Thrombophilia & Recurrent Pregnancy Loss (RPL):
Current state of evidence

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Conflict of interests

- No disclosures.

Aim of this lecture

- What is RPL and what is not?
- Which thrombophilias are problematic for early pregnancies?
- How to investigate?
- How to treat?

What does the evidence say?

What is recurrent pregnancy loss (RPL).

- RPL has been defined in many ways by different organizations.
- **RCOG** defines RPL or recurrent miscarriage (RM) as the spontaneous loss of **three or more consecutive** pregnancies before age of viability. (GTG 17 APL 2014)
- **ASRM** defines RPL as **two** or more failed clinical pregnancy. Ideally threshold of 3 or more should be used for epidemiologic studies, but start clinical evaluation after 2 losses. (ASRM committee opinion 2012)

What is recurrent pregnancy loss (RPL).

- **ESHRE** Early Pregnancy Guideline Development Group (GDG) released its guidelines on November 2017.
- "A diagnosis of Recurrent Pregnancy Loss (RPL) **could** be considered after the loss of **two** or more pregnancies."

However:

- Definition may be further restricted in the future be but currently the data are lacking to do so.
- Some guideline group members would like to stress that they disagree with the suggested definition and will keep a definition of three or more consecutive losses in their clinical practice

Why 2 and not 3?

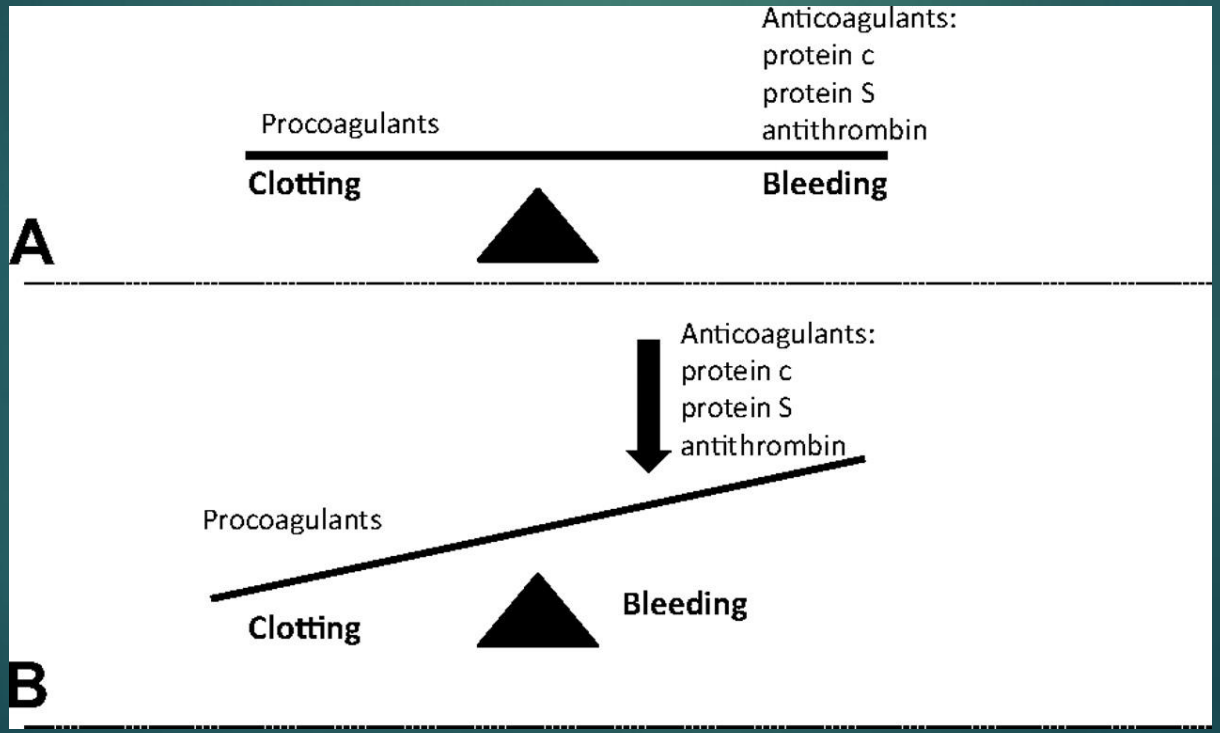
- Will facilitate research, shared decision-making and psychological support to couples. In addition, testing for APS, a treatable sub-diagnosis of RPL, can be performed after two losses.

Why not consecutive?

- NO difference in **prognosis** of unexplained RPL, prevalence of **APS**, prevalence of carrier state of **chromosomal anomalies** and only less than 10% of cases will have 2 or more consecutive losses, so **many cases will be underdiagnosed**.

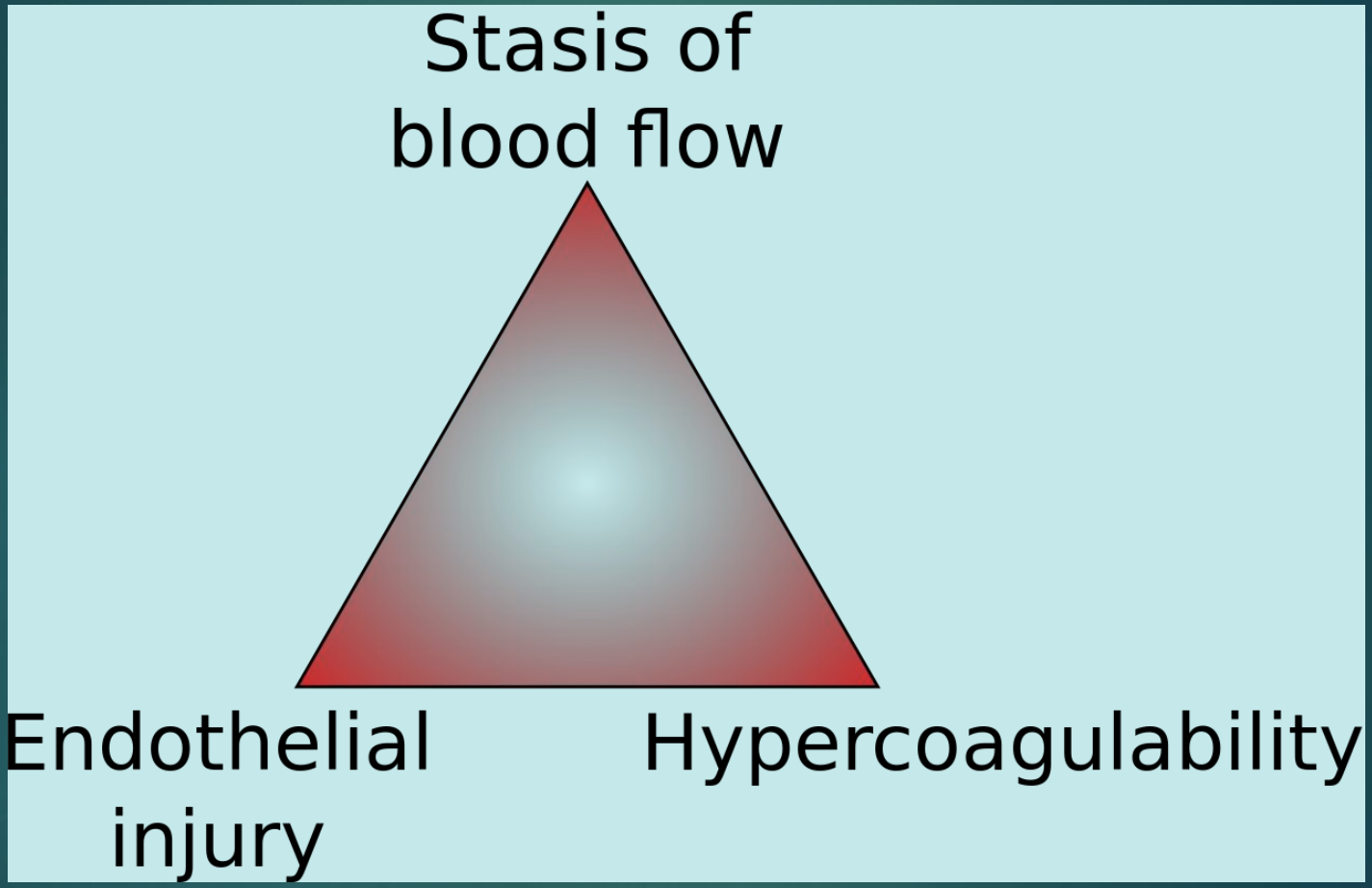
What is thrombophilia?

- It is a state of hypercoagulability.
- Disturbance of the balance between natural procoagulant and natural anticoagulant.



Brea Lipe and Deborah L. Ornstein, Circulation 2011

Pregnancy is thrombogenic



Virchow's triad

Pregnancy is thrombogenic

- In normal pregnancy, there is an increase in the levels of procoagulant factors, such as factors **VII**, **VIII**, **X**, and **fibrinogen**, as early as 12 weeks' gestation.
- However, naturally occurring anticoagulants **antithrombin III** and **protein C** levels remain constant while **protein S** levels decreases by 40-50%.
- Impaired fibrinolysis.

John C Petrozza, Medscape 2016

Table 1. Changes in the Normal Functioning of the Coagulation System During Pregnancy

Coagulant Factors	Change in Pregnancy
Procoagulants	
Fibrinogen	Increased
Factor VII	Increased
Factor VIII	Increased
Factor X	Increased
Von Willebrand factor	Increased
Plasminogen activator inhibitor-1	Increased
Plasminogen activator inhibitor-2	Increased
Factor II	No change
Factor V	No change
Factor IX	No change
Anticoagulants	
Free Protein S	Decreased
Protein C	No change
Antithrombin III	No change

Data from Bremme KA. Haemostatic changes in pregnancy. Best Practice & Research Clinical Haematology. 2003;16:153–68 *and* Medcalf RL, Stasinopoulos SJ. The undecided serpin: the ins and outs of plasminogen activator inhibitor type 2. FEBS J 2005;272:4858–67.

Thrombophilia and RPL?

- Three decades ago, antiphospholipid antibodies (aPL) were proposed to have a causal association with recurrent pregnancy loss (RPL), suspected because of placental clots that were observed after pregnancy loss with subsequent positive serum aPLs.
- Following the hypothesis-inducing investigations, an association was found between aPL and RPL with a causal role of aPL established.

Rai R et al. BMJ. 1997

Types of thrombophilia

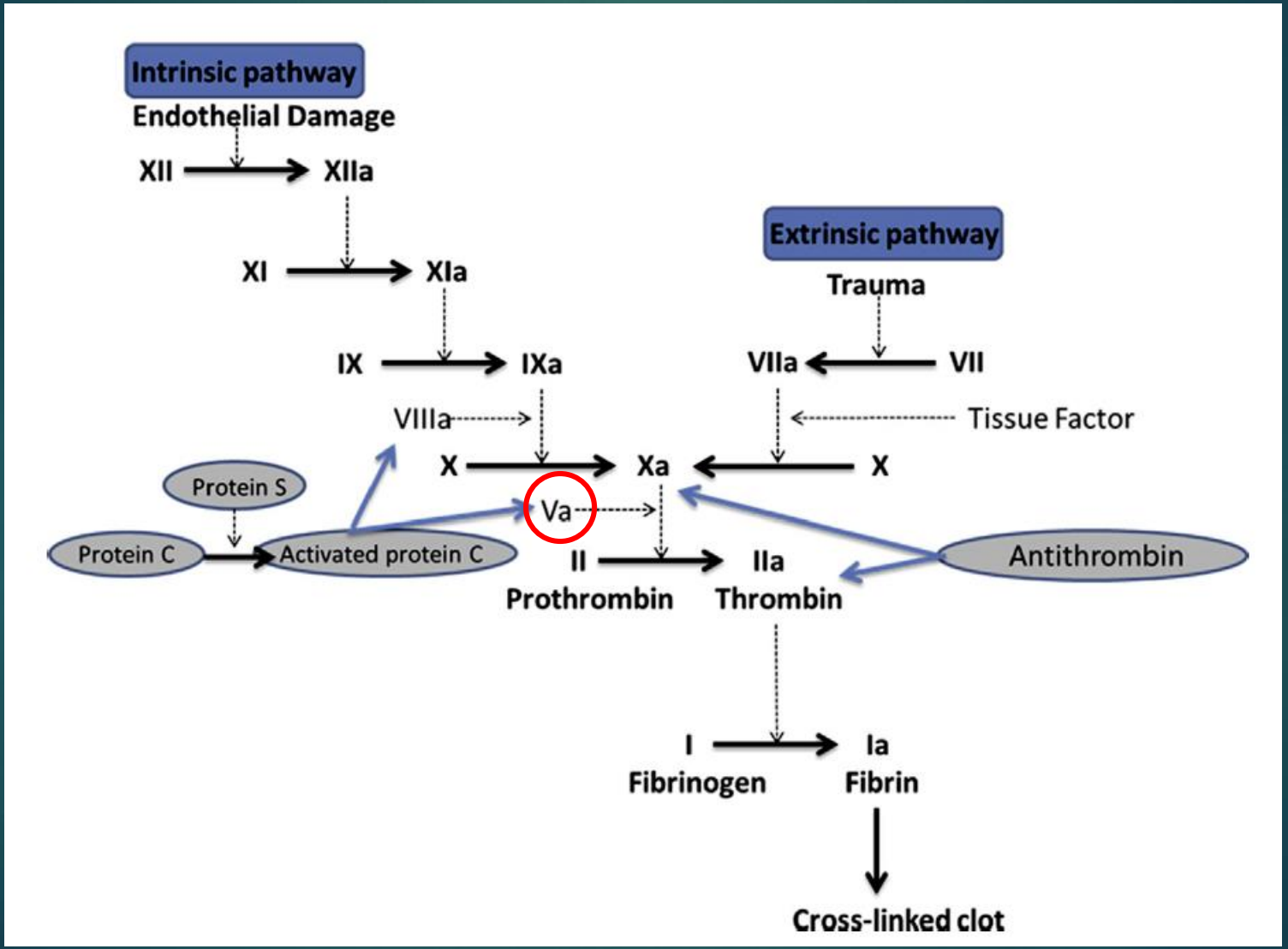
Hereditary

- Factor V Leiden
- Prothrombin G20210A mutation
- Protein C Deficiency and Protein S Deficiency
- Antithrombin Deficiency
- Methylene tetrahydrofolate reductase (MTHFR) gene mutation

Aquired

- Antiphoshpholipid antibody syndrome (APS).

Coagulation cascade



Hereditary thrombophilia

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Hereditary thrombophilia

- **ESHRE 2017 :**
- For women with RPL, we suggest not to screen for hereditary unless in the context of research, or in women with additional risk factors for thrombophilia (Conditional ⊕⊕⊕◻)

Hereditary thrombophilia

- A review of 79 studies and meta-analyses by Robertson et al in 2005 concluded that heterozygous factor V Leiden and prothrombin mutations may be associated with an approximately **two fold** risk of miscarriage, IUFD, preeclampsia, and a 4- to 8-fold risk of abruption.

Hereditary thrombophilia

- However, most prospective studies have failed to find any correlation between inherited thrombophilias and adverse pregnancy outcomes.
- No randomized placebo-controlled clinical trials have confirmed any benefit in the treatment of thrombophilias (other than antiphospholipid antibody syndrome) in terms of decreasing adverse pregnancy outcomes.

Hereditary thrombophilia

TABLE 52-2. Inherited Thrombophilias and Their Association with Venous Thromboembolism (VTE) in Pregnancy

	Prevalence in General Population (%)	VTE Risk per Pregnancy (No History) (%)	VTE Risk per Pregnancy (Prior VTE) (%)	All VTE (%)
Factor V Leiden heterozygote	1–15	0.5–1.2	10	40
Factor V Leiden homozygote	< 1	4	17	2
Prothrombin gene heterozygote	2–5	< 0.5	> 10	17
Prothrombin gene homozygote	< 1	2–4	> 17	0.5
Factor V Leiden/prothrombin double heterozygote	0.01	4–5	> 20	1–3
Antithrombin III activity (< 60%)	0.02	3–7	40	1
Protein C activity (< 50%)	0.2–0.4	0.1–0.8	4–17	14
Protein S free antigen (< 55%)	0.03–0.13	0.1	0–22	3

Adapted from the American College of Obstetricians and Gynecologists, 2013.

Hereditary thrombophilia

TABLE 52-3. Obstetrical Complications Associated with Thrombophilias

Type of Thrombophilia	Early Loss	Recurrent First-Trimester Loss	Nonrecurrent Second-Trimester Loss	Late Loss	Preeclampsia	Placental Abruption	Fetal-Growth Restriction
Factor V Leiden (homozygous)	**2.71 (1.32–5.58)**	—[a]	[a]	1.98 (0.40–9.69)	1.87 (0.44–7.88)	8.43 (0.41–171.20)	4.64 (0.19–115.68)
Factor V Leiden (heterozygous)	**1.68 (1.09–2.58)**	**1.91 (1.01–3.61)[a]**	**4.12 (1.91–8.81)[a]**	**2.06 (1.10–3.86)**	**2.19 (1.46–3.27)**	**4.70 (1.13–19.59)**	2.68 (0.59–12.13)
Prothrombin gene mutation (heterozygous)	**2.49 (1.24–5.00)**	**2.70 (1.37–5.34)**	**8.60 (2.18–33.95)**	**2.66 (1.28–5.53)**	**2.54 (1.52–4.23)**	**7.71 (3.01–19.76)**	2.92 (0.62–13.70)
MTHFR C677T (homozygous)	1.40 (0.77–2.55)	0.86 (0.44–1.69)	NA	1.31 (0.89–1.91)	**1.37 (1.07–1.76)**	1.47 (0.40–5.35)	1.24 (0.84–1.82)
Antithrombin deficiency	0.88 (0.17–4.48)	NA	NA	7.63 (0.30–196.36)	3.89 (0.16–97.19)	1.08 (0.06–18.12)	NA
Protein C deficiency	2.29 (0.20–26.43)	NA	NA	3.05 (0.24–38.51)	5.15 (0.26–102.22)	5.93 (0.23–151.58)	NA
Protein S deficiency	3.55 (0.35–35.72)	NA	NA	**20.09 (3.70–109.15)**	2.83 (0.76–10.57)	2.11 (0.47–9.34)	NA
Anticardiolipin antibodies	**3.40 (1.33–8.68)**	**5.05 (1.82–14.01)**	NA	**3.30 (1.62–6.70)**	**2.73 (1.65–4.51)**	1.42 (0.42–4.77)	**6.91 (2.70–17.68)**
Lupus anticoagulants (nonspecific inhibitor)	**2.97 (1.03–9.76)**	NA	**14.28 (4.72–43.20)**	2.38 (0.81–6.98)	1.45 (0.70–4.61)	NA	NA
Hyper-homocysteinemia	**6.25 (1.37–28.42)**	**4.21 (1.28–13.87)**	NA	0.98 (0.17–5.55)	**3.49 (1.21–10.11)**	2.40 (0.36–15.89)	NA

[a]Homozygous and heterozygous carriers were grouped together; it is not possible to extract data for each state.
Data are presented as odds ratio (OR [95% CI]) and are derived from Robertson, 2005. Bolded numbers are statistically significant.
MTHFR = methylene tetrahydrofolate reductase variant; NA = not available.
From Bates, 2012.

Hereditary thrombophilia

- **ESHRE 2017 :**
- There is no, or a weak association at best, between RPL and hereditary thrombophilia. The recommendation not to screen for hereditary thrombophilia in women experiencing RPL is similar to the recommendations of the guideline on VTE, thrombophilia, antithrombotic therapy and pregnancy of the American College of Chest Physicians (Bates *et al.*, 2012).

Hereditary thrombophilia

- **ESHRE 2017 :**
- If additional risk factors for hereditary thrombophilia are present (for instance family members with hereditary thrombophilia, or previous VTE), screening can be considered. Also in a research setting, screening can be considered to provide further data on the impact of thrombophilia in women experiencing RPL.

Hereditary thrombophilia

- **ESHRE 2017 :**

Justification

	Association	Contributing factor	Prognosis	Treatment
Hereditary thrombophilia*	No/weak	Unclear	Yes	No

** this includes Factor V Leiden mutation - Prothrombin mutation - MTHFR mutation - Protein C, Protein S and Antithrombin deficiency*

Hereditary thrombophilia

- **ESHRE 2017 :**
- Correct interpretation of results and diagnosis of hereditary thrombophilia during pregnancy is possible for the DNA mutations factor V Leiden and prothrombin 20210A, but can be problematic for antithrombin, protein C, and most notably protein S.
- Therefore, it is recommended to postpone screening for hereditary thrombophilia until 6 weeks after the pregnancy loss.

Hereditary thrombophilia

TABLE 52-4. Inherited Thrombophilia Testing

Thrombophilia	Testing Method	Is Testing Reliable During Pregnancy?	Is Testing Reliable During Acute Thrombosis?	Is Testing Reliable with Anticoagulation?
Factor V Leiden mutation	Activated protein C resistance assay (second generation)	Yes	Yes	No
	If abnormal: DNA analysis	Yes	Yes	Yes
Prothrombin gene mutation G20210A	DNA analysis	Yes	Yes	Yes
Protein C deficiency	Protein C activity (< 60%)	Yes	No	No
Protein S deficiency	Functional assay (< 55%)	No[a]	No	No
Antithrombin deficiency	Antithrombin activity (< 60%)	Yes	No	No

[a]In nonpregnant patients, protein S deficiency should be assessed initially by performing a functional assay. A value < 55 percent should be followed with measurement of free protein S levels. A free protein S antigen value < 55 percent is consistent with protein S deficiency. If screening in pregnancy is necessary, threshold values for free protein S antigen levels in the second and third trimesters have been identified at < 30 percent and < 24 percent, respectively.
Adapted from the American College of Obstetricians and Gynecologists, 2013.

Hereditary thrombophilia

Recommendation		
For women with hereditary thrombophilia and a history of RPL, we suggest not to use antithrombotic prophylaxis unless in the context of research, or if indicated for VTE prevention.	Conditional	⊕⊕◯◯

Hereditary thrombophilia

مش قولتلكم مفيش أي علاقة.....اللي بعده

Acquired thrombophilia

- In contrast, an association between APS and adverse pregnancy outcomes has been well-established.
- Furthermore, evidence supports the use of low-dose aspirin and heparin to decrease the risk of early pregnancy loss in women with lupus anticoagulant and aPLs.

aPLs has the following effects

1. Inhibition of villous cytotrophoblast differentiation and extravillous cytotrophoblast invasion into the decidua.
2. Induction of syncytiotrophoblast apoptosis.
3. Initiation of maternal inflammatory pathways on the syncytiotrophoblast surface.

ASRM 2012

International Consensus Classification criteria for the antiphospholipid syndrome (APS) (23, 24).

APS is present if one of the following clinical criteria and one of the laboratory criteria are met.

Clinical criteria

1. Vascular thrombosis
2. Pregnancy morbidity
   a. One or more unexplained deaths of morphologically normal fetuses after the 10^{th} week of gestation by ultrasound or direct examination of the fetus.
   b. One or more premature births of a morphologically normal neonate before the 34^{th} week of gestation because of eclampsia or severe pre-eclampsia or recognized features of placental insufficiency.
   c. Three or more unexplained consecutive spontaneous abortions before the 10^{th} week of gestation with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

1. Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart, or
2. Anticardiolipin antibody of IgG or IgM isotype in serum or plasma present in medium or high titer (>40 GPL or MPL or $> 99^{th}$ percentile), on two or more occasions at least 12 weeks apart, or
3. Anti-β_2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer greater than the 99^{th} percentile), present on two or more occasions at least 12 weeks apart.

Practice Committee. Recurrent pregnancy loss. Fertil Steril 2012.

ESHRE 2017

Recommendations

For women with RPL we recommend screening for antiphospholipid antibodies (LA and ACA [IgG and IgM]), after two pregnancy losses.	Strong	⊕⊕◯◯
For women with RPL screening for aβ2GPI can be considered after two pregnancy losses.	GPP	

ESHRE 2017

Justification

	Association	Contributing factor	Prognosis	Treatment
Antiphospholipid antibodies: LA and ACA (IgG and IgM)	Yes	Yes	Yes	Weak evidence
aβ2GPI	Possible (not statistically significant)	Possible	No data	No data

RCOG 2011

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.

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ESHRE 2017

Recommendations

For women who fulfill the laboratory criteria of APS and a history of three or more pregnancy losses, we suggest administration with low-dose aspirin (75 to 100 mg/day) starting before conception, and a prophylactic dose heparin (UFH or LMWH) starting at date of a positive pregnancy test, over no treatment.	Conditional	⊕◯◯◯
The GDG suggests offering anticoagulant treatment for women with two pregnancy losses and APS, only in the context of clinical research.	GPP	

RCOG 2011

Neither corticosteroids nor intravenous immunoglobulin therapy improve the live birth rate of women with recurrent miscarriage associated with antiphospholipid antibodies compared with other treatment modalities; their use may provoke significant maternal and fetal morbidity.

A

Acquired thrombophilia

- The existing evidence suggests that a combination of heparin (more for UFH than for LMWH) and aspirin improves LBR in women with APS and RPL (three or more PLs, no evidence for two or more PLs).

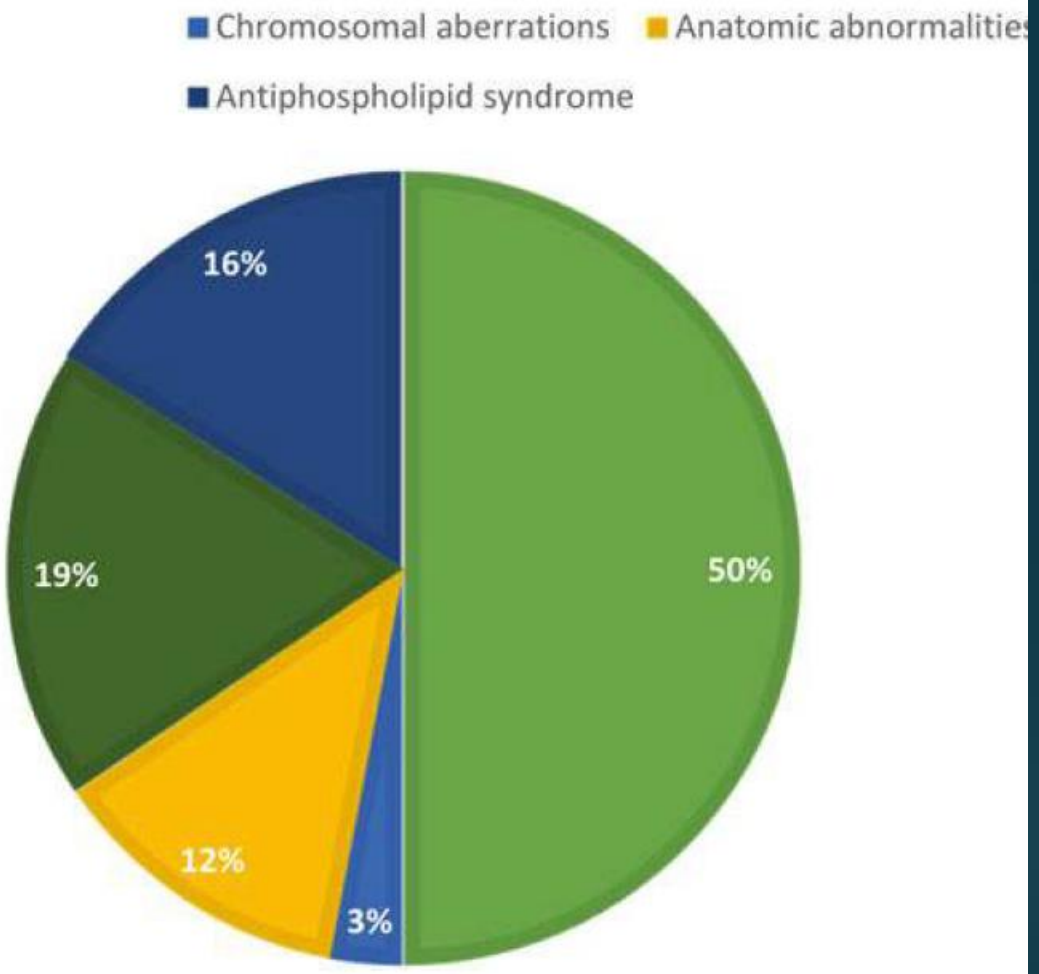
Acquired thrombophilia

- In women with APS, almost no data are available to support the use of aspirin only to prevent recurrent pregnancy loss.
- For thrombosis prophylaxis, LMWH is preferred over UFH, because of a lower risk of osteoporosis and heparin-induced thrombocytopenia (Bates et al., 2012). In clinical practice, women with APS and RPL are prescribed LMWH, but it should be realized that the evidence for efficacy of LMWH in RPL is absent.

Take home message

1. **Don't rush into investigations. Define clearly what is and what is not RPL.**
2. **There is no evidence supporting screening or treatment of inherited thrombophilia for the purpose of RPL.**
3. **Women with RPL should be screened for APS.**
4. **Remember APS is not a lab only diagnosis and confirmation after at least 12 weeks should be done.**

Fig. 1.3 Etiology of RPL



Thank you