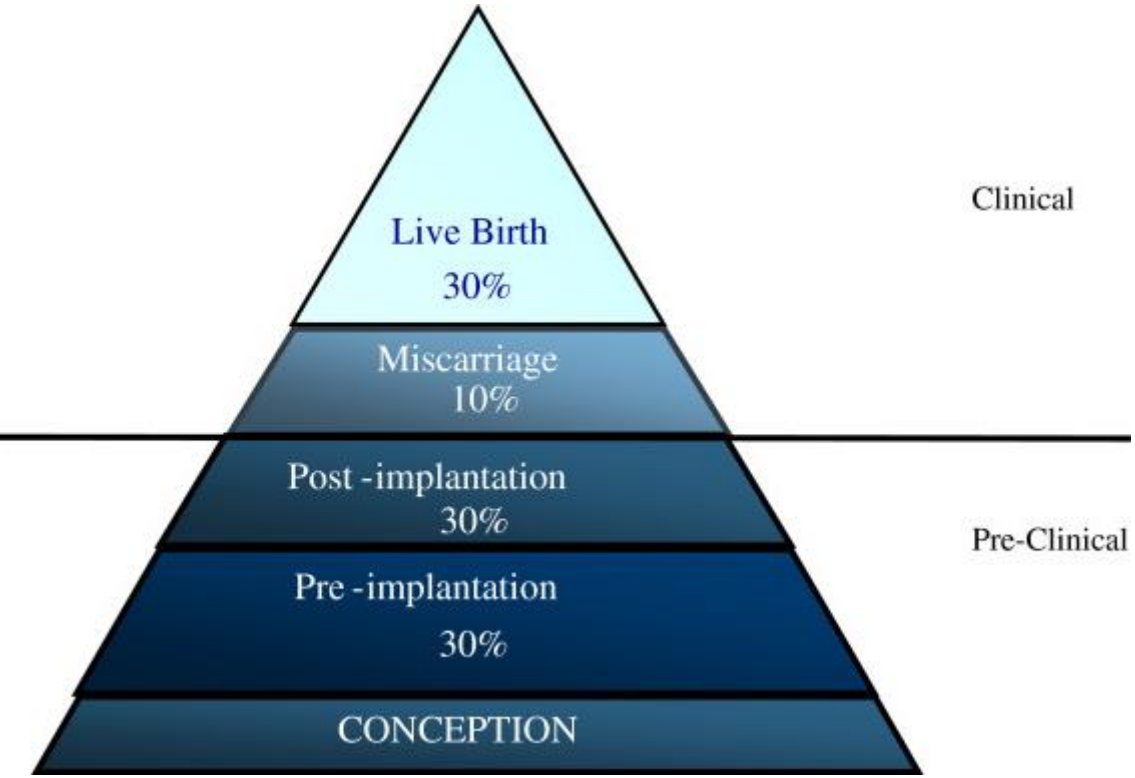
Content

- Recurrent abortions / miscarriages
  - Definition
  - Prevalence
  - Causes
- Antithrombotics
  - How it works in recurrent miscarriages
- Antithrombotics in Recurrent miscarriage
  - Acquired Thrombophilia (Antiphospholipid syndrome)
  - Unexplained recurrent miscarriages
  - Inherited Thrombophilia
- Take Home Message

The Pregnancy Loss Iceberg



Risk to have another miscarriage

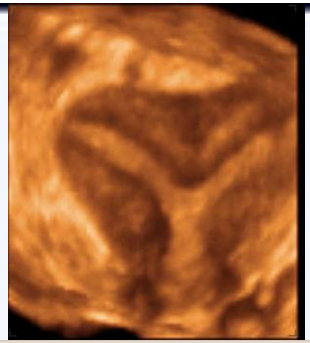
After 1 : 15%

After 2 : 30 % (higher if no liveborn infant)

Miscarriage :
Spontaneous loss of pregnancy before the fetus reaches viability (time of conception until 24 weeks of gestation. (RCOG)

Early Miscarriage ≤12 weeks of gestation (ESHRE)

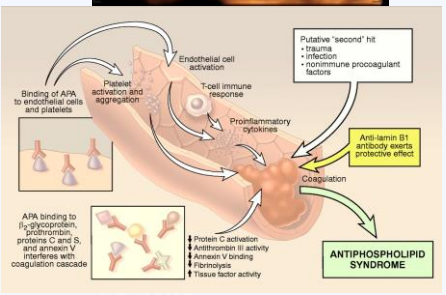
RECURRENT PREGNANCY LOSS):
RCOG 2011 :
THREE or more consecutive losses.
1% of couples / 30-45 % risk of loss
ASRM 2008 :
TWO or more consecutive losses
5% of couples / 30 % risk of loss



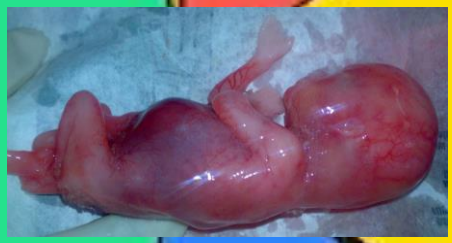
CAUSES OF RM

2%–5% Genetic Factors

10%–15% Anatomic Factors



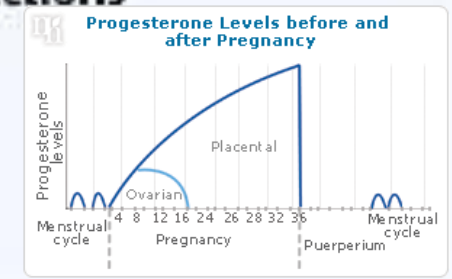
40%–50% Unexplained Including Non-APS Thrombophilias



20% Autoimmune APS

0.5%–5% Infections

17%–20% Endocrine Factors



Recurrent Miscarriage (RM) - Anticoagulants

Acquired Thrombophilia

Antiphospholipid syndrome (APS)

Inherited Thrombophilia

High-Risk thrombophilias

Anti-Thrombin deficiency,
Homozygotes Factor V Leiden mutation (FVL)
Homozygotes for Prothrombin G20210A gene mutation (PGM)

Low-Risk thrombophilias

Heterozygotes for FVL and PGM;
Protein S or C deficiencies

Unexplained

RM - Anticoagulants

- 1990's discovery of association between thrombophilia and placenta-mediated pregnancy complications
  - Early and late pregnancy loss
  - Severe pre-eclampsia
  - Growth restriction
  - Abruptio placenta
- ? Role of antepartum thromboprophlaxis
  - Clinicians, patients, guideline developers and policy makers struggle to address this questions

Rodger 2003,Duhl et al 2007

RM - ANTICOAGULANTS

- Widespread off-label use of LMWH
  - in pregnant women- both **with and without** thrombophilia who had previous pregnancy complications
  - Fuelled by
    - emotional consequences of RM
    - Expert opinion
    - Consensus panels
    - Small non-randomised studies suggesting benefit

Rodger 2003,Duhl et al 2007

Maintenance of pregnancy

Dependent on shift of proinflammatory → anti-inflammatory cytokines

- TNF – pro inflammatory that induces thrombin generation
- IL-8 – polymorph accumulation
  - polymorphs react with fibrin and damaged tissues to form clots

The anticoagulants:

Aspirin

- COX inhibition
  - Selectively irreversibly acetylates the hydroxyl group of one serine residue in cyclooxygenase (COX)
- Inhibit cytokines TNFα
- Inhibit cytokines IL-8

Heparins

- TNF
  - Heparin increases TNF binding protein.
  - LMWH inhibit TNFα production
- Anti-inflammatory
  - Thrombosis results in inflammatory response in the vein wall.
  - Both heparin and LMWH limit anti-inflammatory response including neutrophil extravasation and decreasing vein wall permeability
- Trophoblast
  - Heparin has direct effects on trophoblast - restore the invasive properties of the trophoblast in APS,
  - enchance placental hCG production

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Aspirin and Heparins

- Anti-inflammatory effects
- Anticoagulant effects

Anticoagulants - its Safety

ASPIRIN:

- No adverse fetal outcomes (pre-eclampsia in pregnancy : 81 mg)

Low Molecular Weight Heparin (LMWH)

- Less heparin-induced thrombocytopenia
- Once daily
- Lower risk of heparin-induced osteoporosis

HEPARIN :

Maternal

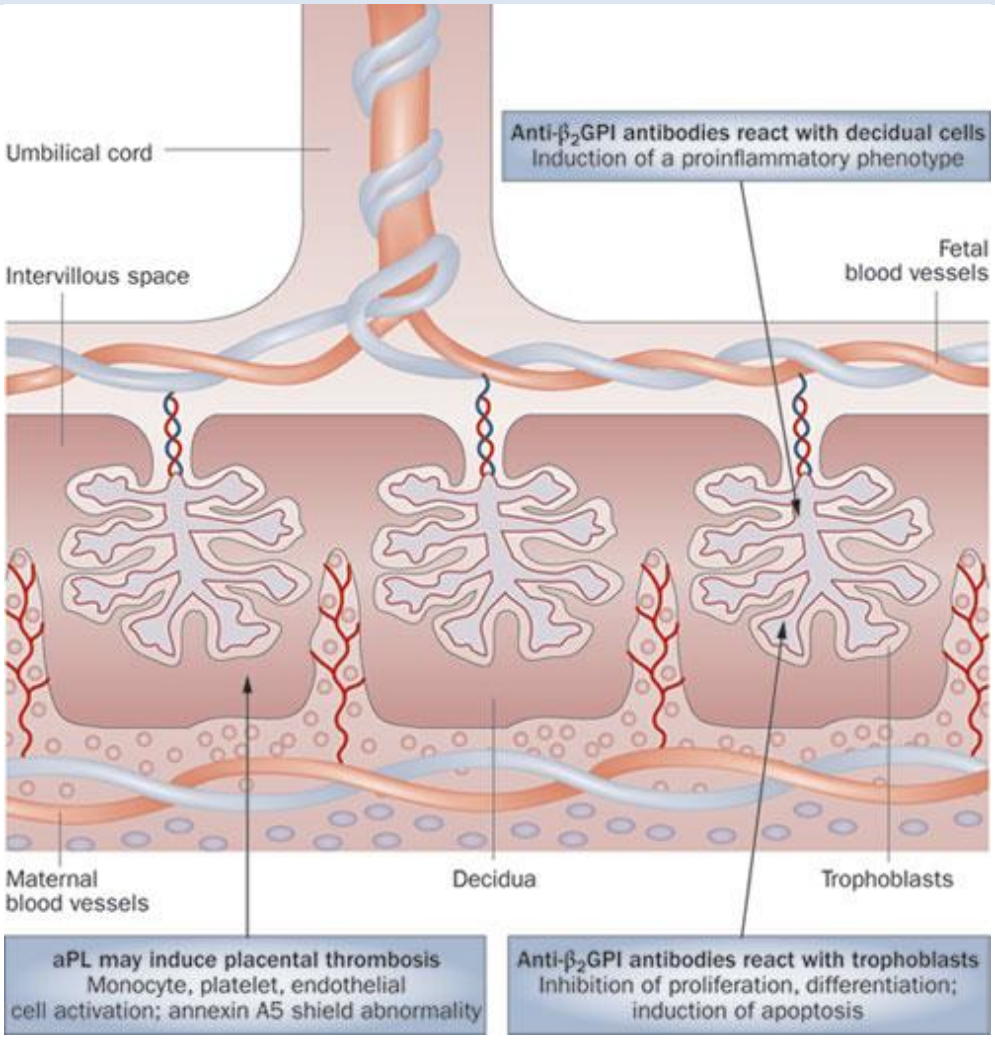
- Bleeding
- Hypersensitivity reactions
- Heparin-induced thrombocytopenia
- Osteopenia
- Vertebral fractures
- Prospective studies – loss bone mineral density at lumbar spine associated with low-dose long-term heparin therapy is similar to that which occurs physiologically during normal pregnancy. (82,83)
- Evidence level 2+

Fetal :

- does not cross placenta – no potential fetal haemorrhage or teratogenicity

Anti-phospholipid syndrome (APS)

RM and APS



APS is the only proven thrombophilia associated with adverse pregnancy outcomes.

aPL- mediated acute placental inflammation → thrombosis

Anti β_2GPI antibodies– recognize their antigen on placental tissues – inhibit growth and differentiation of trophoblasts → defective placentation

Arterial or venous thrombosis

Antiphospholipid syndrome – Sapporo 2006 revised Sydney criteria

Clinical criteria

1. **Vascular Thrombosis or**

1. **Pregnancy Morbidit**

- **Death of normal fetus at ≥10 weeks of gestation**
- **Premature birth at ≤ 34 weeks due to preeclampsia / placenta insuffiiciency**
- **≥3 unexplained, consecutive, spontaneous pregnancy losses <10 weeks of gestation**

Lab criteria

1. **Anti-Cardiolipin (aCL) IgG / IgM (>40 IgG (GPL units)/ml**

2. **Anti β-2 glycoprotein 1 antibodies (GP1) (IgG or IgM > 99th percentile)**

1. **Lupus anticoagulant (LA)**

Definite APS: 1 clinical + 1 Lab criteria

Sapporo criteria 2006

Medium to high titer

At least 2 occasions

APS and Recurrent Pregnancy Loss

- Aspirin only (Three very small trials (total 71 participants)
  - No effect when compared with no treatment
    - RR of pregnancy loss 1.05, 95 % CI 0.66-1.68
- Heparin only
  - LMWH (bemiparin 2500 U) od vs Aspirin (≥2miscarriages <20 weeks gestation)
  - LMWH more benefits than aspirin
    - RR for live birth 1.2, 95 % CI 1.00-1.43

- Empson et al 2005
- Alalaf, 2012

APS and Recurrent Pregnancy Loss

- Heparin + Aspirin
  - UFH + Aspirin (n-103) vs Aspirin alone
    - Reduced first trimester miscarriage compared to aspirin alone (n=109, RR 0.26, 95% CI 0.14-0.48
    - Metaanalysis by Ziakas et al 2010
  - LMWH vs UFH (both + Aspirin)
    - No difference in effects (Noble et al 2005 , Fouda et al 2011)
  - Two doses
    - 40 vs 80 mg Enoxaparin (Fouda et al 2010)
      - No difference in live birth observed (RR1.10, 95% CI 0.81-1.49)
- NO trials to compare heparin(UFH or LMWH) + Aspirin vs no treatment or placebo

- ACCP - 2012
  - Recommend UFH or LMWH +Aspirin for women with APS +≥ 3 miscarriages (Bates et al 2012)
  - But refrain from recommendations for women with APS with single late pregnancy loss or placental insufficiency
- RCOG -2011
  - Pregnant women with APS should be considered for treatment with Low-dose aspirin + heparin to prevent further miscarriage, without further reference toward clinical criteria of APS

- ESHRE Special Interest Group for Early Pregnancy (SIGEP)
  - Need for international collaborative RCT to evaluate
  - Type and duration of thromboprophylaxis in APS
- Currently available evidence with small numbers of participants, clinicians worldwide have adopted topractice to prescribe antithrombotic agents to all women with obstetric APS

Table III Prognosis of live birth after pregnancy loss without pharmacological treatment; results from contemporary observational studies

Author (year)	*n*	Female age in years (range)[a]	Design	Number and type of pregnancy losses (range), timing as defined by authors	Onset of follow-up/ inclusion?[c]	Overall outcome as defined by study authors
Antiphospholipid antibodies						
Single early loss						
Chauleur (2010) (Chauleur *et al.*, 2010)	142 pregnant women with LA, ACA or AB2GP1	Median 28 (20–37)	Prospective multicenter cohort study	One loss <10 weeks' GA	Onset of follow-up unclear	Pregnancy loss 44/142 (31%)
Recurrent early loss						
Sugiura-ogasawara (2008) (Sugiura-Ogasawara *et al.*, 2008)	16 pregnant women with LA or ACA on one occasion	Mean 29 (±2)	Retrospective single-center cohort study	Two or three consecutive losses <20 weeks' GA	Not applicable	Live birth 8/16 (50%)
Rai 1995 Hum reprod (Rai *et al.*, 1995)	20 pregnant women with LA or ACA	Median 32 (23–41)	Prospective single-center cohort study	≥3 (3–11) losses <12 weeks' GA	From presentation to a dedicated early pregnancy clinic	Miscarriage 18/20 (90%)

- aPL-positive
- 4 metaanalyses
- Unfractionated heparin + Aspirin → significantly improed obstetric outcomes
- LMWH – little evidence
- Hep/ASA trial 2009 – biased positivity for ANAntibodies
- Clinical practice 70% of experts devoted to APS prescribe LDASA + LMWH not only women fulfilling criteria for obstetric APS but also to aPL-positive women with a history of a single or 2 early miscarriages

APS and Recurrent Early Miscarriage (REM)

- More than 30 years APS
- APS are at increased risk of recurrent miscarriage, outcome of subsequent pregnancy is not clearly elucidated.
- 2010 Cohn
  - APLAs + recurrent miscarriage vs unexplained recurrent miscarriage
  - 693 women
  - 176 (25 %) APLAs
  - Subsequent live birth

    122 (69%) with APLAs

    324 (63 %) women with unexplained recurrent miscarriage

    no difference found for birth weight , gestational age and IUGR

  Treatment

    Livebirth in APLAs

      53/67 (79 % Aspirin + Heparin had live birth)

      64/104 (62%) Aspirin

    uREM no dirrences in outcome (stratification of treatment)

  Conclusion : The prognosis of a subsequent pregnancy in women with APLAs is good

  Nota clinical trial : combined aspirin and heparin better outcome with APLAs but not women with unexplained recurrent miscarriage

APS and Recurrent Miscarriage

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ORIGINAL ARTICLE

Recurrent miscarriage and antiphospholipid antibodies: prognosis of subsequent pregnancy

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Table 2 Baseline characteristics of women with recurrent miscarriage

	All women (n = 693)	APLAs (n = 165)*	Unexplained recurrent miscarriage (n = 482)*	APLAs, aspirin only (n = 98)†	APLAs, aspirin and heparin (n = 62)†	Unexplained recurrent miscarriage, aspirin only (n = 146)†	Unexplained recurrent miscarriage, aspirin and heparin (n = 36)†	Unexplained recurrent miscarriage, no treatment (n = 294)†
Mean age, years (SD)	32 (5.6)	32 (5.3)	32 (5.7)	32 (5.9)	32 (4.2)	33 (5.6)	33 (5.6)	31 (5.5)
Number of previous miscarriages‡								
2	196 (30%)	46 (28%)	150 (31%)	26 (27%)	20 (32%)	42 (29%)	9 (25%)	98 (33%)
3	263 (41%)	75 (46%)	188 (39%)	46 (47%)	25 (40%)	60 (40%)	13 (36%)	113 (39%)
4	99 (15%)	24 (14%)	75 (15%)	17 (17%)	7 (11%)	22 (15%)	8 (22%)	45 (15%)
5	46 (7%)	9 (5%)	37 (8%)	7 (7%)	1 (2%)	8 (6%)	4 (11%)	23 (8%)
>5	43 (7%)	11 (7%)	32 (7%)	2 (2%)	9 (15%)	14 (10%)	2 (6%)	15 (5%)

APLAs, antiphospholipid antibodies; SD, standard deviation. *Reproductive history was not recorded in 11 women with APLAs and 35 women with unexplained recurrent miscarriage. †Treatment was not recorded in five women with APLAs and six women with unexplained recurrent miscarriage. ‡Miscarriage within 24 weeks of gestation.

Miscarriage (< 13 weeks) occurred in 49/176 women with APLAs (28%) and in 176/517 women with unexplained recur- rent miscarriage (34%), OR 0.7 (95% CI 0.5–1.1) (Table 4).

Late pregnancy loss (13–24 weeks) occurred in 3/176 women with APLAs (2%) and in 15/517 women with unexplained recurrent miscarriage (3%), OR 0.6 (95% CI 0.2–2.0), and still- birth (> 24 weeks) occurred in 2/176 women with APLAs (1.1%) and in 2/517 women with unexplained recurrent miscarriage (0.4%), OR 3.0 (95% CI 0.4–21) (Table 4).

Table 3 Pregnancy outcome in women with recurrent miscarriage

	All women (n = 693)	APLAs (n = 176)	Unexplained recurrent miscarriage (n = 517)	APLAs, aspirin only (n = 104)*	APLAs, aspirin and heparin (n = 67)*	Unexplained recurrent miscarriage, aspirin only (n = 163)*	Unexplained recurrent miscarriage, aspirin and heparin (n = 43)*	Unexplained recurrent miscarriage, no treatment (n = 305)*
Live birth, n (%)	446 (64%)	122 (69%)	324 (63%)	64 (62%)	53 (79%)	93 (57%)	25 (58%)	204 (67%)
OR live birth (95% CI)		1.3 (0.9–1.9)	1 (ref)					
OR live birth adjusted (95% CI)†		1.4 (0.9–2.0)	1 (ref)					
OR live birth (95% CI)				1 (ref)	2.4 (1.2–4.8)			
OR live birth adjusted (95% CI)†				1 (ref)	2.7 (1.3–5.8)			
OR live birth (95% CI)						0.7 (0.4–1.0)	0.7 (0.4–1.3)	1 (ref)
OR live birth adjusted (95% CI)†						0.8 (0.5–1.1)	0.7 (0.4–1.4)	1 (ref)

APLAs, antiphospholipid antibodies; OR, odds ratio; CI, confidence interval. *Treatment was not recorded in five women with APLAs and six women with unexplained recurrent miscarriage. †Adjusted for age and number of previous miscarriages.

Table 4 Secondary outcomes in women with recurrent miscarriage

	All women (n = 693)	APLAs (n = 176)	Unexplained recurrent miscarriage (n = 517)
First trimester miscarriage (loss < 13 weeks), n (%)	225 (33%)	49 (28%)	176 (34%)
OR miscarriage (95% CI)	–	0.7 (0.5–1.1)	1 (ref)
OR miscarriage adjusted (95% CI)*	–	0.7 (0.5–1.1)	1 (ref)
Late miscarriage (loss between 13 and 24 weeks), n (%)	18 (3%)	3 (2%)	15 (3%)
OR late pregnancy loss (95% CI)	–	0.6 (0.2–2.0)	1 (ref)
Stillbirth (pregnancy loss > 24 weeks), n (%)	4 (0.6%)	2 (1.1%)	2 (0.4%)
OR stillbirth	–	3.0 (0.4–21)	1 (ref)
Mean birth weight, grams (SD)	3211 (692)	3168 (603)	3265 (665)
Mean difference, grams (95% CI)	–	−96 (−240–48)	
Mean gestational age, weeks (SD)	39 (2.6)	39 (2.4)	39 (2.8)
Mean difference, weeks (95% CI)	–	−0.3 (−0.9–0.3)	
IUGR, n (%)	36 (9%)	7 (7%)	29 (10%)
OR IUGR	–	0.6 (0.3–1.5)	1 (ref)
Premature delivery, n (%)	33 (8%)	8 (7%)	25 (8%)
OR premature delivery	–	0.9 (0.4–2.0)	1 (ref)

APLAs, antiphospholipid antibodies; IUGR, intrauterine growth restriction; OR, odds ratio; CI, confidence interval. *Adjusted for age and number of previous miscarriages.

- **Recurrent early pregnancy loss and antiphospholipid antibodies: where do we stand?**

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- **Abstract**
- Evidence from basic science studies supports a causative relationship between antiphospholipid antibodies (aPL) and recurrent early miscarriage (REM) (prior to 10 weeks of gestation). However, human studies have not consistently found a relationship between aPL and REM. Members of the Obstetric Task Force of the 14th International Congress on Antiphospholipid Antibodies performed a literature review of the association of aPL and REM and searched for clinical trials in women with REM who tested positive for aPL. Of the 46 studies that investigated the relationship between aPL and REM, 27 found a positive association, seven found no association, and the remaining 12 papers could not report an association (lack of control group). The main identified problems for such conflicting results were varying definitions of REM (two or three abortions, not necessarily consecutive; different gestational age at which pregnancy losses occurred); analysis of patients with previous fetal death (>10 weeks) in the same group of REM; and different definitions of "positive aPL" (cutoffs not following international recommendations; small number of studies confirmed persistence of positive aPL after six to 12 weeks). The 10 identified randomized trials with proposed treatments for women with REM who test positive for aPL also had heterogeneous inclusion criteria, with only one trial limited to subjects who would meet the current criteria for antiphospholipid syndrome (APS) by both clinical and laboratory criteria. Against this background, we conclude that the association between REM and aPL remains inconclusive and that the findings of treatment trials are at best inconsistent and at worst misleading. More convincing data are critically needed. Studies that identify, or at least stratify, according to international consensus criteria and include standardized core laboratory testing results are crucial if we are to establish an evidence-based association between aPL and REM and treatment recommendations.

APS - REM

- aPL-positive women experiencing REM present a favorable outcome regardless of therapeutic intervention
- Aspirin + Heparin does not confer improvement in obstetric outcome among patients with prior REM

Cohn et al 2010

RM : ANTIPHOSPHOLIPID SYNDROME

- Obstetric Task Force of the 14th International Congress on Antiphospholipid syndrome : confirmed the continuing lack of evidence supporting an association between aPL and recurrent early miscarriage (REM)
  - Absence of consistent predictable clinical outcomes from therapeutic trials and suggested potential
  - causes
  - Studis – heterogenous selection protocls/variable lab inclusion criteria and small sample sizes
  - Lack pathological or genetic evaluation to determine nature of pregnancy losses when ocured

APS and Recurrent Pregnancy loss

- Few clinical trials
- Cochrane – empson et al 2005

APS and REM

- 1988-994
  - ASA / P VS PLACEBO
  - Not met the criteria
- 2000-2004
  - Hep / ASA vs ASA alone
  - Fulfilling Sapporo criteria
  - ≥ 2 early losses and ≥ 3 early losses
    - No etiological difference between women with 2 vs 3 early losses
    - If aPL were associated with REM, then the presence of antibody not the number of losses should be determinant
    - To address extremely slow patient accrual

aPL and REM

- Patients with persistent moderate to high levels of aPL are rarely seen
  - 2.7 % of 2257 patients with persistent confirmed LAC over 6 years
  - 0.8% patients with ≥ 2 moderate to high aCL or IgM over about 4 years
  - Triple positive aPL in 3.6 % of 1520 patients over 4 years
- Vast majority of women with REM have low levels or no aCL or LAC
- Regardless of aPL positivity, women with REM have a good prognosis for subsequent live birth, independent of treatment with ASA alone, LMWH/ASA or unfractionated heparin/ ASA

PROMISSE STUDY (Predictors of pRegnancy Outcome : bioMarkers In antiphospholipid antibody syndrome and Systemic Lupus Erythematosus)

- Prospective, observational investigations of aPL and pregnancyoutcome (regardless of presence or absence of clinical criteria of APS, but excluding pregnancies that end before the first tirmester)
- 2003-211, multicenter international study includes only stringently evaluated, high-risk patients who fulfill APS lab criteria
- 144 aPL positive 9.7 % late losses
- 144 aPL positive
  - Absence of LAC strong predictor of uncomplicated pregnancies regardless of presence of aCL or anti-β2-glycoprotein 1 antibody
  - Persistent LAX – associated with sporadic stillbirth, IUGR and HELLP syndrome a
  - Persistent aPL associated with preterm delivery

- 2 general presentations
  - Most common includes women with low levels of aCL (but not LAC) and a history of exclusively early losses but no thrombosis (in the absence of an concomitant risk factors such as surgery, oral contraception or the postpartum period)
    - Have a high likelihood of live birth in a pregnancy subsequent to presentation regardless of therapeutic protocol, negligible risk of postpartum thrombosis and good longterm prognosis
  - Less frequent includes women with persistently high evels of aPL including LAC, a history of second or third trimester loss(es), and possibly a history of thrombotic events
    - Have unpredictable pregnancy course regardless of therapeutic protocol
    - Longterm prognosis – potentially higher risk of thrombotic events despite continuous anticoagulation

- Remission rates for APS
  - no data

- Collective, multicenter, retrospective analysis of results from all pregnancy-related observational and therapeutic trials
  - Late adverse obstetric events (with or without thrombosis) and persistently high aPL

Current Recommendations

Pregnancy	Fetal protection
• Asymptomatic aPL	no treatment
• Single loss <10wks	no treatment
• Recurrent loss* <10wks ASA after(?)	prophylactic heparin +ASA up to 6-12 wks postpartum,
• Recurrent loss < 10 wks + thrombosis	therapeutic heparin + ASA, warfarin postpartum
• Prior thrombosis	therapeutic heparin + ASA warfarin postpartum

* Late fetal loss
IUGR
severe pre-eclampsia

Regimen?

- Aspirin – arterial thrombosis
- Heparin – venous thrombosis

- Aspirin for women with cPL and clinical
- ASA 50-100 mg per day beginning when conception is attempted
- Prophylactic dose LMWH upon confirmation of IU pregnancy

conclusion

Unexplained RPL

- 50 % unexplained after thorough evaluation
- Prognosis for live birth rate 50 – 80 % without intervention with evidence-based treatments and supportive care
- 60 % chromosomal abnormalities
- Not related to thrombotic events
- Anticoagulants not recommended

RM IN APS - THROMBOPROPHYLAXIS

- ASA alone vs ASA + LMWH
  - Significantly
  - reduced pregnancy loss (RR 0.46, 95% CI 0.29-0.71)
  - First trimester pregnancy loss (OR 0.39, 95% CI 24-0.65
  - Increased in live births (RR 1.3, 95% CI 1.04 – 1.63)

- **Recurrent pregnancy loss —** The association between recurrent pregnancy loss and APS is based on observational studies, which consistently report that aPL are detected in a higher proportion of women with recurrent pregnancy loss than in controls (up to 20 percent versus <5 percent)

ASPIRIN IN APS - EVIDENCE

LMWH IN APS - EVIDENCE

Aspirin and LMWH

- Dose ? And regime

Antithrombotic therapy for APS

RCOG 2011 (Royal College of Obstetricians and Gynaecologists, 2011)	ACCP 2012 (Bates et *al.*, 2012)	ASRM 2012/2013 (ASRM, 2012; ASRM, 2013)	SIGEP/ESHRE (Farquharson et *al.*, 2005; Jauniaux et *al.*, 2006)
Pregnant women with antiphospholipid syndrome should be considered for treatment with low-dose aspirin plus heparin to prevent further miscarriage (Grade B)	For women who fulfill the laboratory criteria for APLA syndrome and meet the clinical APLA criteria based on a history of three or more pregnancy losses, we recommend antepartum administration of prophylactic- or intermediatedose UFH or prophylactic LMWH combined with low-dose aspirin, 75 to 100 mg/day, over no treatment (Grade 1B)	Women with persistent, moderate-to-high titres of circulating antiphospholipid antibodies can be treated with a combination of prophylactic doses of UFH and low-dose aspirin	Treatment with aspirin and/or LMWH for women presenting with APS requires more RCTs

Diagnostic test for APS

RCOG 2011 (Royal College of Obstetricians and Gynaecologists, 2011)	ACCP 2012 (Bates et *al.*, 2012)	ASRM 2012/2013 (ASRM, 2012; ASRM, 2013)	SIGEP/ESHRE (Farquharson et *al.*, 2005; Jauniaux et *al.*, 2006)
All women with recurrent first-trimester miscarriage and all women with one or more second-trimester miscarriage should be screened before pregnancy for antiphospholipid antibodies (Grade D)	For women with recurrent early pregnancy loss (three or more miscarriages before 10 weeks of gestation), we recommend screening for APLAs (Grade 1B)	These may include: screening for lupus anticoagulant, anticardiolipin antibodies and anti-beta 2 glycoprotein I	All women with a history of three or more early pregnancy losses, that is, before 10 weeks, or one or more unexplained deaths at $\geq$10 weeks of a morphologically normal fetus, or one or more premature births at $\leq$34 weeks with severe pre-eclampsia or placental insufficiency, should be offered a testing for lupus anticoagulant and anticardiolipin antibodies to exclude an antiphospholipid syndrome

2. Unexplained Recurrent Pregnancy Loss (uRPL)

40 – 50 % of RPL is unexplained

Presumed benefit of anticoagulants therapy and the lack of side effects with LMWH, aspirin or both.

The use of anticoagulants were extended to :

- unexplained pregnancy loss even in absence of thrombophilia
- Even without proven benefits

Thromboprophylaxis in Unexplained RPL

Aspirin

Randomized trial

- LDA is ineffective in prevention

Prospective observational study (75mg Aspirin daily)

- No benefit in previous early pregnancy losses (OR 1.24; 95% CI 0.93-1.67)
- Previous late miscarriage has higher live birth rate (OR 1.88; 95% CI 1.04 – 3.37)

- **Empirical use of LDA in women with unexplained recurrent early miscarriage is not justified**

Heparin

- Randomized control trial
  - Suggests heparins may raise the live birth rate
- Enoxaparin vs aspirin in women screened without thrombophilia
  - **No difference in the live birth rate (80 %)**

Rai et al 1997, Badawey et al 2008, Dolitzky et al 2006

Cochrane

Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia

Nine studies, including data of 1228 women, were included in the review evaluating the effect of either LMWH (enoxaparin or nadroparin in varying doses) or aspirin or a combination of both, on the chance of live birth in women with recurrent miscarriage, with or without inherited thrombophilia. Studies were heterogeneous with regard to study design and treatment regimen and three studies were considered to be at high risk of bias. Two of these three studies at high risk of bias showed a benefit of one treatment over the other, but in sensitivity analyses (in which studies at high risk of bias were excluded) anticoagulants did not have a beneficial effect on live birth, regardless of which anticoagulant was evaluated (risk ratio (RR) for live birth in women who received aspirin compared to placebo 0.94, (95% confidence interval (CI) 0.80 to 1.11, n = 256), in women who received LMWH compared to aspirin RR 1.08 (95% CI 0.93 to 1.26, n = 239), and in women who received LMWH and aspirin compared to no-treatment RR 1.01 (95% CI 0.87 to 1.16) n = 322).

Authors' conclusions:

There is a limited number of studies on the efficacy and safety of aspirin and heparin in women with a history of at least two unexplained miscarriages with or without inherited thrombophilia. Of the nine reviewed studies quality varied, different treatments were studied and of the studies at low risk of bias only one was placebo-controlled. No beneficial effect of anticoagulants in studies at low risk of bias was found. Therefore, this review does not support the use of anticoagulants in women with unexplained recurrent miscarriage. The effect of anticoagulants in women with unexplained recurrent miscarriage and inherited thrombophilia needs to be assessed in further randomised controlled trials; at present there is no evidence of a beneficial effect.

Habenox study - 2011

A randomised multicentre trial, 50 % thrombophilia cases

≥ 3 miscarriages (< 13 weeks), ≥ 2 (13-24 weeks) miscarriages or one third trimester fetal loss

- 7weeks :
  - Enoxaparin 40 mg + placebo
  - Enoxaparin 40 mg + aspirin 100mg
  - Aspirin 100 mg
- Results
  - Live birth rate : 71 % vs 65 % vs 61 %
  - Live birth rate for women with three or more miscarriages : 65 % for all group
- Conclusion :
  - no beneficial effect of LMWH with (aspirin or placebo) compared to aspirin in women with or without thrombophilia and RPL

Visser 2011

ALIFE (Anticoagulant for LIving FEtus) 2010

Large randomized controlled trial

364 patients (≥2 RM attempting pregnancy or < 6 weeks pregnant)

(inherited thrombophilia not ruled out, 16 %)

299 pregnant

Aspirin and LMWH (Nadroparin 2850 IU sc) (started 6 weeks after confirm viability)	Aspirin (80mg) only (started soon was randomized/ preconception)	Placebo

Live birth rates : 67 % vs 62 % vs 70 %

There was NO advantage of treatment over placebo

Kaandorp et al N.Eng J.Med 2010

SPIN (Scottish Pregnancy Intervention) 2010

Multicenter, RCT

294 women with ≥2 consecutive unexplained RM < 24 weeks

HABENOX, ALIFE AND SPIN :
DOES NOT SUPPORT USE OF ASPIRIN OR LMWH IN UNEXPLAINED RPL

E
A
150 women

+

Intensive surveillance

Life birth rate 78 % vs 79 %

Rate of Pregnancy Loss : 22 % vs 20%

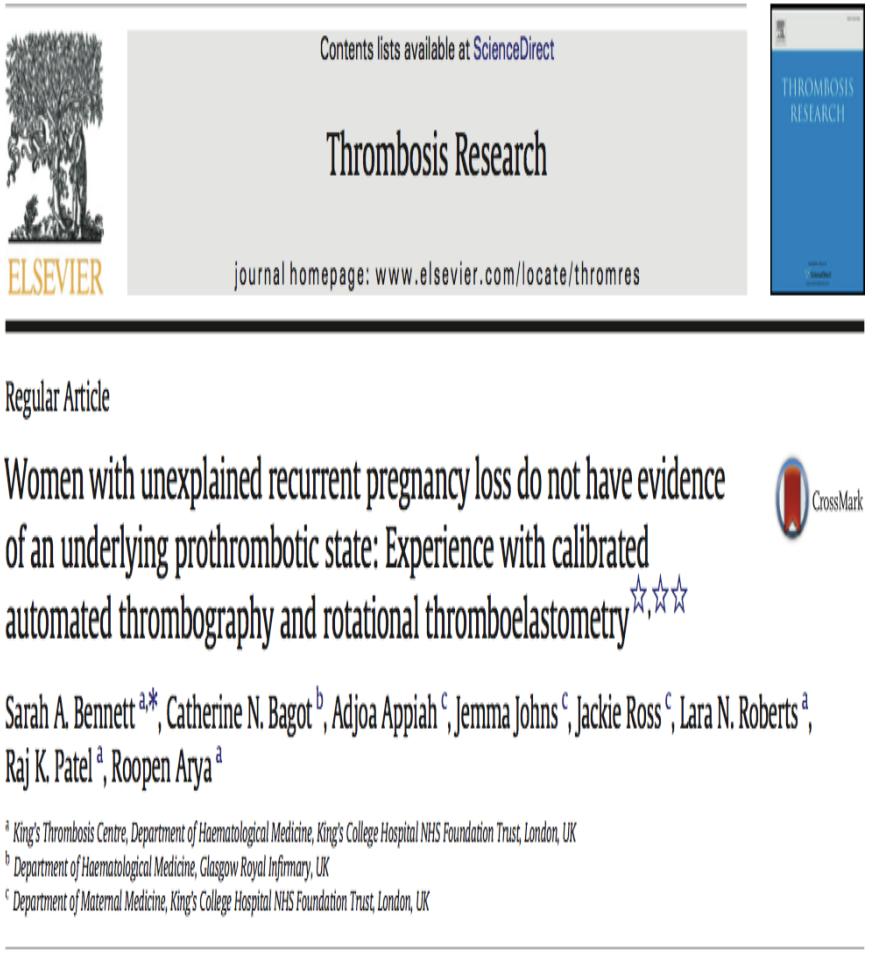
Intensive surveillance alone

Clark et al, Blood 2010

Unexplained RM – prognosis ?

- 50 % of RM are unexplained
- Live birth rate :
  - No antenatal care vs antenatal counseling and psychological support
  - 33 % vs 86 %
- Live birth rate of Antenatal surveillance alone
  - Upto 80 %

- Lifestyle modification – body mass index / tobaco/alcohol/caffeine
- Progesterone
- Aspirin with or without heparin
- Human chorionic gonadotrophin (hCG)
- Human Menopausal Gonadotrophin
- Clomiphene citrate
- In vitro fertilization and preimplantation genetic diagnosis
- Gestational Carrier
- Oocyte donation
- Combination therapy



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Regular Article

Women with unexplained recurrent pregnancy loss do not have evidence of an underlying prothrombotic state: Experience with calibrated automated thrombography and rotational thromboelastometry☆,☆☆

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Idiopathic recurrent miscarriage is caused mostly by aneuploid embryos

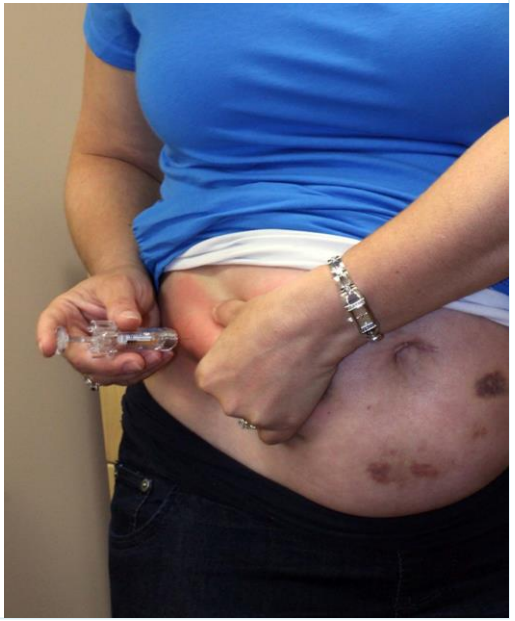
Result(s)
A total of 2,282 embryos were analyzed, of which 35% were euploid and 60% were aneuploid. There were 181 embryo transfer cycles, of which 100 (55%) became pregnant with an implantation rate of 45% (136 sacs/299 replaced embryos) and 94 pregnancies (92%) were ongoing (past second trimester) or delivered. The miscarriage rate was found to be only 6.9% (7/102), compared with the expected rate of 33.5% in an RPL control population and 23.7% in an infertile control population.

Conclusion(s)
Current PGS results with aCGH indicate a significant decrease in the miscarriage rate of idiopathic RPL patients and high pregnancy rates. Furthermore, this suggests that idiopathic recurrent miscarriage is mostly caused by chromosomal abnormalities in embryos.

Hodes-Wertz2012

Anticoagulants and uRPL - conclusion

- It is time to put the LMWH needles away and not offer this therapy to women with prior recurrent pregnancy loss in the absence of thrombophilia



Anti thrombotic in Unexplained RM

RCOG 2011 (Royal College of Obstetricians and Gynaecologists, 2011)

Women with unexplained recurrent miscarriage have an excellent prognosis for future pregnancy outcome without pharmacological intervention if offered supportive care alone in the setting of a dedicated early pregnancy assessment unit (Grade B)
Evidence regarding the efficacy of antithrombotic therapy for women with unexplained recurrent miscarriage is judged as *level I +* and no recommendation for or against treatment is included

ACCP 2012 (Bates *et al.*, 2012)

For women with two or more miscarriages but without APLA or thrombophilia, we recommend against antithrombotic prophylaxis (Grade 1B)

ASRM 2012/2013 (ASRM, 2012; ASRM, 2013)

SIGEP/ESHRE (Farquharson *et al.*, 2005; Jauniaux *et al.*, 2006)

The data on the use of anticoagulants for the treatment of RM in women without APS are too limited to recommend their routine use within this context

Inherited Thrombophilias

High-Risk thrombophilias

- Anti-Thrombin deficiency,
- Homozygotes Factor V Leiden mutation (FVL)
- Homozygotes for Prothrombin G20210A gene mutation (PGM)

Low-Risk thrombophilias

Heterozygotes for FVL and PGM;
Protein S or C deficiencies

Venous thromboembolism

Hereditary Thrombophilias and RPL

LMWH treatment might be beneficial for women with RPL

2003 : Carp et al

INCREASED RISK – Retrospective studies

2005 Dizon-Townso et al

2010 Said JM et al

Theoretical relation Inherited Thrombophilia and RPL :

- Thrombosis of the placenta (microvasculature)
- Inhibition of extravillous trophoblast differentiation

Hereditary Thrombophilias and RPL

NO ASSOCIATION - Prospective studies

2008 Clark et al

2010 Silver RM et al

Thrombophilias and pregnancy loss :
The European Prospective Cohort on Thrombophilia (EPCOT)

843 women with thrombophilia – 571 with 1524 pregnancies
541 control with 1019 pregnancies

- ✓ The **overall rate of fetal loss** was increased in women with thrombophilia (29.4 versus 23.5 percent, OR 1.35, 95% CI 1.01-1.82).
- ✓ However, the OR was statistically significant only for **stillbirth** (OR 3.6, 95% CI 1.4-9.4 for stillbirth; versus OR 1.27, 95% CI 0.94-1.71 for miscarriage).
- ✓ The OR for stillbirth in women with **multiple thrombophilias** was 14.3 (95% CI 2.4-86.0), suggesting a dose-response effect
- ✓ The ORs for stillbirth for individual defects were**: AT deficiency** 5.2 (95% CI 1.5-18.1), protein C deficiency 2.3 (95% CI 0.6-8.3), protein S deficiency 3.3 (95% CI 1.0-11.3), and FVL 2.0 (95% CI 0.5-7.7).

Preston 1996

Thrombophilias and pregnancy loss :
The European Prospective Cohort on Thrombophilia (EPCOT)

843 women with thrombophilia – 571 with 1524 pregnancies
541 control with 1019 pregnancies

Thrombophilia

- late fetal loss
- no statistically association between either thrombophilias in general or specific thrombophilic defects (eg, multiple defects, PGM, protein C or S deficiency, FVL) and miscarriage;
  the only exception was AT deficiency.

Preston 1996

Meta-analysis - 31 case-control, cohort, and cross-sectional studies

Conclusion:

- Thrombophilia is not related with early RPL
- Increased overall rate of fetal loss with thrombophilia
  - after 10 weeks
  - non recurrent loss after 20 weeks
  - isolated late
- Statistically significant for increased still birth but not RPL

Rey 2003

Thrombophilias and early pregnancy loss(es)

Case-control studies

Presence of one or more maternal thrombophilias

- ✓ protective of recurrent losses at < 10 weeks
- ✓ Increased risk of losses > 10 weeks

Conclude :

Maternal thrombophilias are protective of early loss

Pathophysiology

- ✓ Early pregnancy is normally associated with a low oxygen environment

oxygen pressures

17+/- 6.9 mm Hg at 8-10 weeks of gestation

60.7 +/- 8.5 mm Hg at 13 weeks of gestation

- ✓ Trophoblast plugging of the intervillous space,
- ✓ Low Doppler flow of the uteroplacental circulation

Oxygen - harmful during embryonic period

Adverse effect maternal thrombophilias on uteroplacental blood flow and oxygen delivery would be expected to be harmful to the late, but not early first trimester pregnancy

Jaffe 1993, Kocher 2007

Thrombophilia : Randomized trial

- Enoxaparin 40 mg vs Aspirin
- 160 women with inherited thrombophilia + 1 prior late pregnancy loss (> 10 weeks of gestation)
- Live birth rate
  - 86% vs 29 %
  - Fetal loss
    - After 8th week 42.5 %
    - Before 8th week 7 %

Griss et al 2004

Thrombophilia with RM

- Aspirin alone
  - No RCT
- Heparin alone
  - Only observational
  - Retrospective cohort
    - Enoxaparin vs no intervention (livebirth 70 vs 43%) Carp 2003
  - Prospective cohort 50 women
    - Enoxaparin 40 vs 80 (livebirth 75 % vs 20 % in previous pregnancies) Brenner et al 2000
    - Live-Enox, n=180, enox 40 vs 80 od Brenner 2005, (APS nMTHFR 6TT + hyperhomocyseinemia. Lack of control. Live birth rate 84 vs 78 %
  - No RCT

- Heparin + Aspirin
  - Awaiting RCT – ALIFE2

The LIVE-ENOX – RM thrombophilia

Multicenter

Enoxaparin 40 mg / day vs 80 mg /day

Treatment between 5–10 weeks of gestation, continued throughout pregnancy and 6 weeks postpartum because these women, who also had thrombophilia, needed to prevent thrombosis

The live birth rate before the study was approximately 28 %

The live birth rate

- 40 mg-dose-arm : 84 %
- 80 mg-dose-arm : 78 %

No statistical difference in the live birth rate between the two doses

80 mg is safe, but 40 mg suffice for treatment

Brenner et al 2005

TIPPS : 2014

The prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS)

Open-label randomised trial, 36 tertiary centers Multinational : Five country, Year 2000 – 2012, 292 women with thrombophilia

Dalteparin 5000 IU/day up to 20 weeks' gestation to twice daily thereafter till 37 weeks vs no dalteparin

Conclusion :

No benefit in subgroups with recurrent early loss (n=44) or those with prior late loss (n=81)

Antepartum prophylactic dalteparin does not reduce the occurrence of venous thromboembolism, pregnancy loss, or placenta-mediated pregnancy complications in pregnant women with thrombophilia at high risk of these complications and is associated with an increased risk of minor bleeding.

Marc A Rodger et al The Lancet 2014

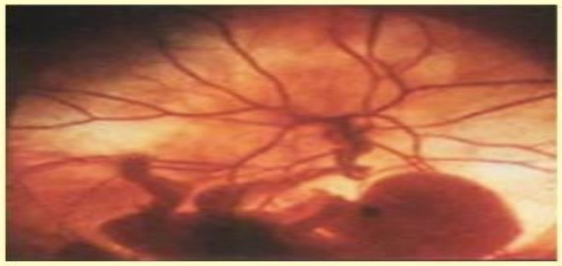
RCT for thrombophilia and RPL

X SPINN 2010 (3.5 %)

X ALIFE 2010 (16 %)

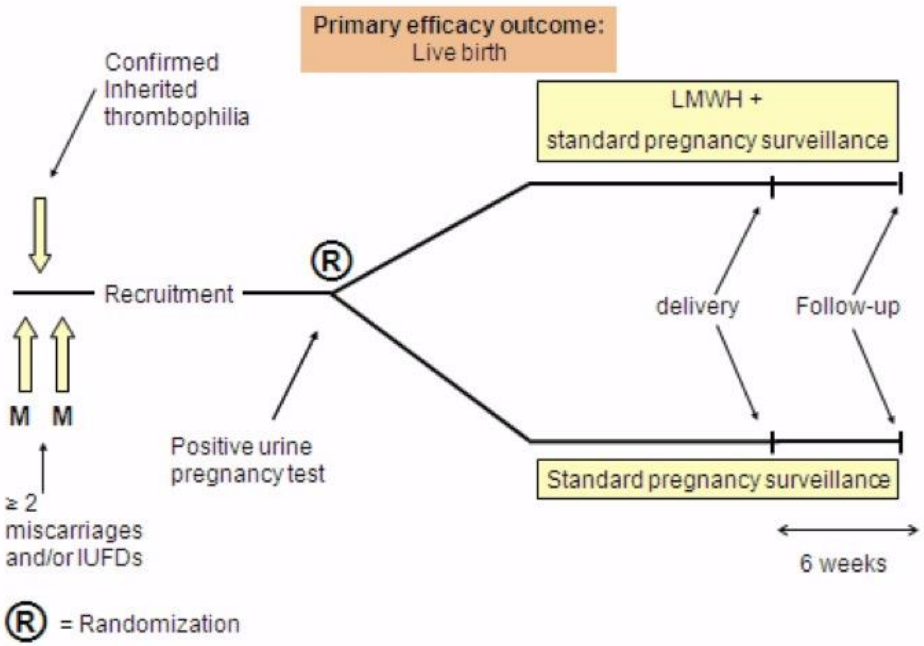
X Habenox 2011 (24.6 %)

Subgroup analyses – insufficiently powered to address antithrombotic in thrombophilic women



ALIFE2

Anticoagulants for LIving FEtuses in women with recurrent miscarriage and inherited thrombophilia



1. Placebo
2. Aspirin
3. open label

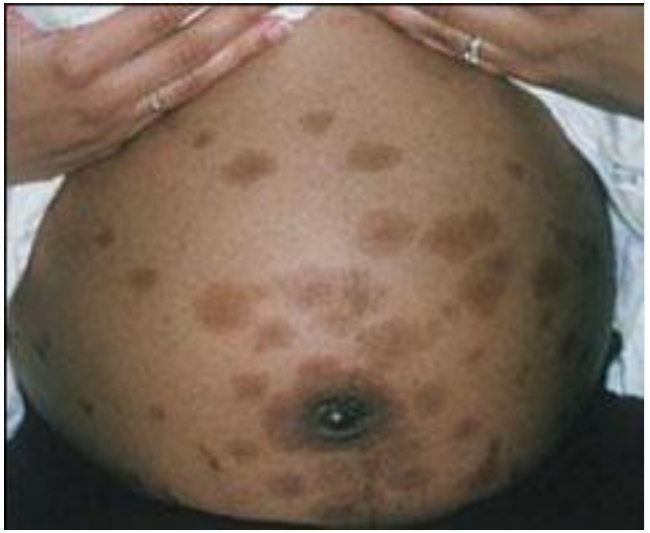
   Aspirin + low molecular weight heparin (LMWH).

- Placebo and Aspirin are packed in identical sachets and favourably started preconceptionally and continued until 36 weeks of gestation.
- G3 : Aspirin will be combined with LMWH (Fraxiparine 2850 EH/day) as soon as a vital intrauterine pregnancy is diagnosed. LMWH will be continued throughout the pregnancy until 12 hours before labour.

2012 – 3 years

Anticoagulant and Thrombophilia with RPL

- Until ALIFE 2, LMWH should not be offered to women outside of clinical trials based on the weak association and the lack of good-quality evidence to support benefit.



Antithrombotic – Inherited thrombophilia

RCOG 2011 (Royal College of Obstetricians and Gynaecologists, 2011)

There is insufficient evidence to evaluate the effect of heparin in pregnancy to prevent a miscarriage in women with recurrent first-trimestermiscarriage associated with inherited thrombophilia
(Grade C)
Heparin therapy during pregnancy may improve the live birth rate of women with second-trimester miscarriage associated with inherited thrombophilias
(Grade A)

ACCP 2012 (Bates *et al.*, 2012)

For women with inherited thrombophilia and a history of pregnancy complications, we suggest not to use antithrombotic prophylaxis
(Grade 2C)

ASRM 2012/2013 (ASRM, 2012; ASRM, 2013)

SIGEP/ESHRE (Farquharson *et al.*, 2005; Jauniaux *et al.*, 2006)

Treatment with aspirin and/or LMWH for women presenting with (multiple) inherited thrombophilias requires more RCTs

Diagnostic tests Thrombophilia

RCOG 2011 (Royal College of Obstetricians and Gynaecologists, 2011)	ACCP 2012 (Bates et *al.*, 2012)	ASRM 2012/2013 (ASRM, 2012; ASRM, 2013)	SIGEP/ESHRE (Farquharson et *al.*, 2005; Jauniaux et *al.*, 2006)
Women with second-trimester miscarriage should be screened for inherited thrombophilias including factor V Leiden, factor II (prothrombin) genemutation and protein S (Grade D)	For women with a history of pregnancy complications, we suggest not to screen for inherited thrombophilia (Grade 2C)	Routine testing of women with RPL for inherited thrombophilias is not currently recommended	Thrombophilia screening is recommended in the context of a trial

Take Home Message

- Antiphospholipid syndrome
- Unexplained recurrent Pregnancy Loss
  - Enough evidence of not to use anticoagulants
    - ALIFE and SPINN – 2 large RCT
    - 60 % aneuploidy
    - No prothrombic activities
    - > 80 % prognosis with antenatal surveillance alone
- Inherited thrombophilia
  - Limit to clinical trials
    - ALIFE 2 - RCT with placebo 2016