



# Recurrent miscarriage – From Witchcraft to Evidence

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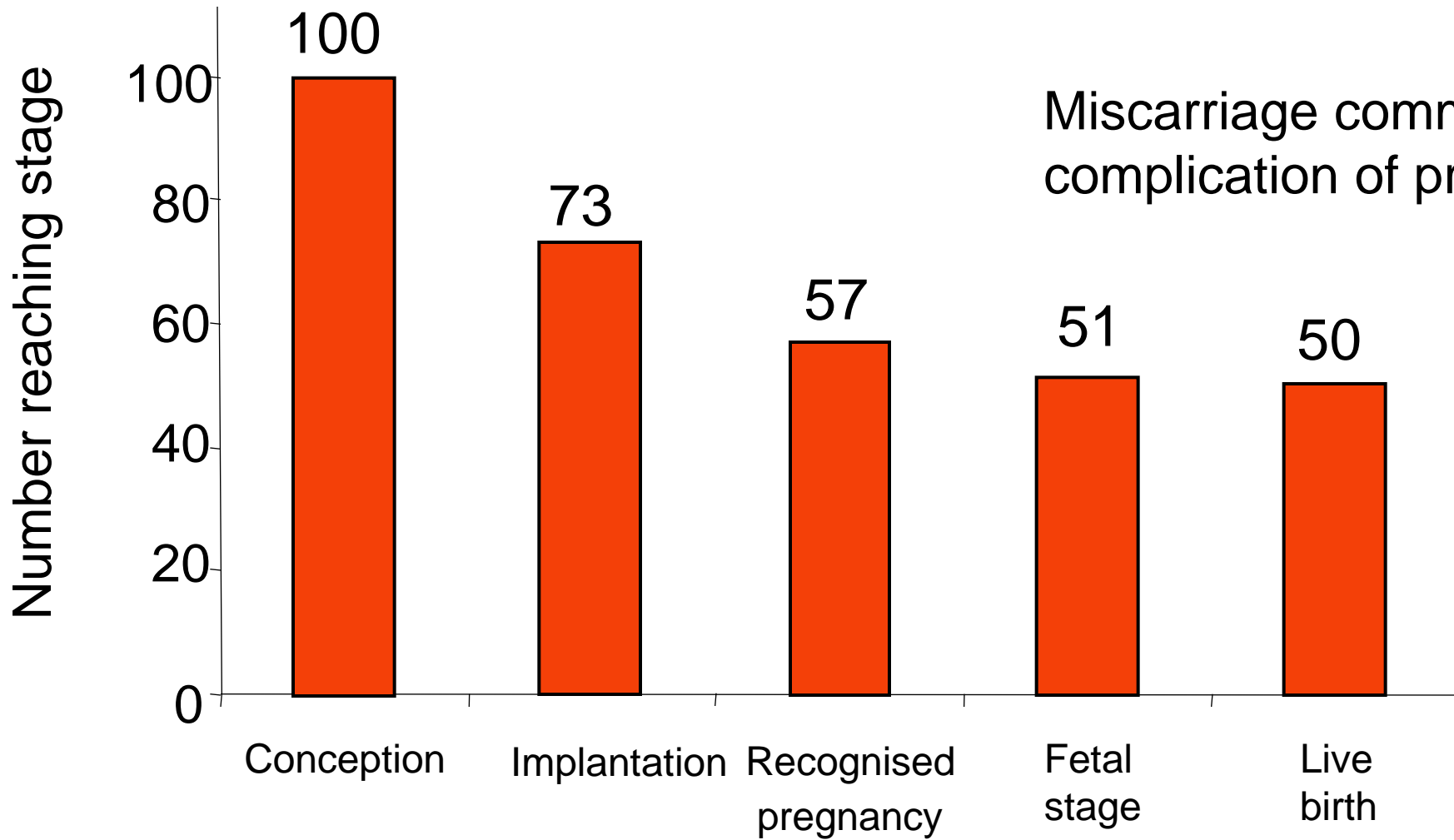


# Recurrent miscarriage

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- ◆ Overview of miscarriage
- ◆ Natural Killer cells
- ◆ Antiphospholipid Syndrome
- ◆ Reproductive haemostasis
- ◆ Evidence – based advice - ? Role for aspirin  
Supportive care

# Fate of the fertilised egg - POOR



Miscarriage commonest complication of pregnancy

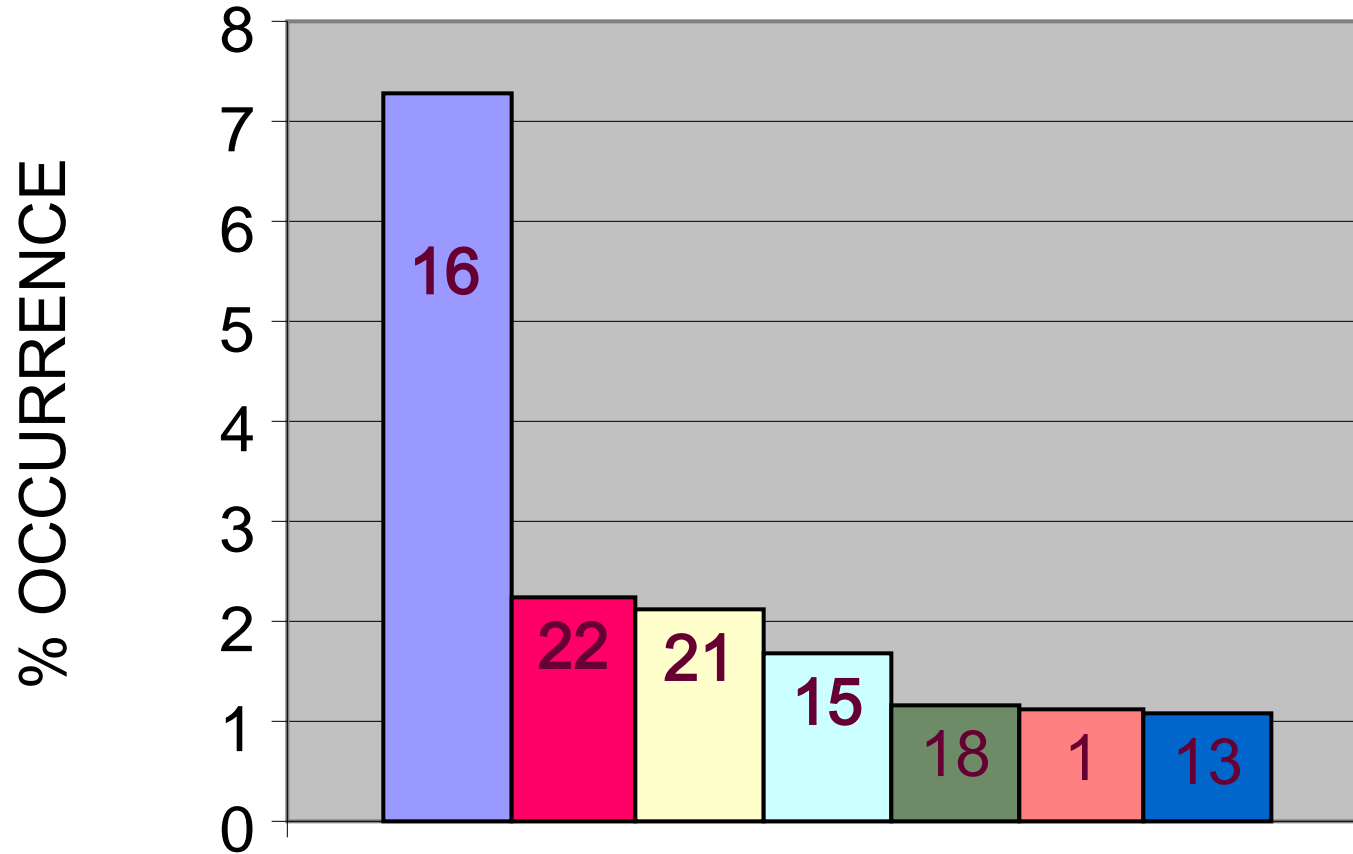


## Sporadic miscarriage

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- ◆ Commonest complication of pregnancy
- ◆ 15% of recognised pregnancies miscarry
- ◆ 25% of women will experience a sporadic miscarriage

# Frequency of individual trisomies in POC



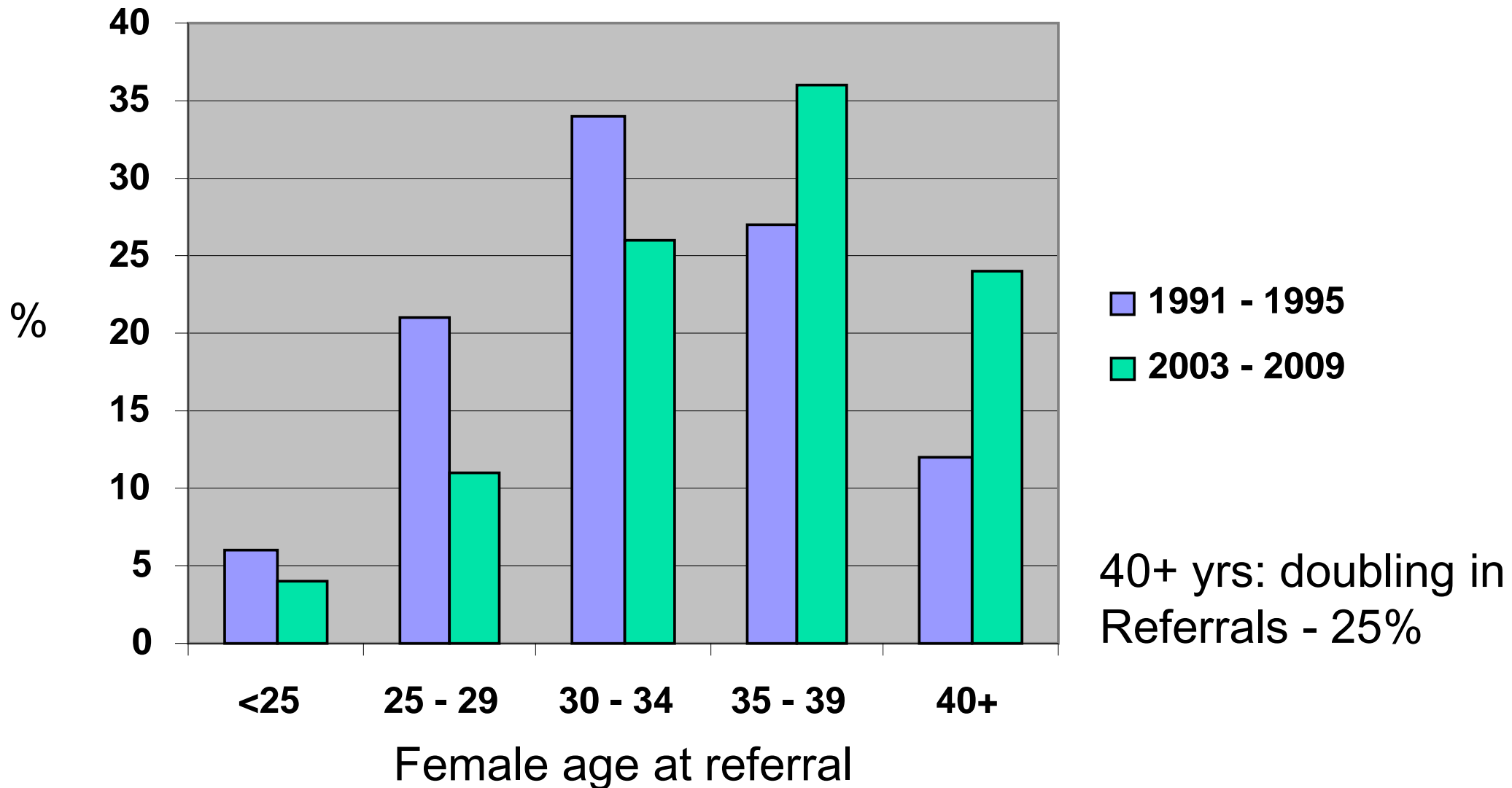


# Increasing birth rates in over 40s: 1994 - 2008

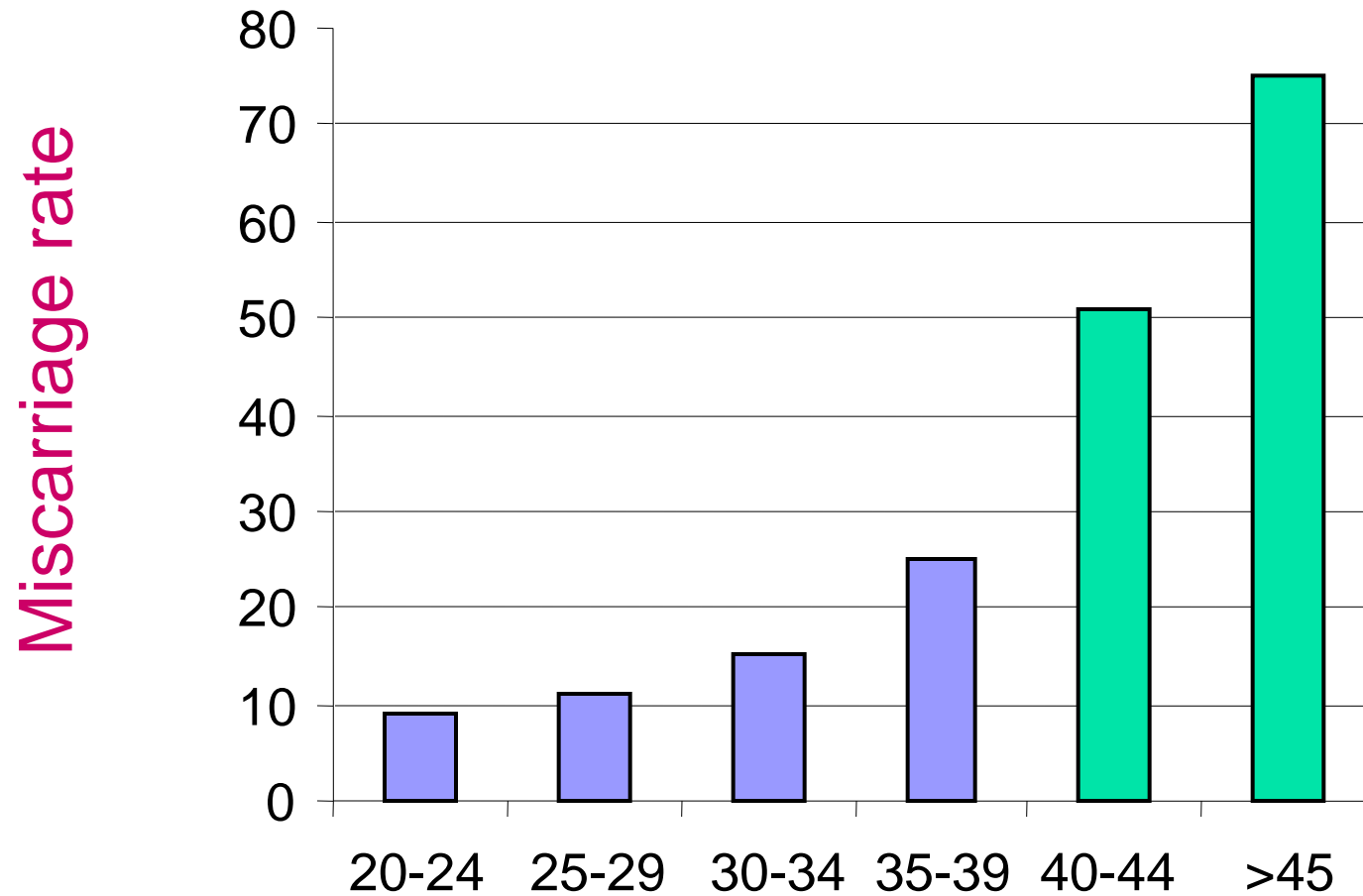
## Significant societal changes in our reproductive pattern

	1994	2008	% increase
35 - 39	63061	102228	62
40 - 44	10241	19884	94
≥ 45	488	909	86

# RMC - Referral pattern by female age

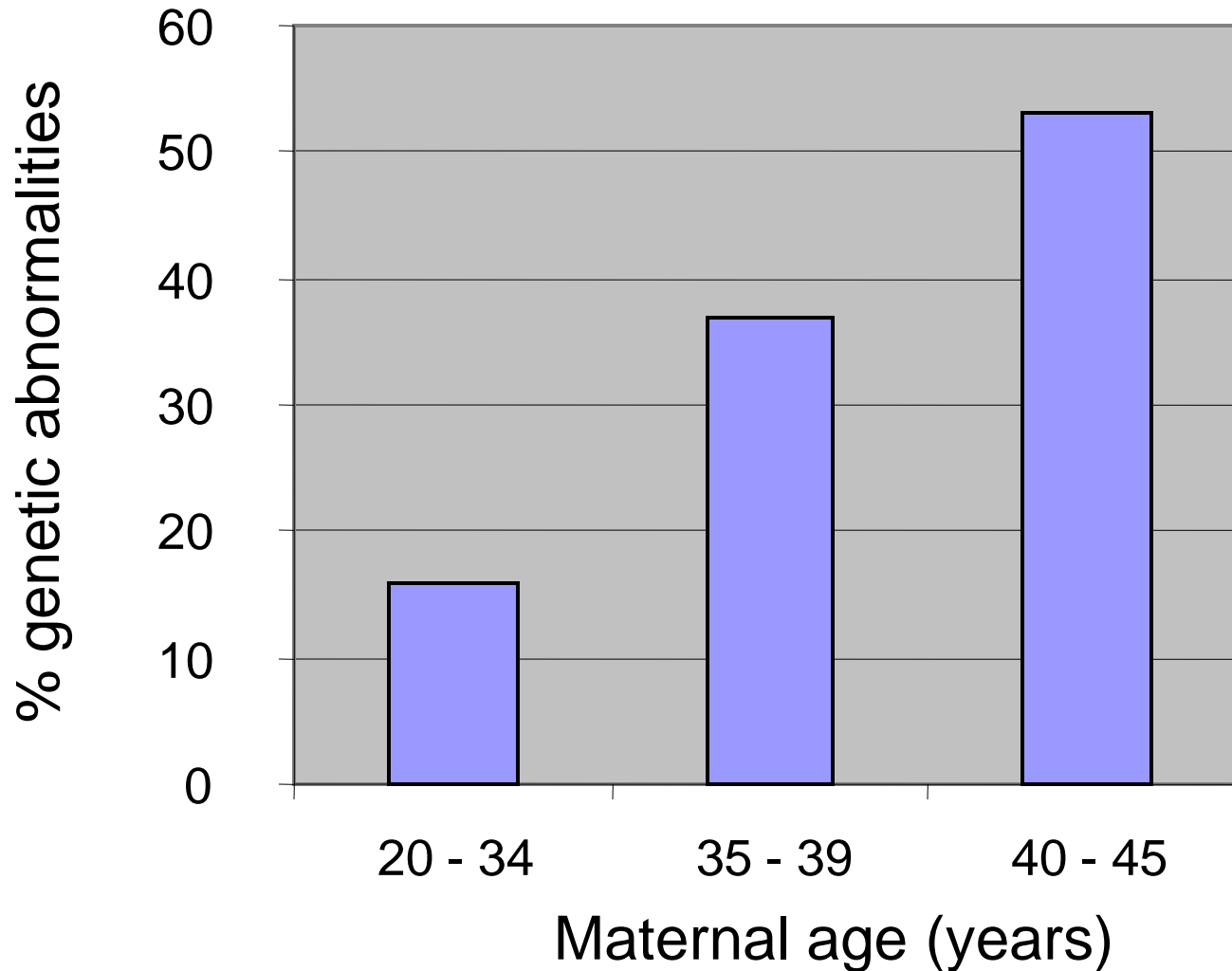


# Increasing miscarriage rate with advancing female age





# Increasing rate of genetic abnormalities with advancing maternal age





# Recurrent miscarriage

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## Definition

Loss of 3 or more consecutive pregnancies

## Expected incidence

$$15\% \times 15\% \times 15\% = 0.34\%$$

## Observed incidence

$$= 0.8\% - 1.0\%$$



## Previous history key determinant of future performance

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### Cambridge EPL study ( n = 407 )

#### Risk of recurrence

- ◆ After 1 misc 20%
- ◆ After 2 misc 28%
- ◆ After 3 misc 43%

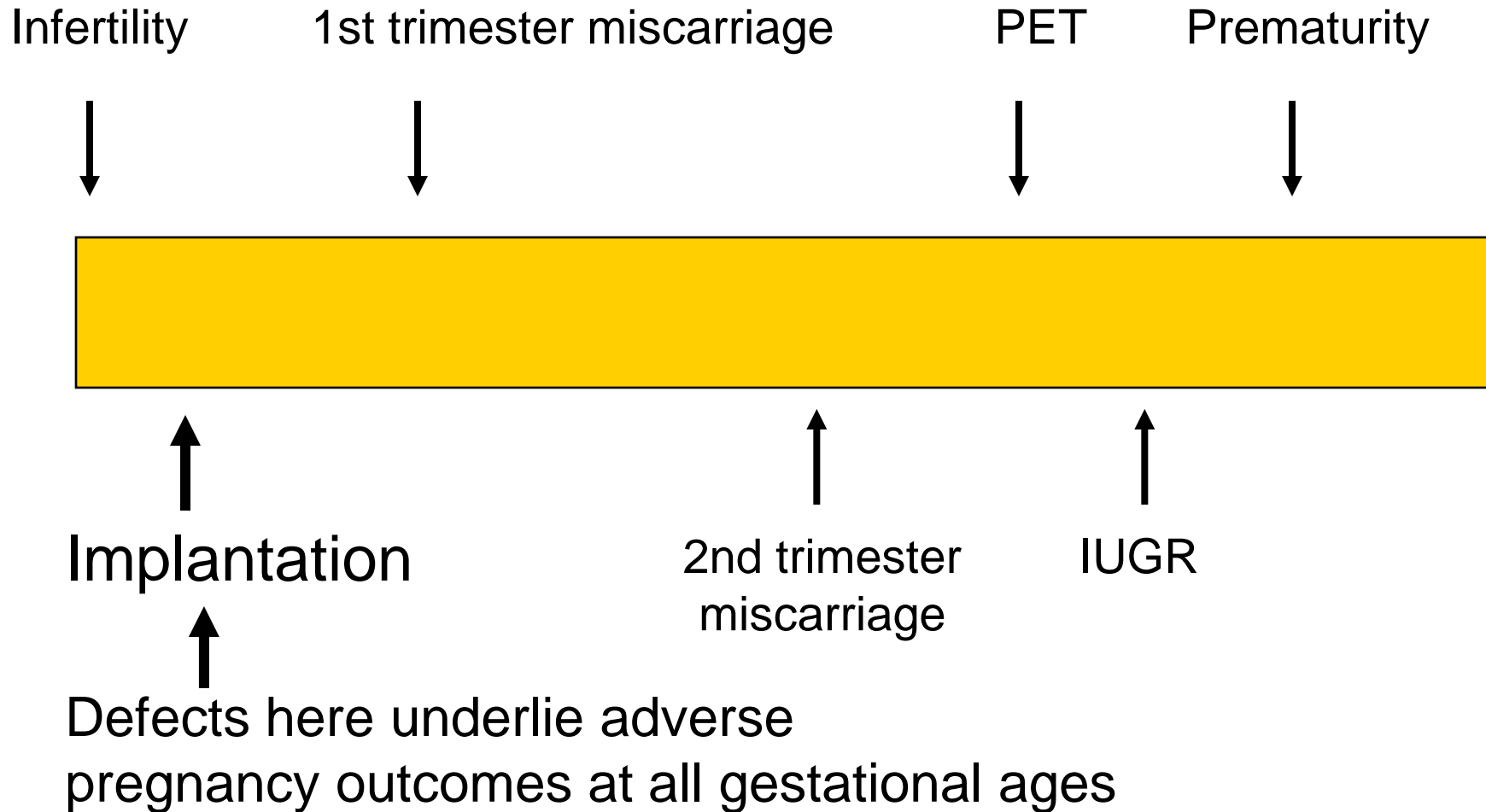


# Recurrent miscarriage - background

- **Sporadic miscarriage** –
  - commonest complication of pregnancy
  - 25% of couples - sporadic miscarriage
  - random fetal chromosome abnormality
- **Recurrent miscarriage**
  - 1% of couples (expected by chance alone = 0.34%)
  - risk ↑ with female age & no. of previous losses
  - lose chromosomally normal pregnancies
  - 6,000 couples / year in UK
  - financial cost of £28 million / year
  - significant psychological sequelae



# Implantation spectrum of adverse pregnancy outcome





# Recurrent miscarriage - Investigation & Treatment

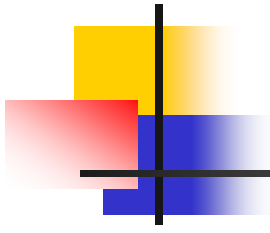
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- Anecdotal evidence
- Historical beliefs
- Small uncontrolled studies

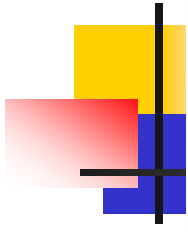


- Treatments of NO proven efficacy
- Some of these harmful

Rai et al (1996) Br J Obstet Gynaecol



In modern times the exploitation of the expectations of the sick for a cure have been so increased by the successes of science that even the most outrageous quackery markets itself with scientific jargon.



# FREE METRO

19.02.2010  
metro.co.uk

Still sexy after all these years  
  
Jeff Bridges P10



My little miracle: Angie Baker with her baby girl, Raiya  
Picture: PA

## The £20 miracle that made me a mother after 18 miscarriages

SHE went through the unimaginable pain and loss of 18 miscarriages.

But, thanks to a pioneering treatment which costs just £20, Angie Baker now has a baby girl to call her own.

The 33-year-old, who had been trying to start a family for 13 years, calls ten-week-old daughter Raiya her 'little miracle'.

Ms Baker said: 'I never gave up. I was desperate for a baby so I persevered. It seems like a dream and I still have to pinch myself. She's perfect in every way.'

Doctors gave her the £20 steroid treatment after discovering she had high levels of a type of white blood cell which treated foetuses as foreign bodies and

By **Joel Taylor**

attacked them. From the age of 20, Ms Baker's failed pregnancies took place again and again, between five and eight weeks after conception – but doctors told her it was 'just one of those things'.

After her 17th miscarriage, Ms Baker contacted Dr Hassan Shehata, a recurrent miscarriage expert who works at Epsom and St Helier University Hospitals NHS Trust.

He discovered her level of Natural Killer white blood cells was much higher than average and prescribed a steroid treatment.

When she fell pregnant for the 18th time, it was discovered that she was diabetic and the high sugar levels caused by the steroids resulted in yet another miscarriage.

Dr Shehata then adjusted Ms Baker's insulin levels and her next

pregnancy was successful. The treatment is pioneering because it starts before conception and doses are higher than previously used.

Dr Shehata said: 'This is the most unusual case I've come across. You're more likely to win the lottery than have 18 miscarriages through bad luck.'

Lab equipment for the cell tests costs up to £200,000, with each test an additional £200. But the treatment itself – one 25mg tablet a day for two weeks before conception and 12 weeks after – costs just £20.

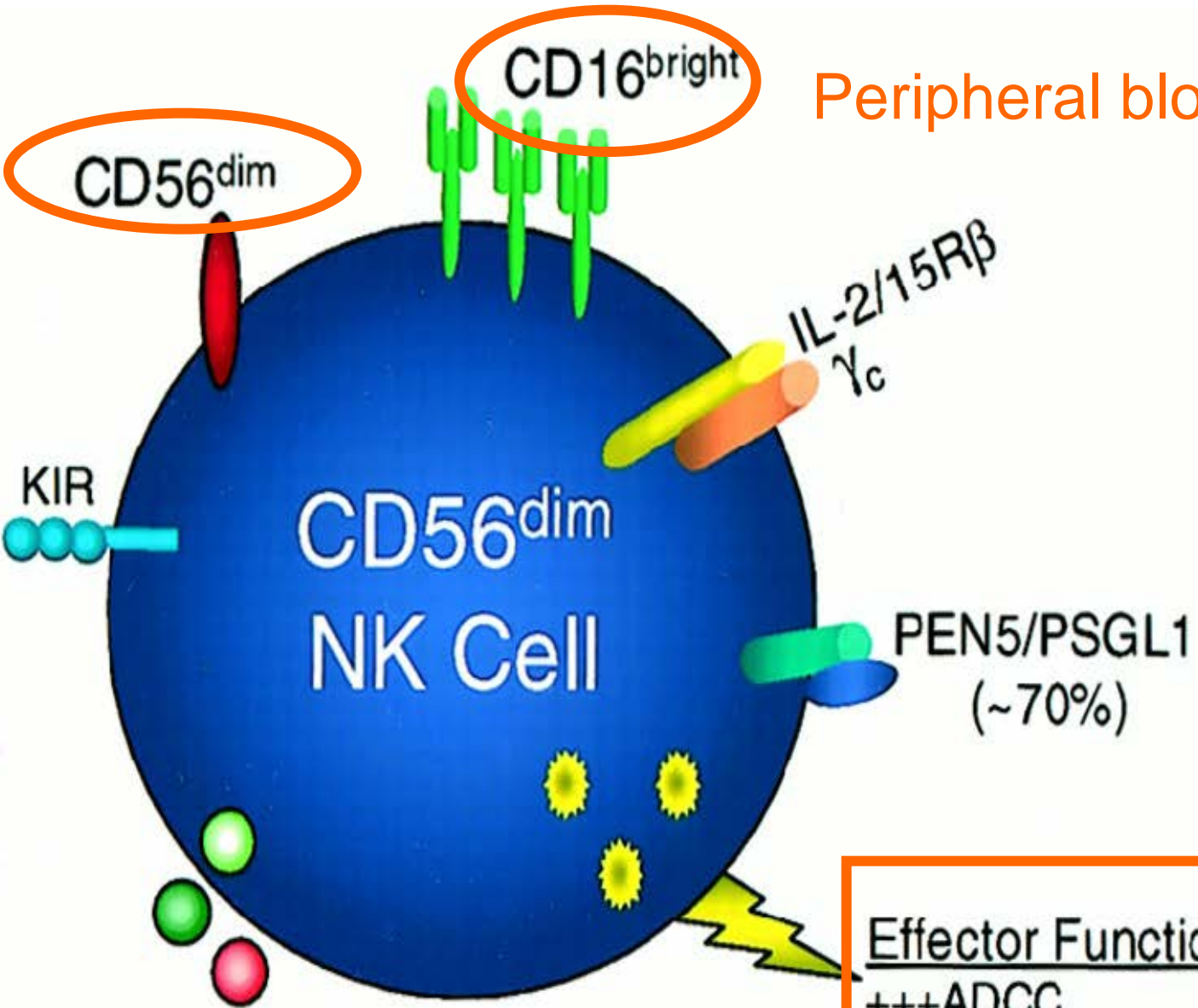
Ms Baker, who had considered adopting with partner Lee Gibson, is revelling in motherhood. 'I enjoy every moment. It's so precious. I can't believe she's here and she's mine,' she said.

The couple, from Peacehaven, near Brighton, are now hoping to have a brother or sister for Raiya.

**'I can't believe she's here and she's mine'**



Peripheral blood NK



NKRs  
+++ KIR  
+ CD94/NKG2A

Effector Functions  
+++ADCC  
+++LAK  
+++Natural Cytotoxicity

Low Cytokine Production

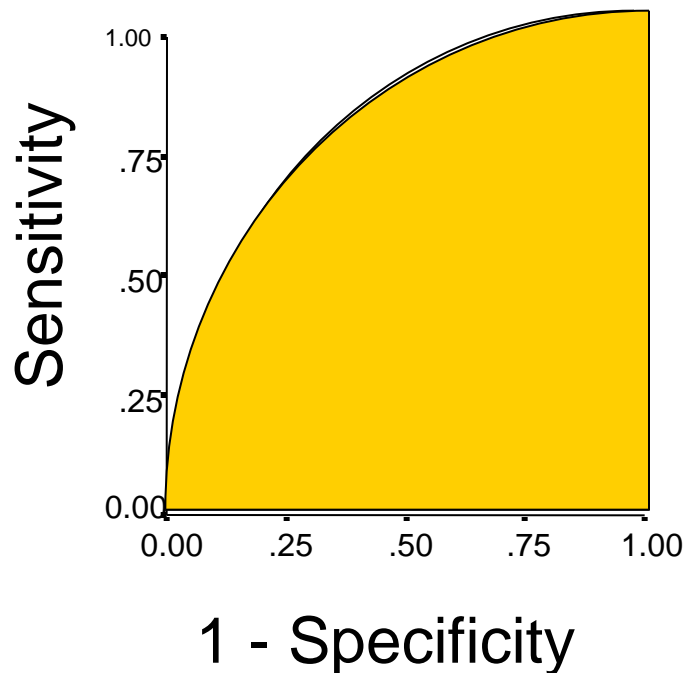
### To establish

- Is there is a correlation between PBNK and uNK cell levels
- Relationship between PBNK and pregnancy outcome amongst women with RM

# PBNK and pregnancy outcome - ROC curve analysis

## Receiver operator curve (ROC)

Graphical plot of the sensitivity of a test (PBNK level) Vs (1-specificity) for a binary classifier (live birth or miscarriage)



Perfect test - AUC = 1.0  
Worthless test - AUC = 0.5

CD56<sup>+</sup>/CD16<sup>+/-</sup> AUC = 0.61  
CD56<sup>+</sup>/CD16<sup>+</sup> AUC = 0.60  
CD56<sup>+</sup>/CD16<sup>-</sup> AUC = 0.56



# Diagnostic pitfalls in PBNK cell testing

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## ■ What is a raised NK cell number???

Traditionally > 12% but NO basis for this

## ■ Levels dependent on

Whole blood or fractionated cells

Time of day sample is taken

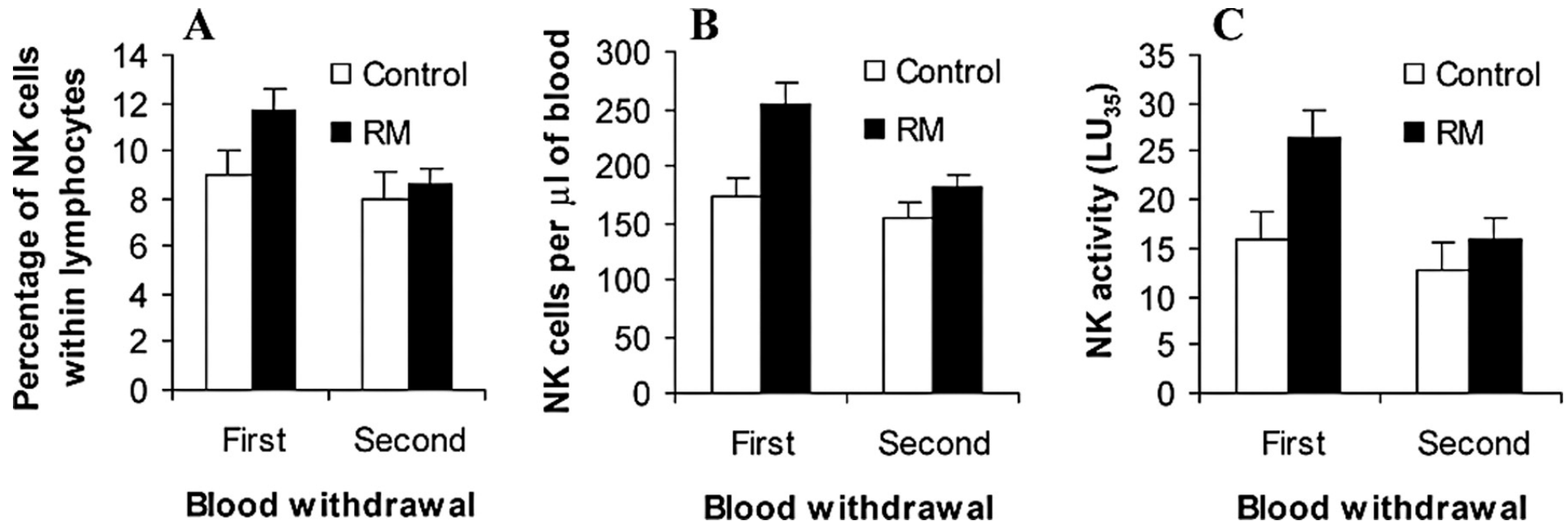
Physical exercise

Parity

Whether tubes or heparinised or not

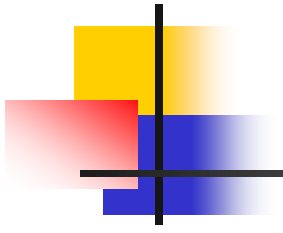
FACS analysis gating

# NK cell indices (mean {+/-} SE) in the first and second blood withdrawal in women with recurrent miscarriage and controls



Shakhar, K. et al. Hum. Reprod. 2006 21:2421-2425; doi:10.1093/humrep/del131

NK cells express beta adrenergic receptors;  
levels increase in response to Cathecholamine levels



# Antiphospholipid Syndrome and miscarriage

- Beyond thrombosis



## Antiphospholipid antibodies (aPL)

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- ◆ Family of ~20 antibodies directed against phospholipid binding proteins

Lupus anticoagulant (LA)

Anti-cardiolipin antibodies (aCL)

Anti-phosphotidyl serine, -phosphotidyl ethanolamine



## Anti-phospholipid Syndrome & recurrent miscarriage

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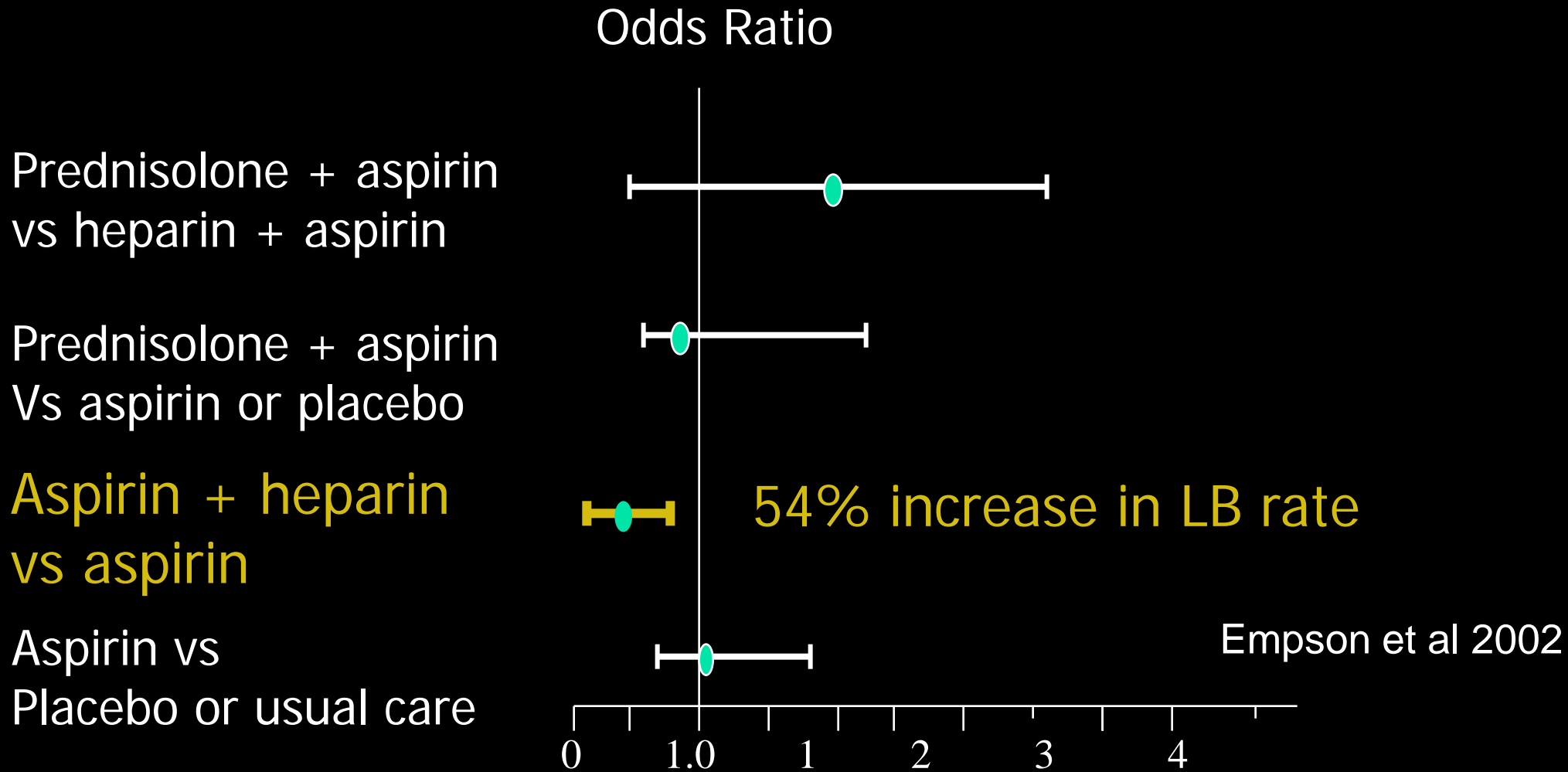
- ◆ Association between lupus anticoagulant / anticardiolipin antibodies & RM
- ◆ Most important treatable cause of RM
- ◆ 15% of recurrent miscarriers have APS
- ◆ Untreated - Prospective fetal loss rate as high as 90%  
Increased incidence of IUGR; preterm labour; pre-eclampsia
- ◆ Pathogenesis of fetal loss: thrombotic



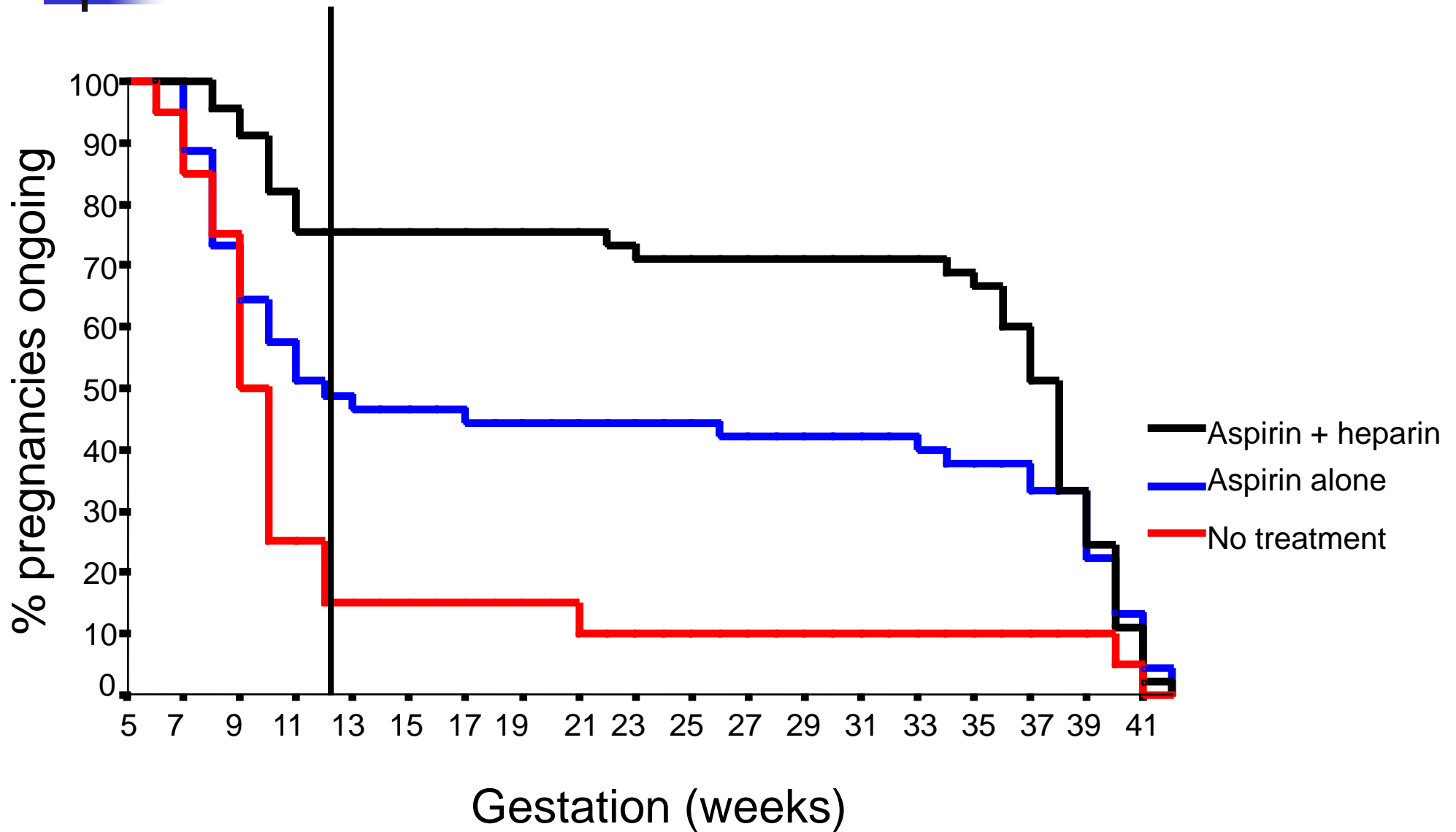
aPL and pregnancy loss – thrombosis in a 3<sup>rd</sup> trimester placenta



# Treatment in aPL-pregnancies – meta-analysis



# Prospective outcome of treated and untreated aPL pregnancies

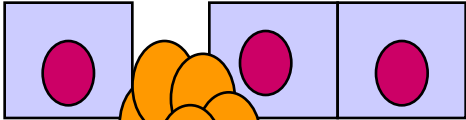
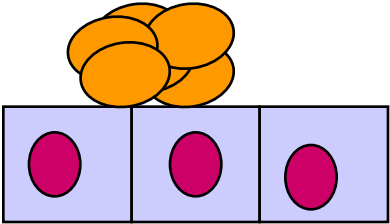
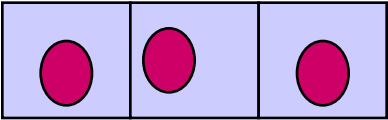


# Implantation - key event in the establishment of pregnancy

Apposition

Adhesion

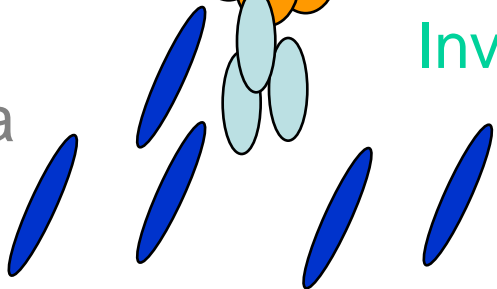
Invasion



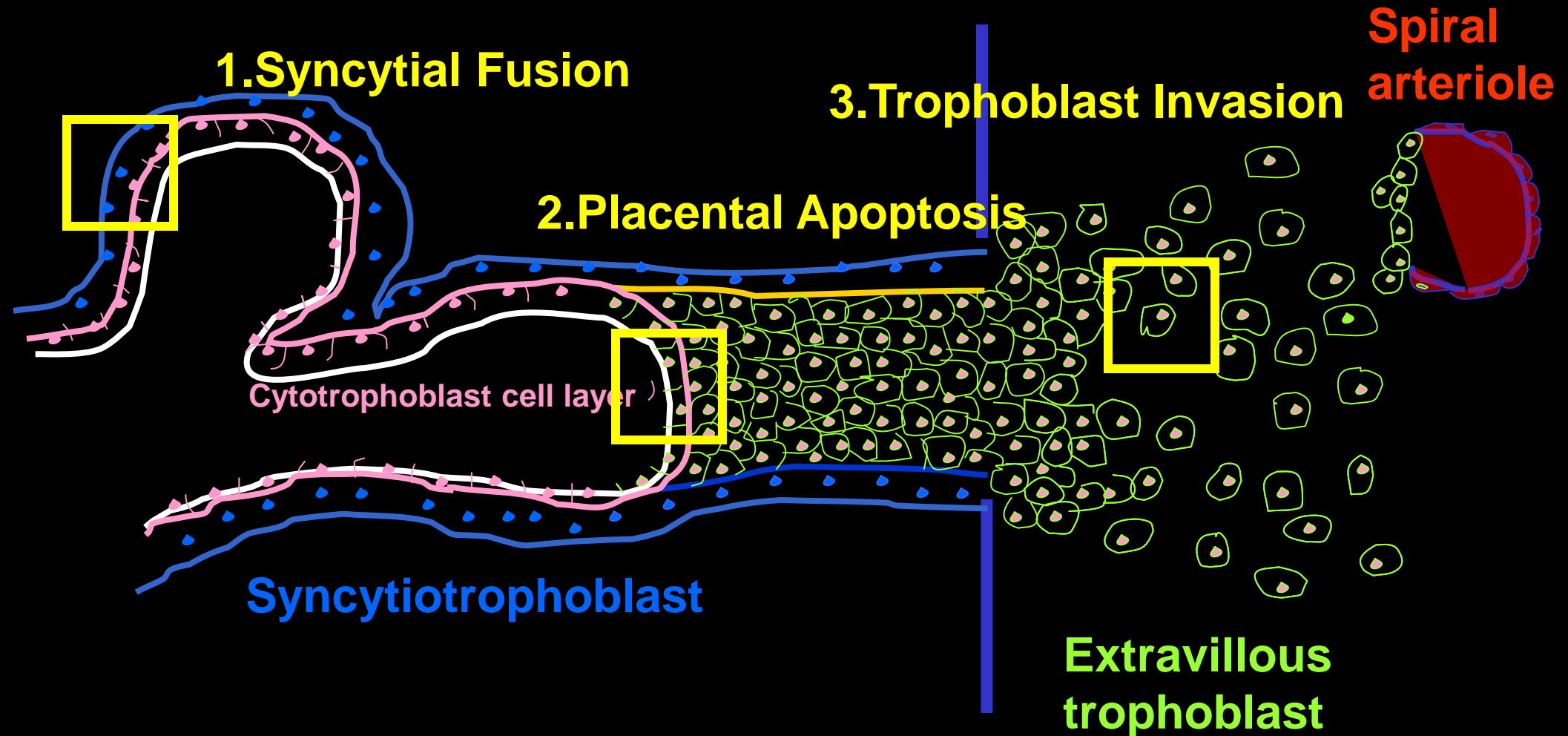
Uterine epithelium

Endometrial stroma

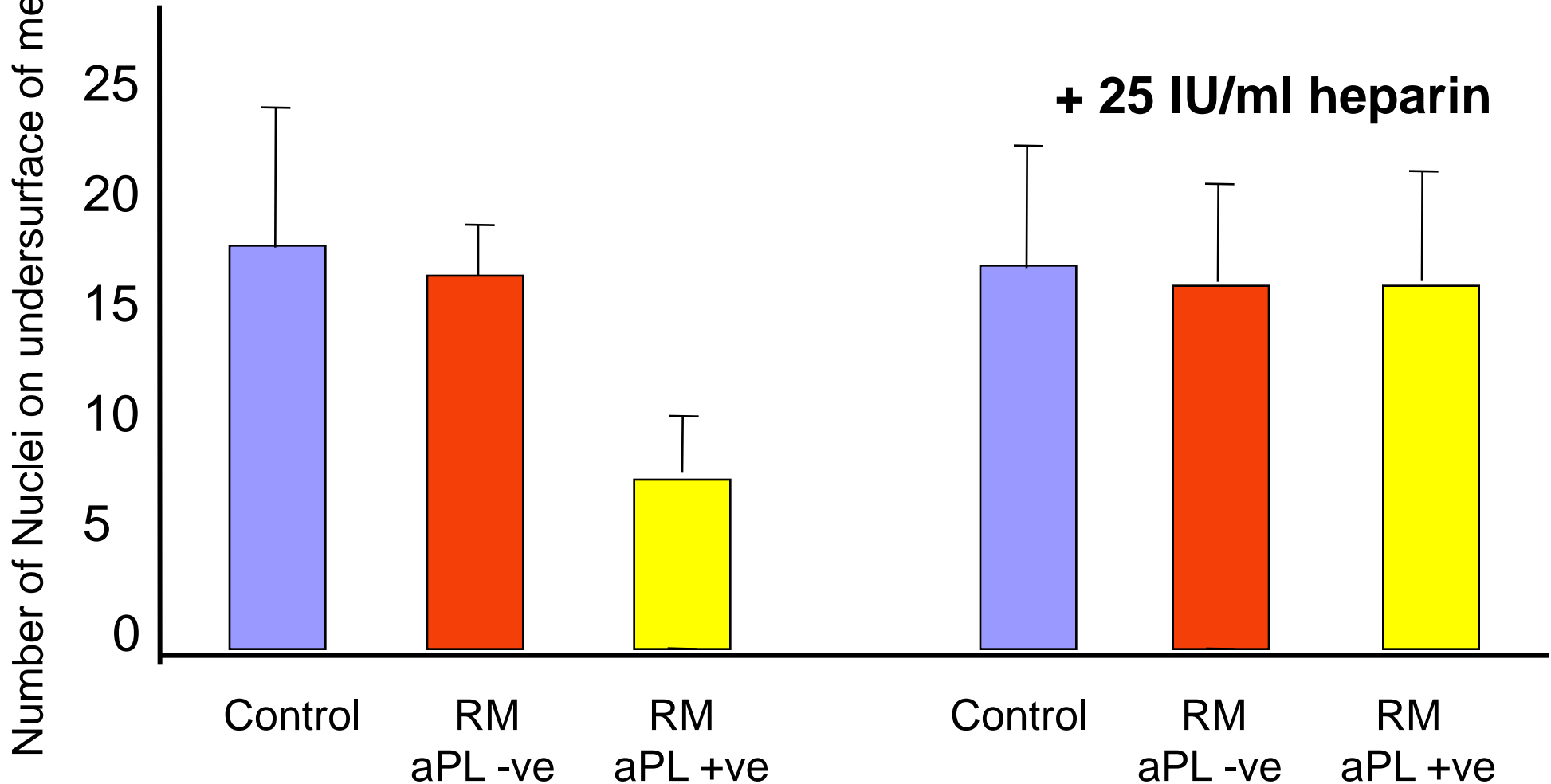
Invading trophoblast



# aPL affect trophoblast function

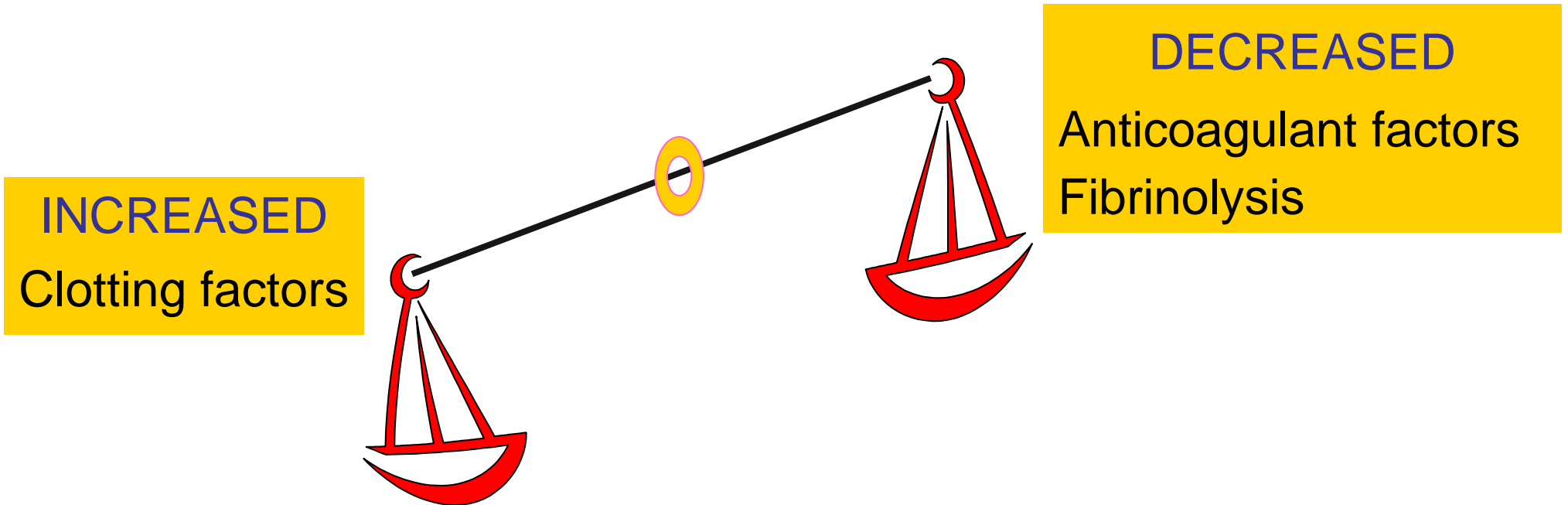


Matrigel invasion assay –  
aPL Sera Reduces EVT Invasion  
Unfractionated Heparin Promotes EVT Invasion





# Pregnancy is a hypercoaguable state



Counteracts inherent instability of haemochorial placentation



# Haemostatic system and pregnancy

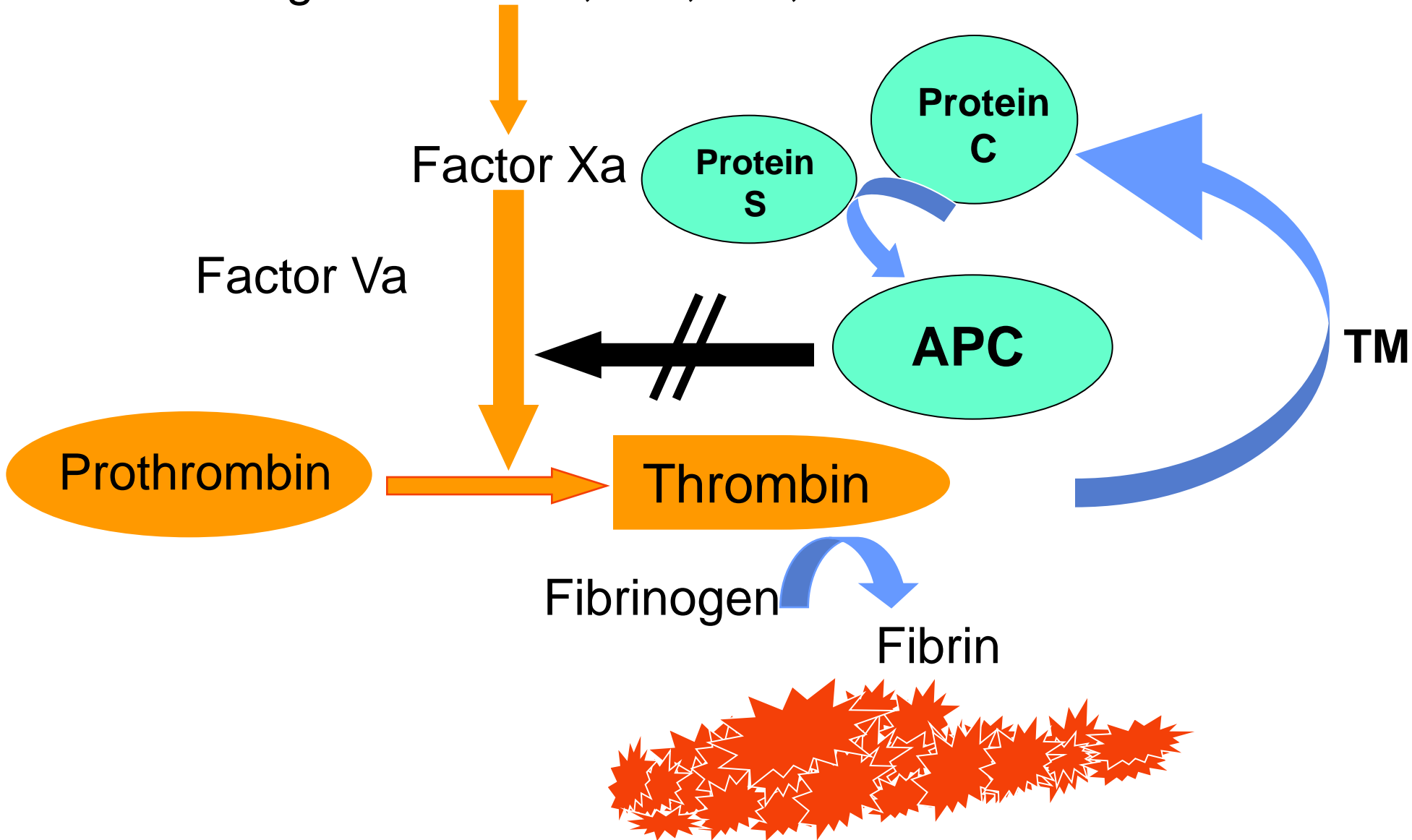
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## Coagulation & fibrinolytic pathways - Key role in

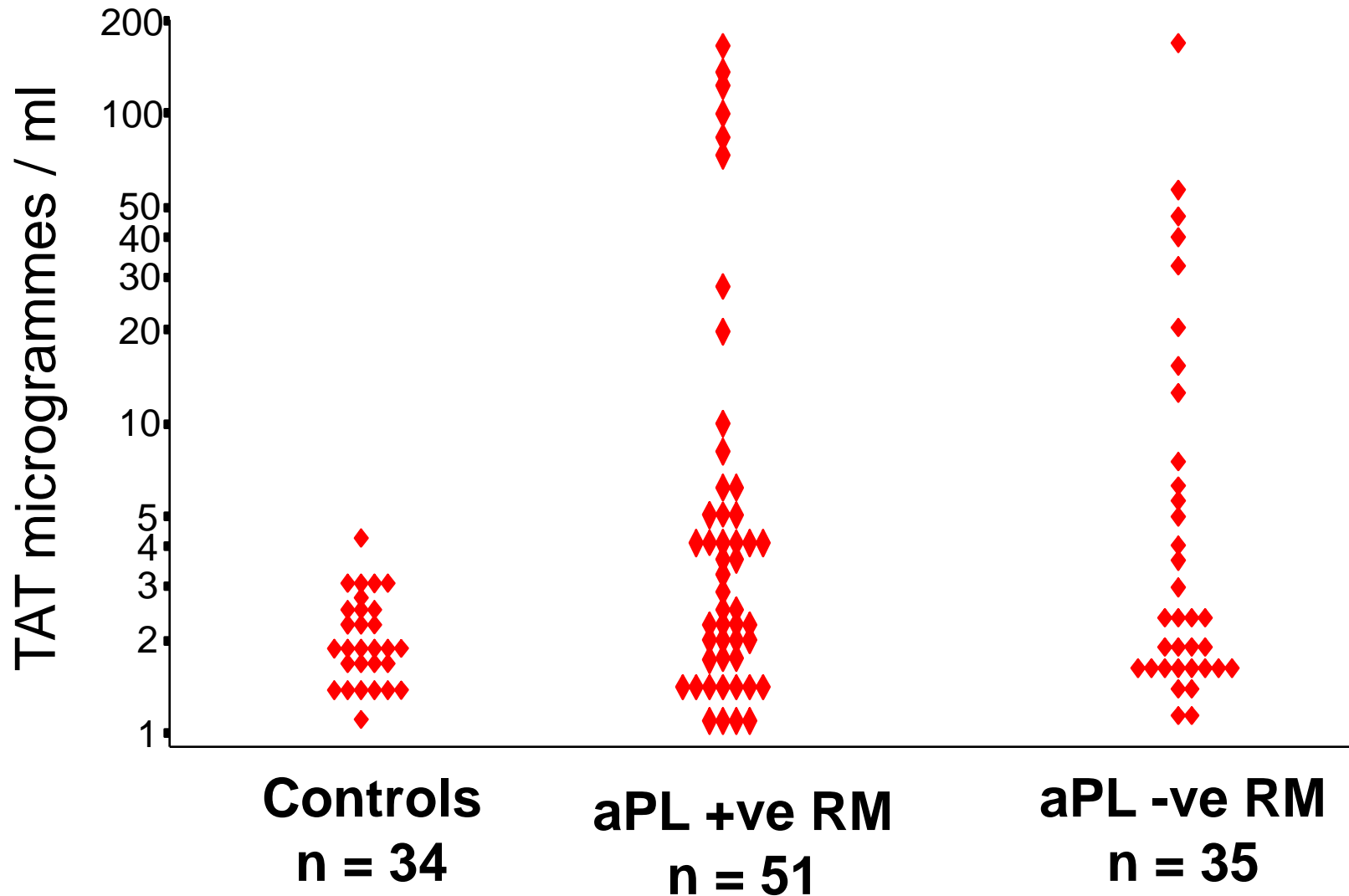
- ◆ implantation
- ◆ trophoblast invasion
- ◆ placentation



Tissue factor  
Clotting factors VIIa, IXa, XIa, XIIa



# TAT levels amongst non – pregnant women with RM





## Ischaemic heart disease & miscarriage

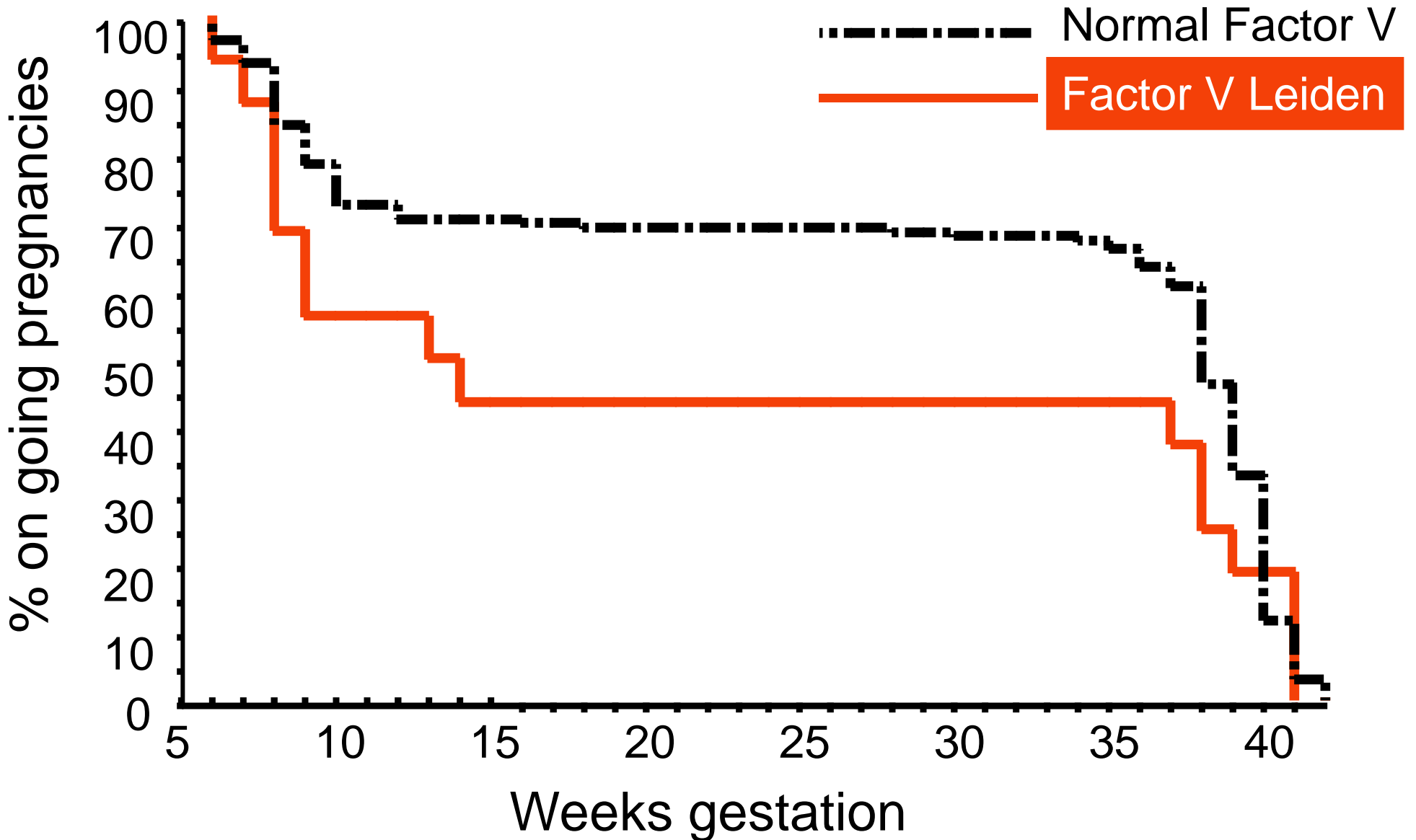
	0 n = 118000	1 – 2 n = 11400	3+ n = 381
No of events	<b>261 (0.2%)</b>	<b>48 (0.4%)</b>	<b>4 (1.0%)</b>
Crude Hazard ratio	<b>1.0</b>	<b>1.44</b> <b>(1.06 – 1.97)</b> <b>P = 0.02</b>	<b>2.34</b> <b>(0.87 – 6.32)</b> <b>P = 0.09</b>

Smith et al 2003

## Factor V Leiden

- ◆ Common inherited cause of venous thrombosis
- ◆ Single point mutation G → A at position 1691 in the factor V gene
- ◆ Mutated Factor V resistant to inactivation by Activated protein C
  - ➔ prothrombotic state

# Prospective pregnancy outcome of women with RM



## **Aspirin plus heparin or Aspirin alone in women with Recurrent Miscarriage**

Kaandorp et al NEJM 2010

- ALIFE
- Does aspirin or aspirin + heparin increased the live birth rate in women with ‘unexplained recurrent miscarriage’?

## ALIFE - Results

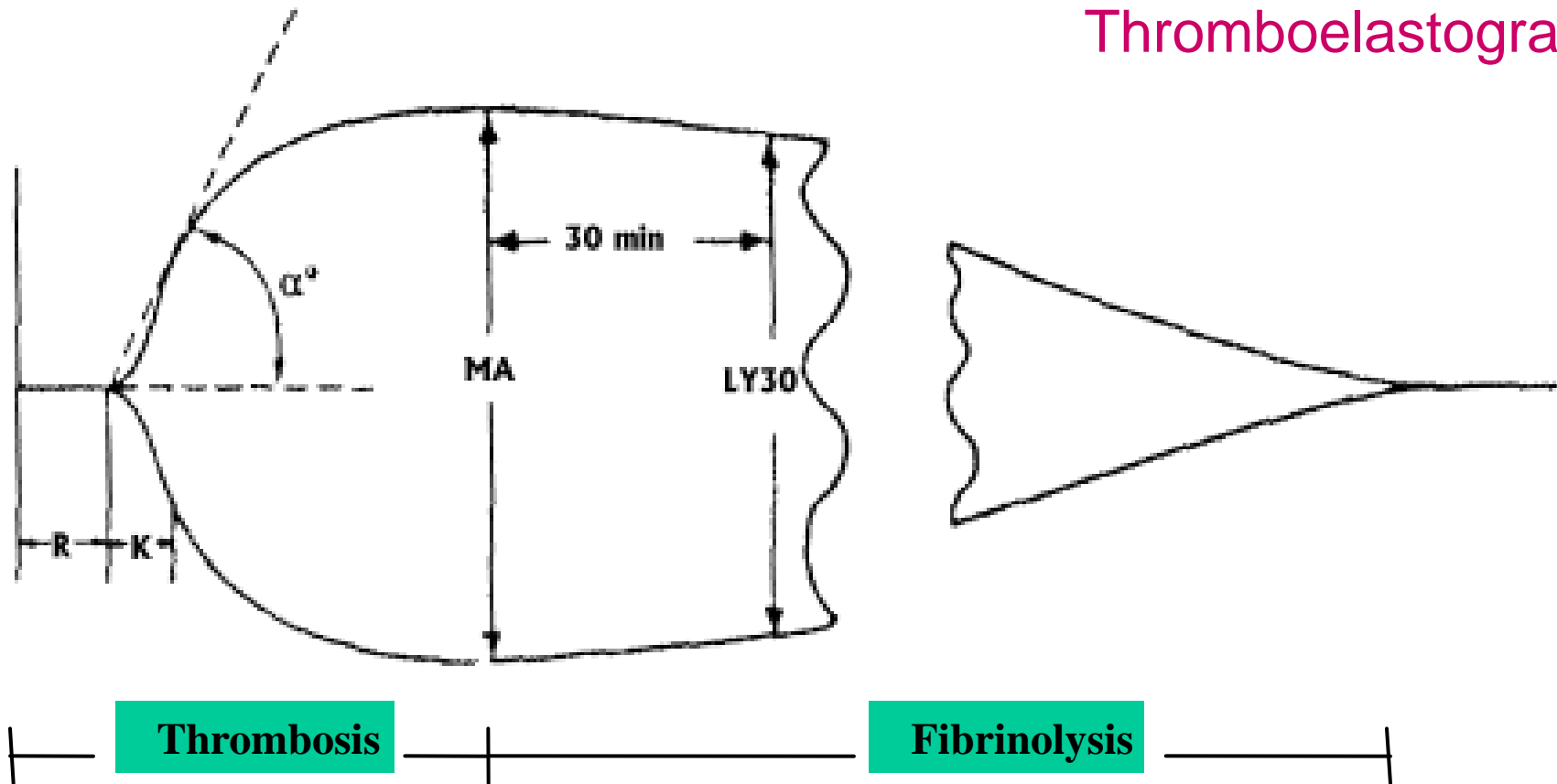
	Aspirin + Heparin	Aspirin alone	Placebo	P value
No of patients	123	120	121	
Live birth	67 (54.5%)	61 (50.8%)	69 (57.0%)	0.63
RR	0.96 (0.76 – 1.19)	0.89 (0.71 – 1.13)	1.0	
Absolute difference in LBR %	-2.6 (-15.0 – 9.9)	- 6.2 (-18.8 – 6.4)		

# Thromboelastogram

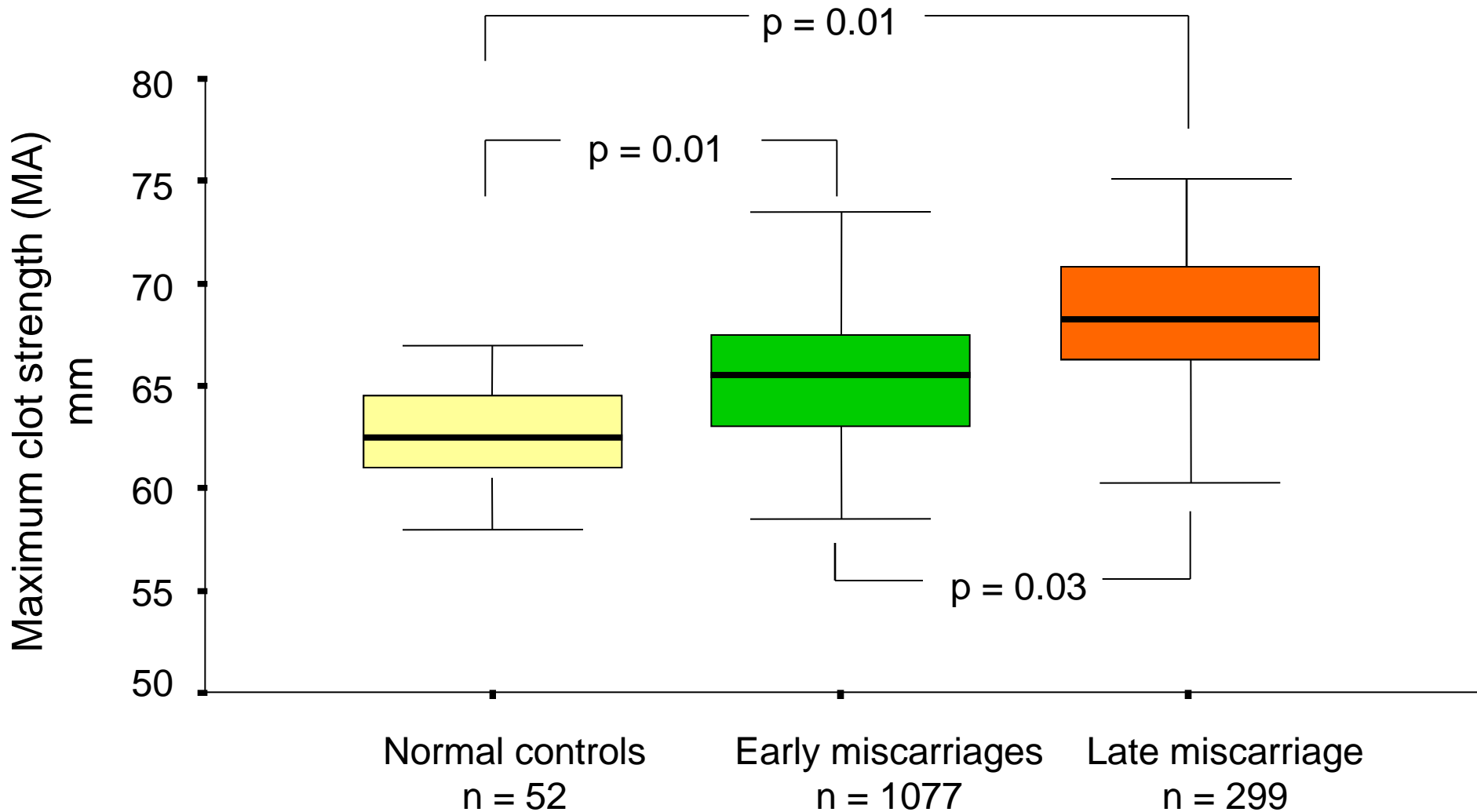




# Thromboelastograph



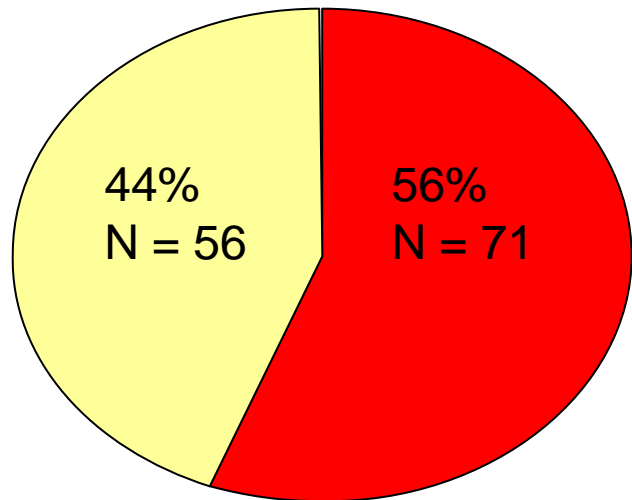
The Thromboelastograph



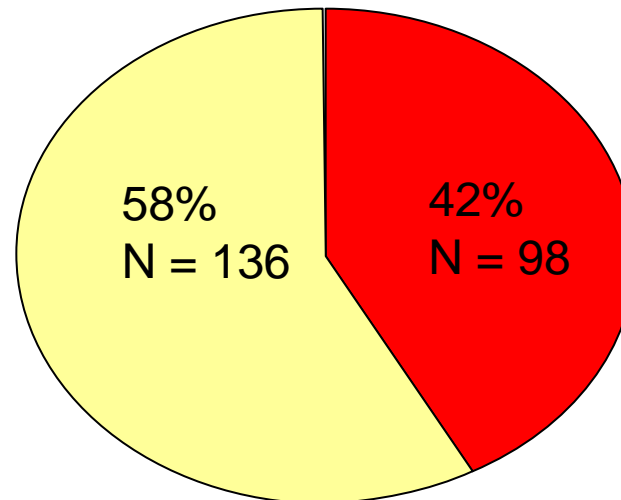
MA is significantly increased amongst women with recurrent miscarriage compared with controls

# Pregnancy outcome - raised MA

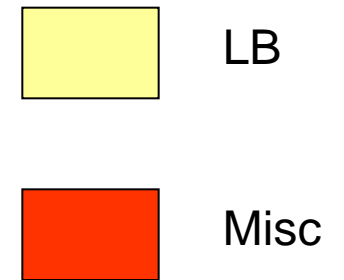
OR = 1.76; 95% CI = 1.14 – 2.72

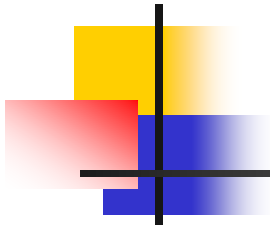


**No aspirin**  
**N = 127**



**Aspirin (150 mg / day)**  
**N = 234**





First trimester progesterone therapy therapy  
in women with a history of unexplained recurrent miscarriage:  
A randomised double blind, placebo – controlled multicentre trial

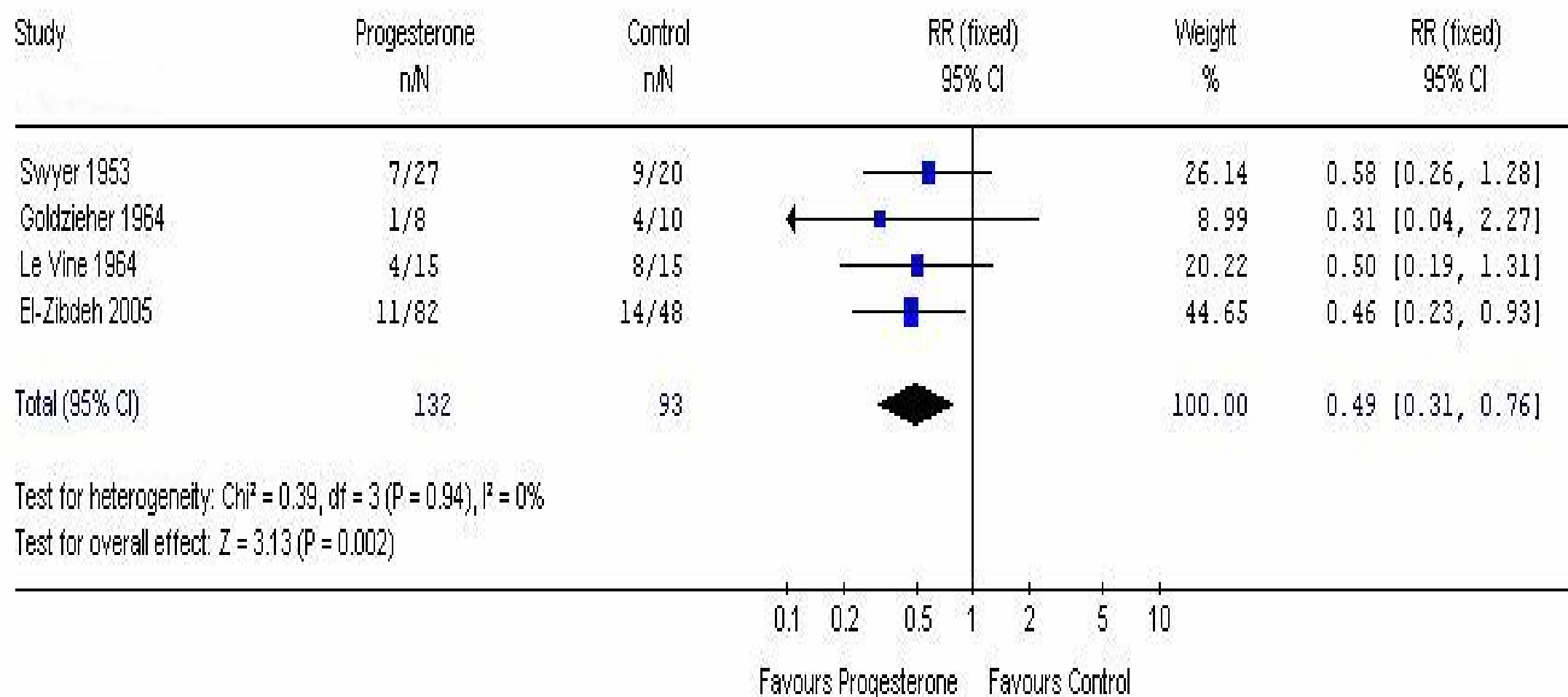
## **PROMISE**

HTA funded - £1.5 million

- **Principal objective:**

To test the hypothesis that amongst women with unexplained RM that progesterone supplementation started between a +ve PT and no later than 6 weeks and continued until 12 weeks increases the live birth rate by at least 10% compared with placebo

# Progesterone & recurrent miscarriage – Randomised studies



Modified Jadad Quality Scores between 0/5 to 2/5)



# Promise

## Limitations of existing data

- Small numbers of patients
- No standardisation of treatment protocols
- Included women with 2 or more miscarriages
- No stratification by age / no of previous losses
- Different types of progesterone supplementation

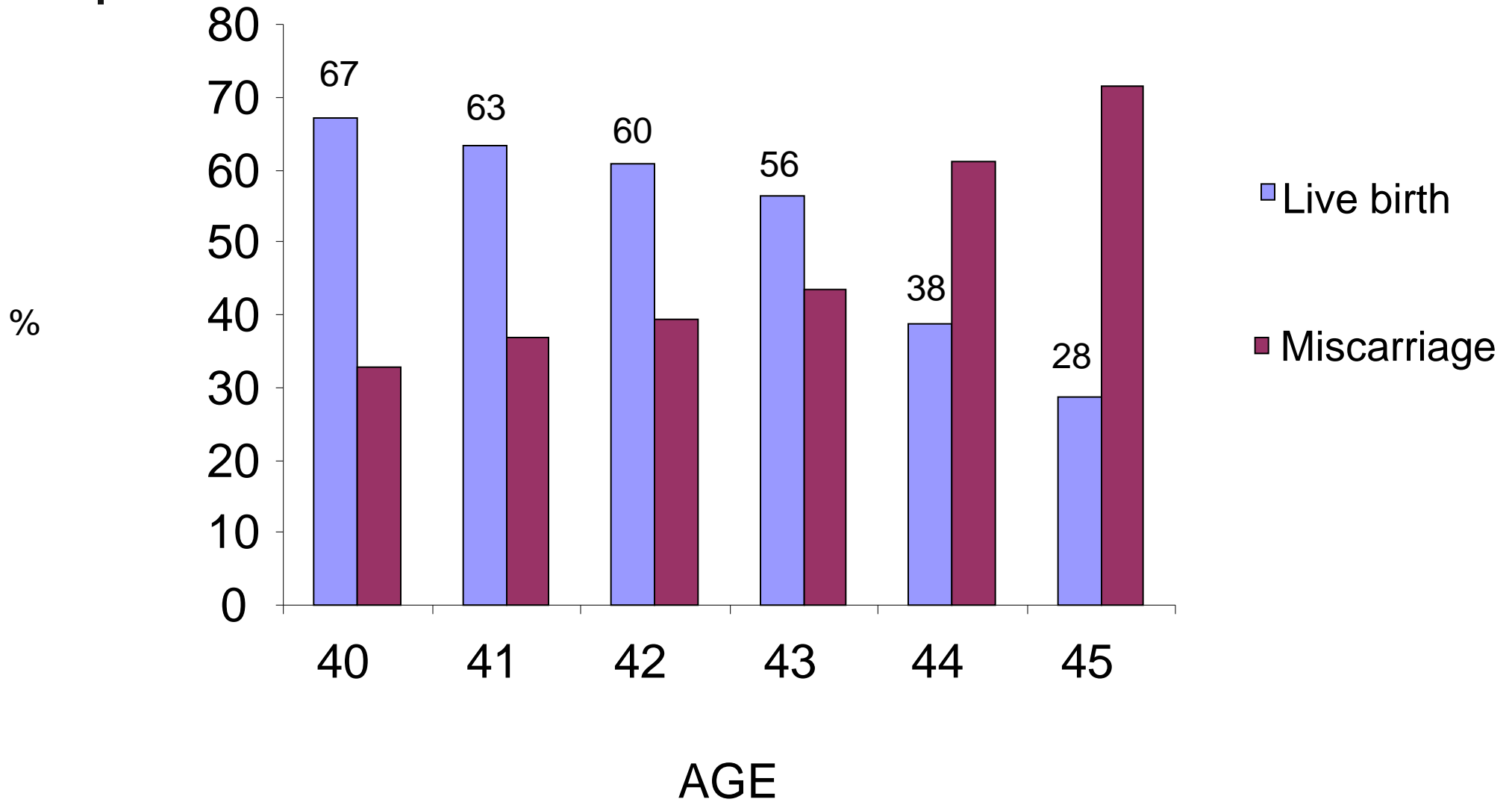
## PROMISE

- Important opportunity to answer the 50 year old question  
– ‘does progesterone supplementation decrease miscarriage rate?’

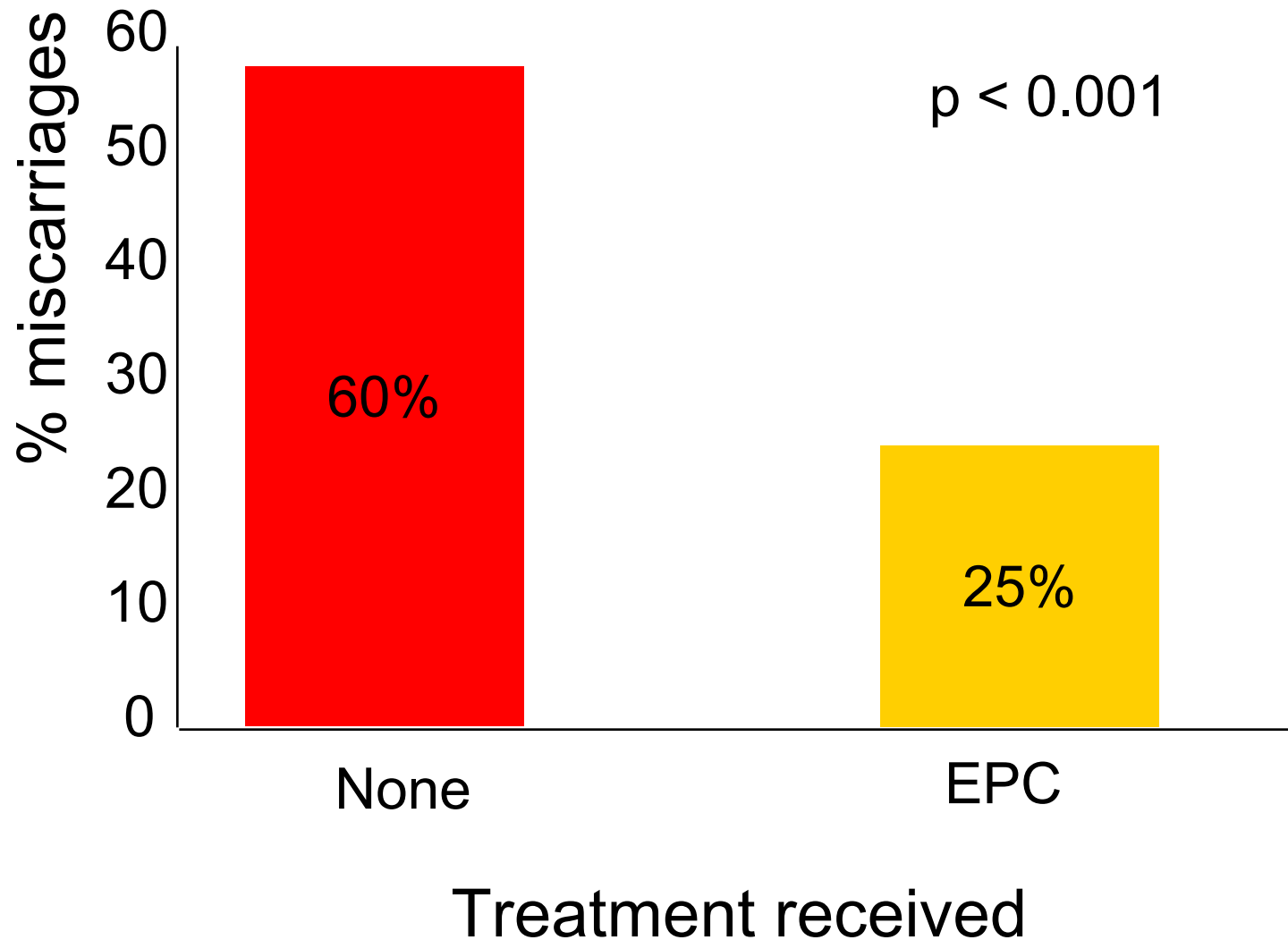
- Trial design
  - Randomised, double-blind, placebo controlled
- Setting
  - 8 centres (6 England; 1 Scotland; 1 Holland)
- Number of participants
  - 790 (50% from St Mary's)



# Pregnancy outcome women > 40 years with RM



# Recurrent miscarriage – SUPPORTIVE CARE





# Recurrent miscarriage - Summary

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- ◆ Occupies a cardinal position in Reproductive Medicine
- ◆ Defective implantation - pregnancy loss at all gestational ages
- ◆ Recent studies emphasise the need for evidence- based practice
  - not aspirin or aspirin / heparin for all
- ◆ Protect patients from vocal advocates pedalling new tests / treatments
  - largely based on pseudo - science