

# **The evidence for early pregnancy support and treatment intervention**

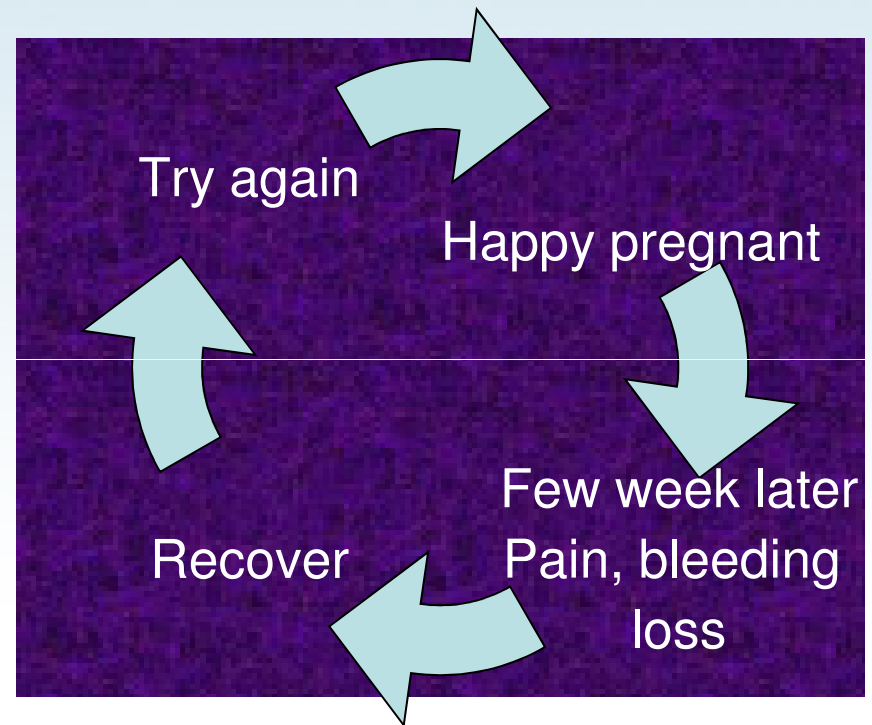
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University of Warwick

# What is recurrent miscarriage?

- 3 consecutive miscarriages
- Very distressing
- Occurs over 1-2 years
  - Increasingly desperate for baby
- 50% cases no known cause in 30 blood tests
- 3% couples trying for a baby
- 600,000 births in UK per year
- 18,000 couple in UK per year

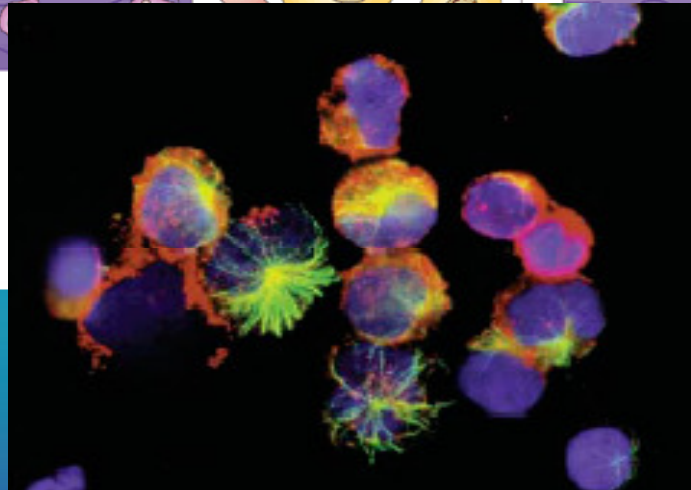
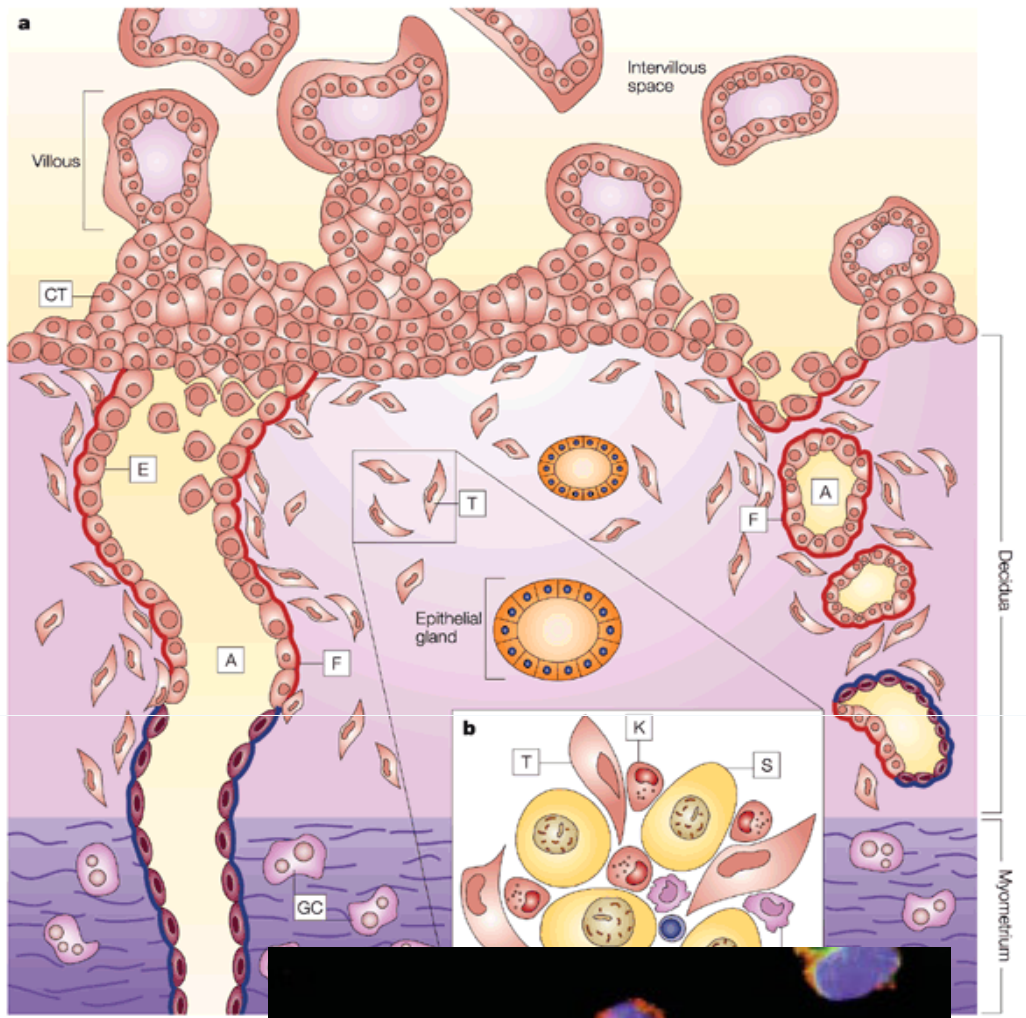
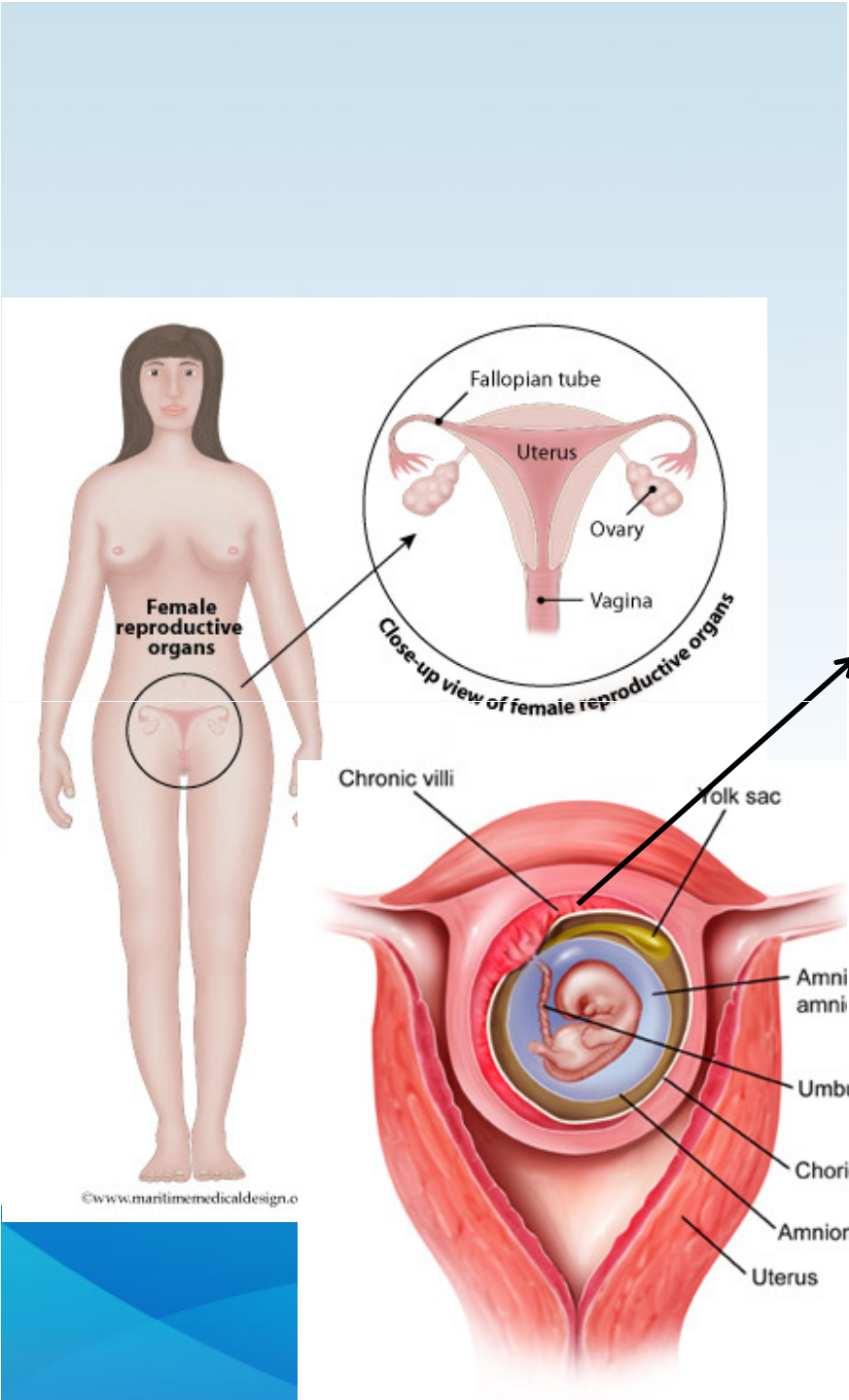


# Historical perspective

- Definition RM: 3 consecutive pregnancy losses before the 20<sup>th</sup> weeks
- Sporadic miscarriage rate is 15%
- RM rate  $0.15^3 = 0.3-0.4\%$ .
- The actual prevalence of RM is 1-3%

# Karyotypical abnormality

- High (29-57%) in RM population
  - Stern *et al.*, 1996,
  - Ogasawara *et al.*, 2000,
  - Carp *et al.*, 2001,
  - Stephenson *et al.*, 2002
- Same rate recurrent and spontaneous miscarriage



ology

# Introduction

- Anti-thrombotic
  - Aspirin
  - Heparin
- Hormonal
  - Progesterone
  - thyroxine
- Immunotherapy
  - IVIG

# One treatable cause APS

- ACA
  - IgG, IgM
- Lupus anticoagulant
  - DRVVT
  - Platelet neutralisation
  - 2 +ve tests six weeks apart

# Pathophysiology APS

- First trimester
  - Placental histology
  - not thrombosis or infarcts
    - (Sebier et al., 2003)
  - Lack of trophoblast invasion
    - (Sebier et al., 2002)
- Second trimester
  - Placental thrombosis is identified



# Antithrombotic

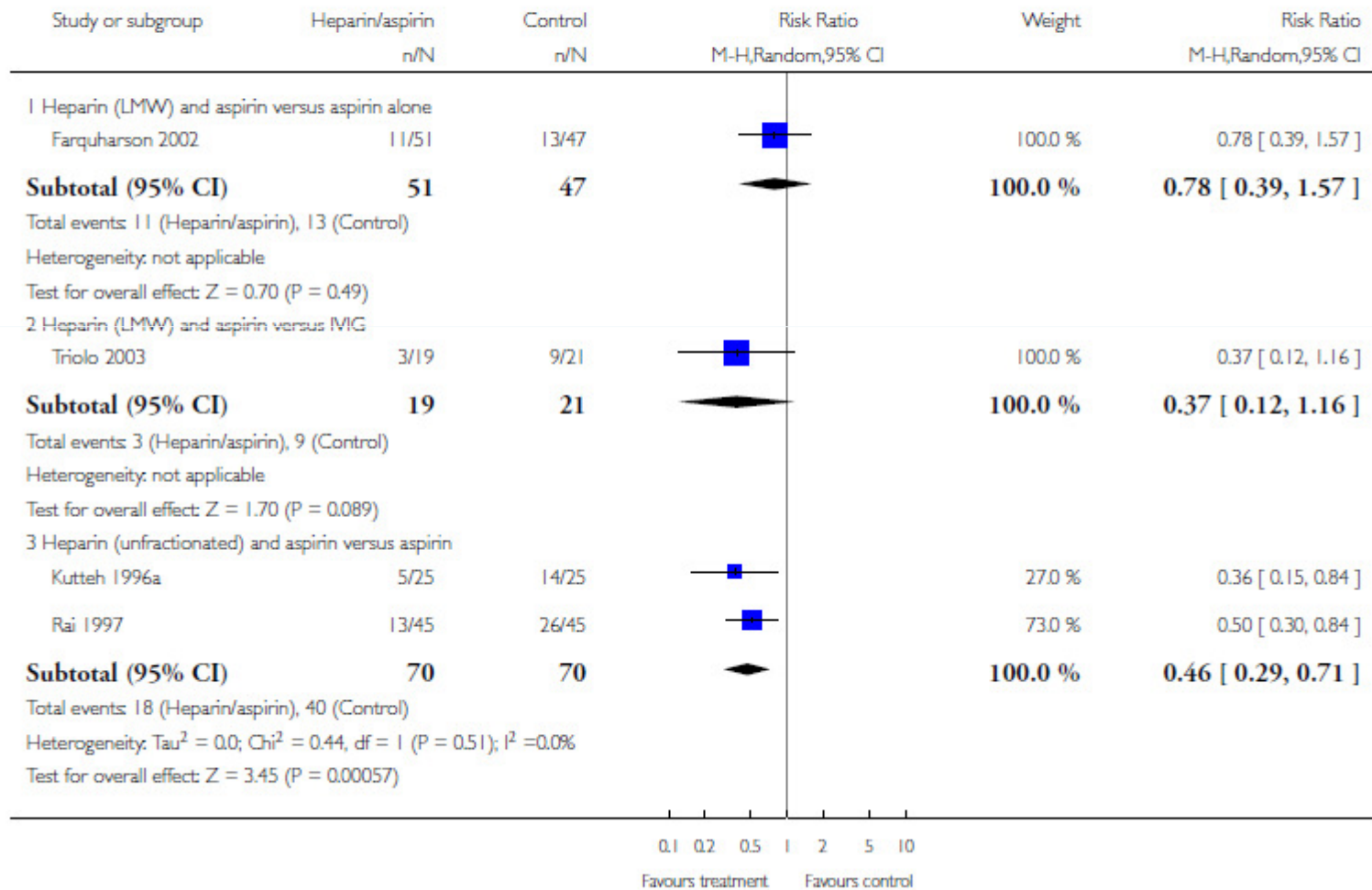
- APS
- Cochrane review Empson et al., 2010

### Analysis 3.1. Comparison 3 Heparin (LMW and unfractionated) and aspirin versus aspirin or IVIG, Outcome 1 Pregnancy loss.

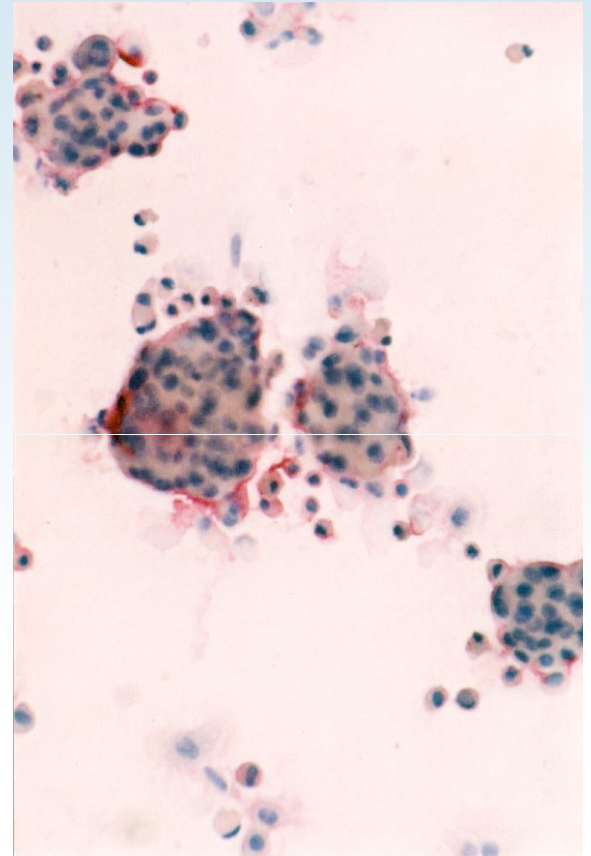
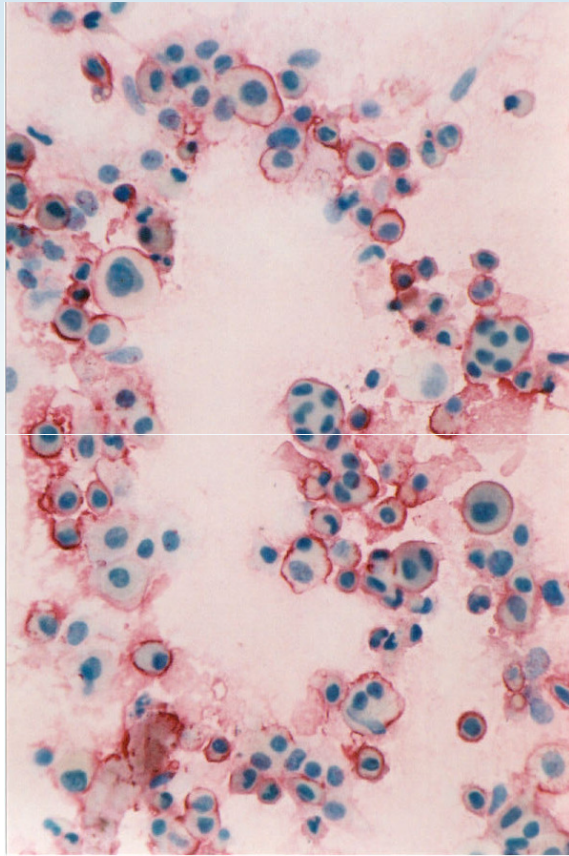
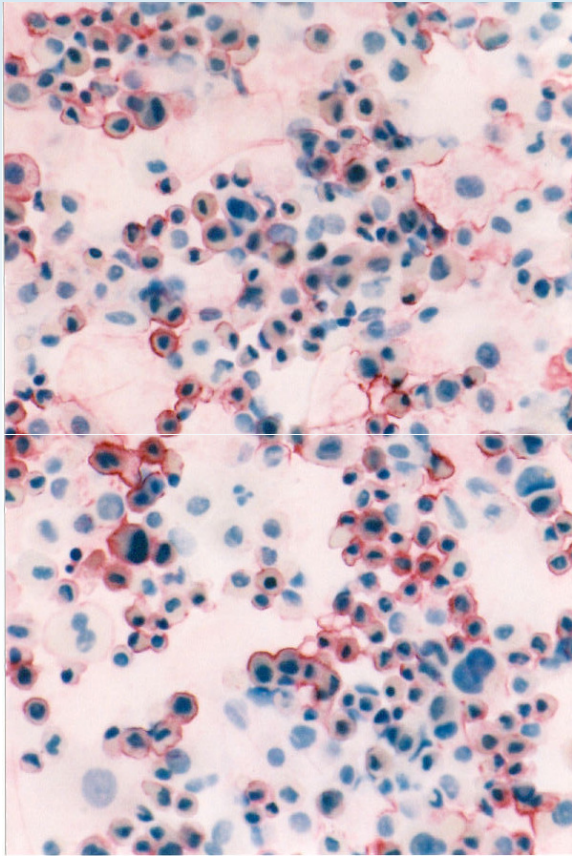
Review: Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant

Comparison: 3 Heparin (LMW and unfractionated) and aspirin versus aspirin or IVIG

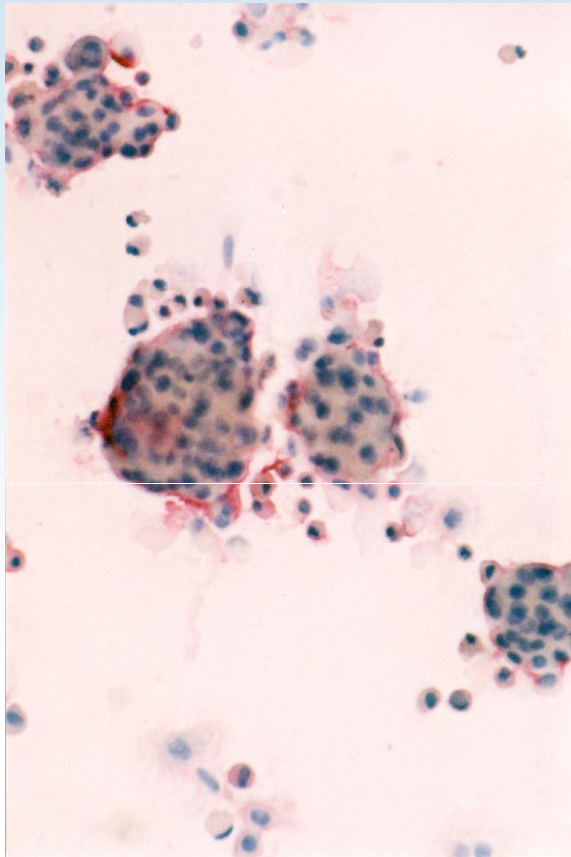
Outcome: 1 Pregnancy loss



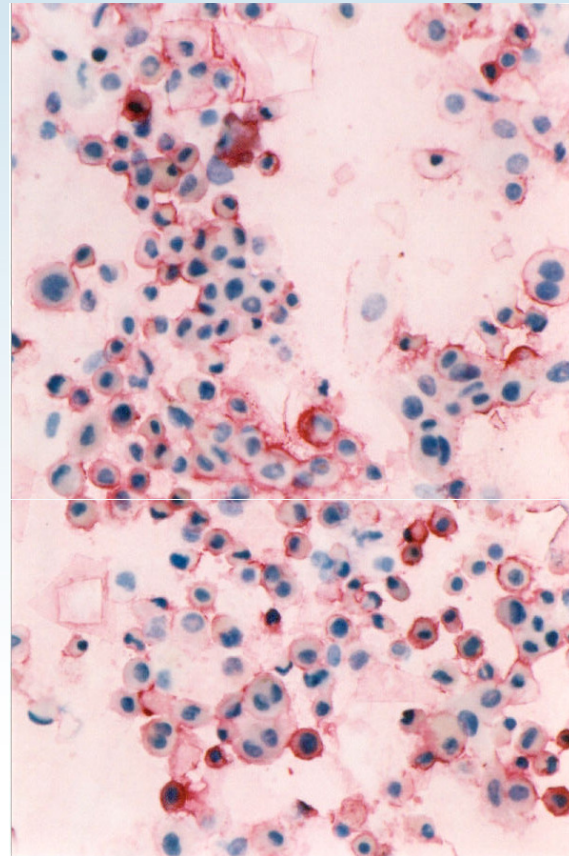
# HEPARIN ON TROPHOBLAST







Ab- 48hrs



ID2 48hrs

# Inflammation and APS

- ACA activate complement

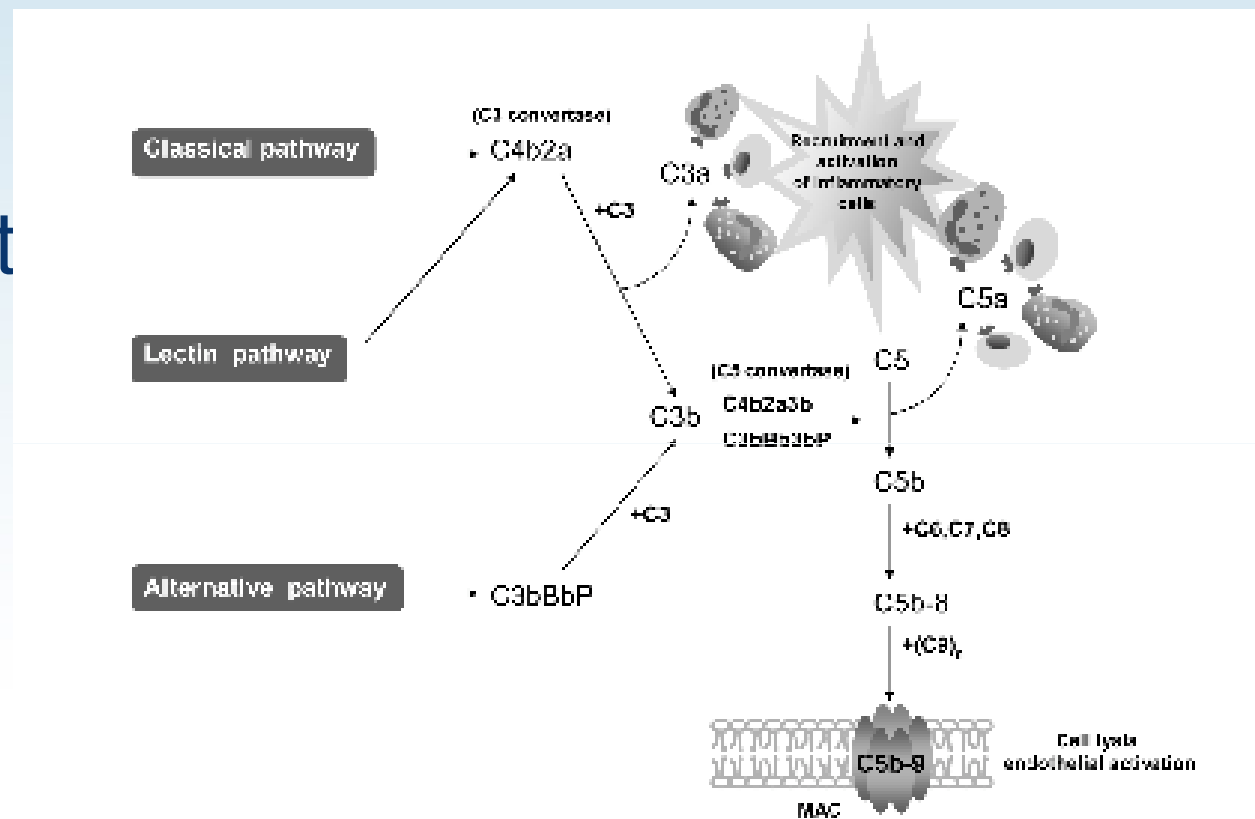
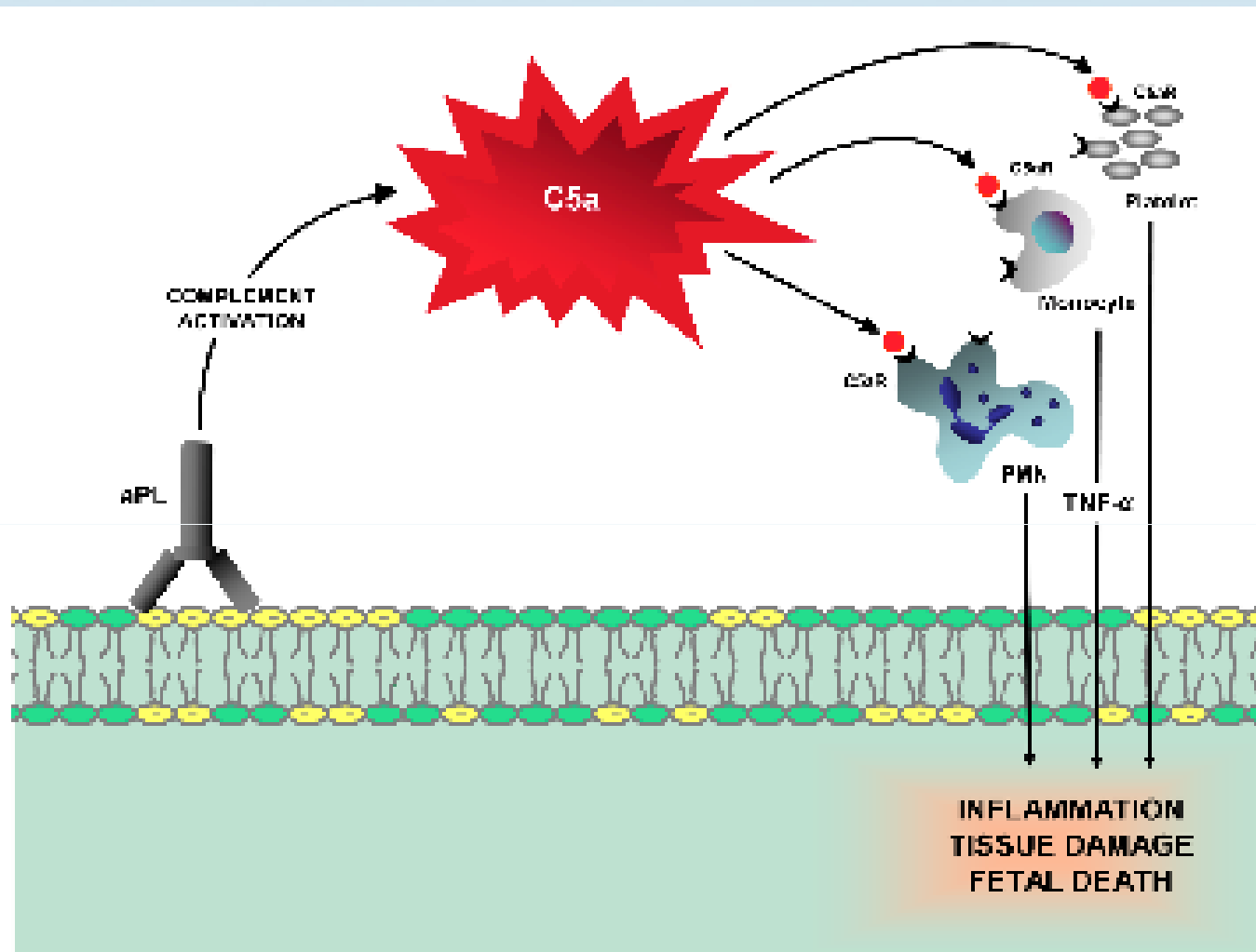
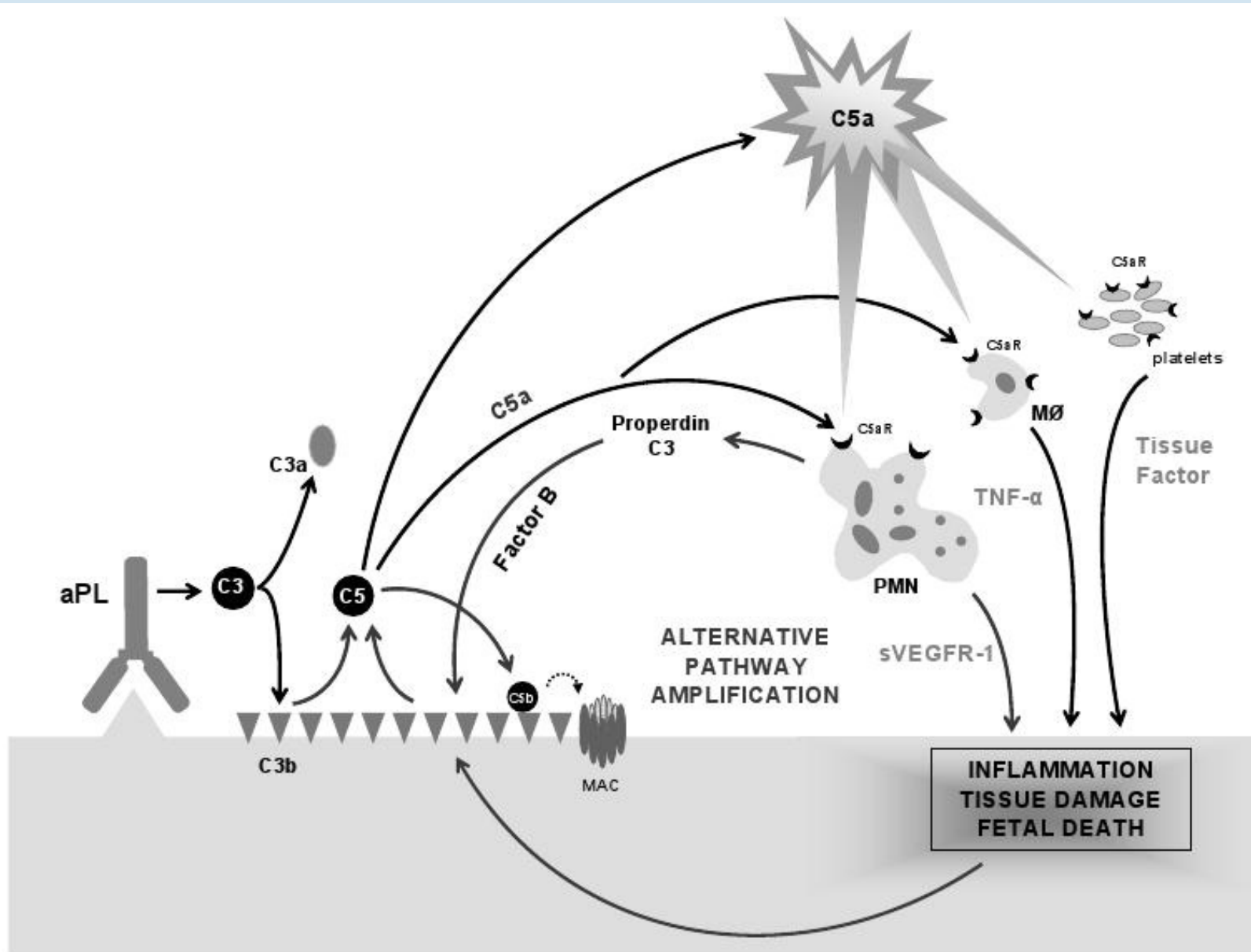


Figure 1.

Complement cascade. Schematic diagram of the three complement activation pathways and the products they generate. From Hughes Syndrome, 2<sup>nd</sup> Edition, Khamashta, MA (Ed.), 2006, page 396, chapter 31, by Girardi, G and Salmon, J, Figure 31.1. With kind permission of Springer Science and Business Media.







- LMWH inhibited this
  - Salmon et al., 2007

**TABLE 1**  
*Heparins prevent pregnancy loss and inhibit complement activation*

	Anticoagulation	Prevention of pregnancy loss	Complement inhibition
UFH (10 U)	-	+	+
UFH (20 U)	+	+	+
LMWH	+	+	+
Fondaparinux	+	-	-
Hirudin	+	-	-

LMWH, low molecular weight heparin; UFH, unfractionated heparin.

# Trophoblast surface

- Protein C Pathway on surface of trophoblast
  - Human and mouse
  - Thrombomodulin, tissue factor, annexin V
- Factor V leiden mice
  - Fetal loss without thrombosis
  - Alteration proteins C pathway on surface trophoblast
  - Defective trophoblast development
    - Sood et al., 2007
  - Fetal leiden status

# APCR resistance

Dawood et al., 2008

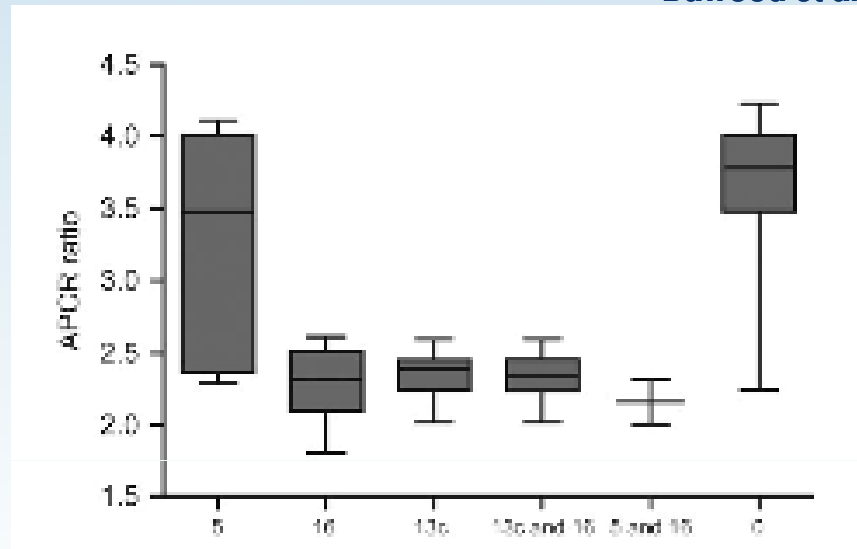


Table 2: Number (percentage) of women with each SNP in each group

Polymorphism	Study group (n = 51) Number (%)	Pareus control group (n = 24) Number (%)	Idiopathic RM control group (n = 15) Number (%)	ANOVA
Exon 13a 2379 A→G Heterozygous	7 (14)	3 (12.5)	1 (7)	$P = 0.7631$
Exon 13b 2298 C→T 2325 T→C 2391 A→G Heterozygous	20 (42.5)	7 (29)	5 (33)	$P = 0.6845$
Exon 13a 2298 C→T 2325 T→C 2391 A→G Homozygous	3 (6)	0 (0)	0 (0)	$P = 0.305$
Exon 13b 2627 C→T 2684 C→T Heterozygous	17 (33)	5 (21)	0 (0)	$P < 0.0273$
Exon 13b 2627 C→T 2684 C→T Homozygous	12 (24)	0 (0)	0 (0)	$P = 0.005$
Exon 13c 2863 T→C Heterozygous	12 (24)	0 (0)	0 (0)	$P = 0.005$
Exon 5 910+7 C→T Heterozygous	9 (18)	4 (17)	1 (7)	$P = 0.5656$
Exon 16 5470 A→G Heterozygous	28 (55)	0 (0)	0 (0)	$P < 0.0001$

# Fetal genome

- Mutation carriage in either partner equally important in predicting miscarriage
  - Jivrai et al., 2006
- Hutterite population
  - No increase in loss in MTHFR, FVL
  - Children of carriers deficit of FVL therefore more losses of fetus with FVL
    - Seirra and Stephenson 2006

# Idiopathic first trimester miscarriage and heparin

- Canada, Laskin et al 2008 N=88
  - included APS, thrombophilia, antinuclear antibodies
  - **Asp: 78% V asp+LMWH 79%**
- Metanalysis Cochrane -2009
  - n=189, Idiopathic
  - **Asp 81% v placebo 81%**
  - **Asp 82% v LMWH 84%**
- Netherlands N=299, Kaandorp et al 2010
  - Included idiopathic, thrombophilia, excluded APS
  - **Asp: 62% V asp+ LMWH 69% v placebo 67%**
- Scotland, SPIN, N=294, Clark et al., 2010
  - Included idiopathic, thrombophilia, excluded APS
  - **Standard care 80%V asp+LMWH 78%**

# Aspirin

- Netherlands study
  - Placebo v aspirin
  - Absolute risk that causes miscarriage is 5.2
  - CI (-6.1-16.6)
  - Kaandorp et al 2010

# Remaining questions

- Heparin and aspirin work second trimester loss?
- Type and dose?
- Recurrent IVF failure?

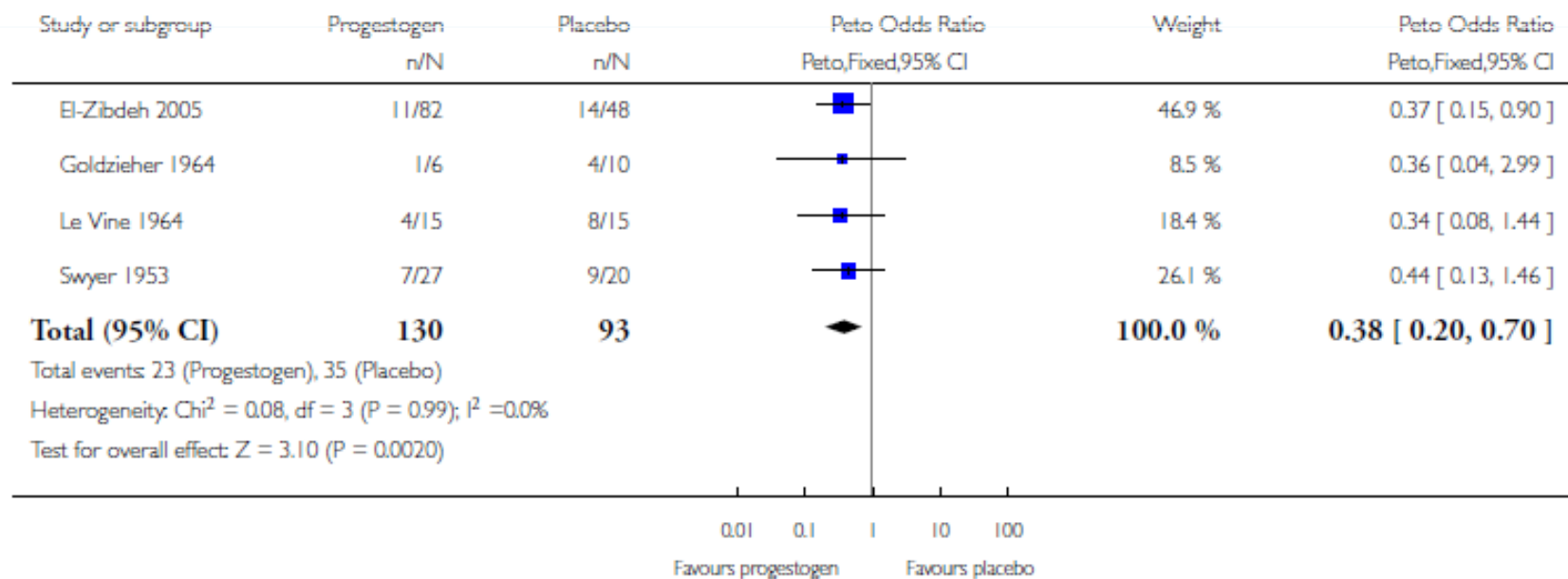
# Progesterone

## Analysis 1.3. Comparison 1 Progestogen versus placebo/no treatment, Outcome 3 Miscarriage (women with previous recurrent miscarriage only).

Review: Progesterone for preventing miscarriage

Comparison: 1 Progestogen versus placebo/no treatment

Outcome: 3 Miscarriage (women with previous recurrent miscarriage only)





# Sub clinical hypothyroidism

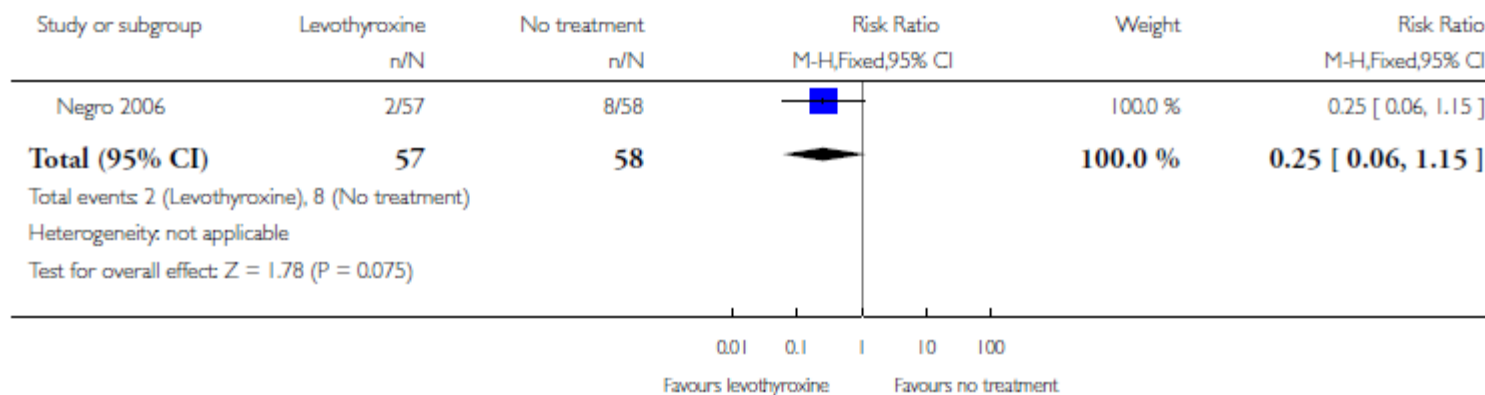
Reid et al., 2010

## Analysis 1.3. Comparison 1 Levothyroxine versus no treatment, Outcome 3 Miscarriage (first trimester).

Review: Interventions for clinical and subclinical hypothyroidism in pregnancy

Comparison: 1 Levothyroxine versus no treatment

Outcome: 3 Miscarriage (first trimester)



# Immunotherapy

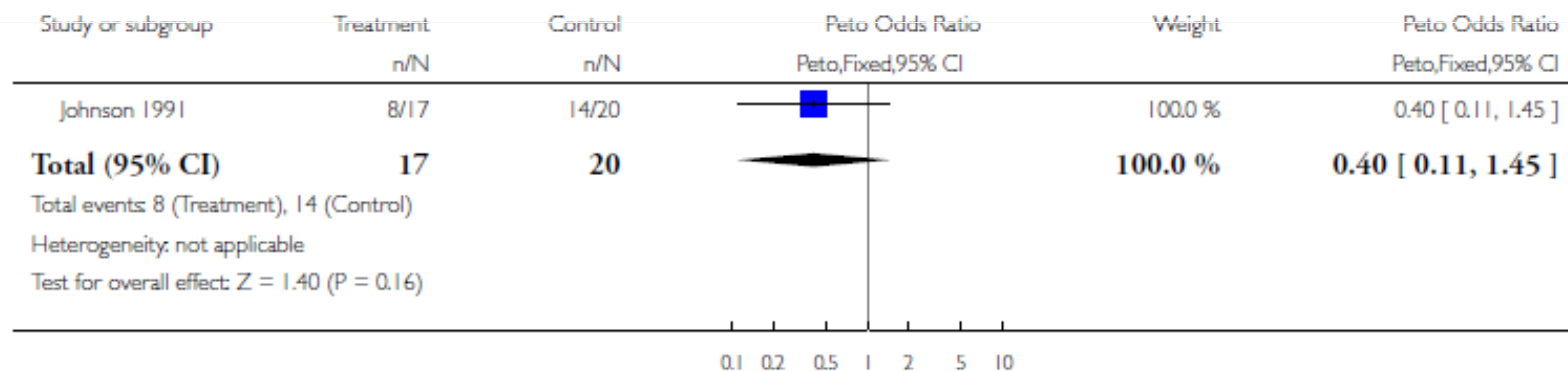
- Porter et al 2010 Cochrane

### Analysis 3.1. Comparison 3 Trophoblast membrane immunization, Outcome 1 Live birth rate.

Review: Immunotherapy for recurrent miscarriage

Comparison: 3 Trophoblast membrane immunization

Outcome: 1 Live birth rate

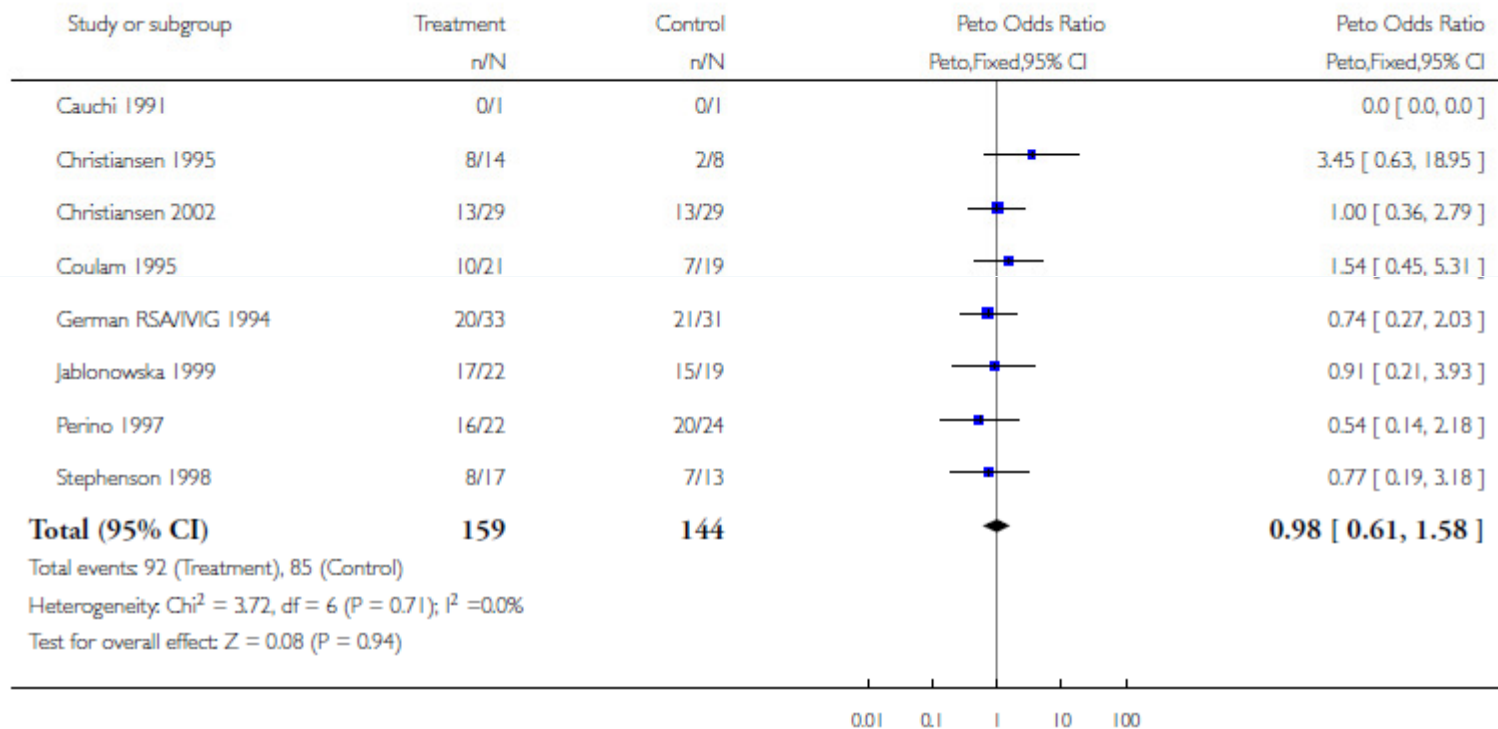


### Analysis 4.1. Comparison 4 Intravenous immune globulin, Outcome 1 Live birth rate.

Review: Immunotherapy for recurrent miscarriage

Comparison: 4 Intravenous immune globulin

Outcome: 1 Live birth rate

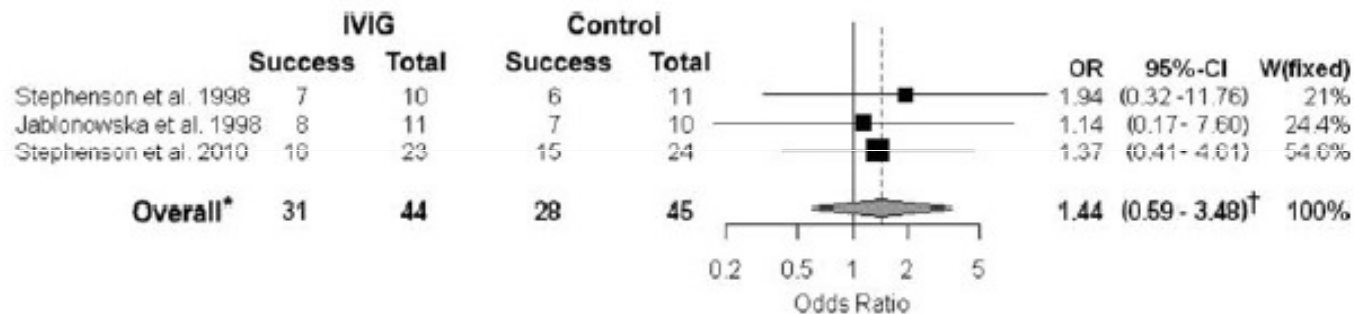


# Cochrane Porter 2010

- “A specific assay to diagnose immune-mediated early pregnancy loss and a reliable method to determine which women might benefit from manipulation of the maternal immune system are urgently needed”

# Secondary RM

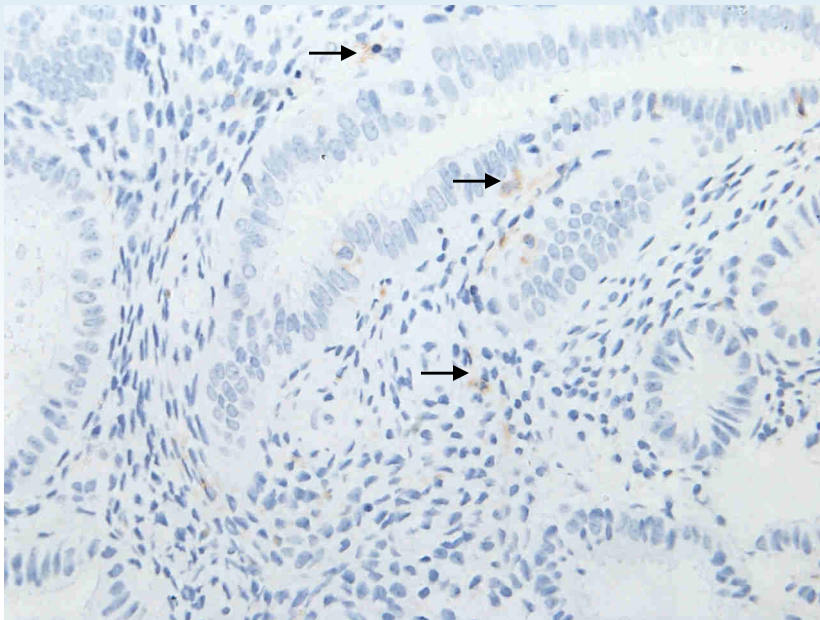
## Stephenson et al., 2010



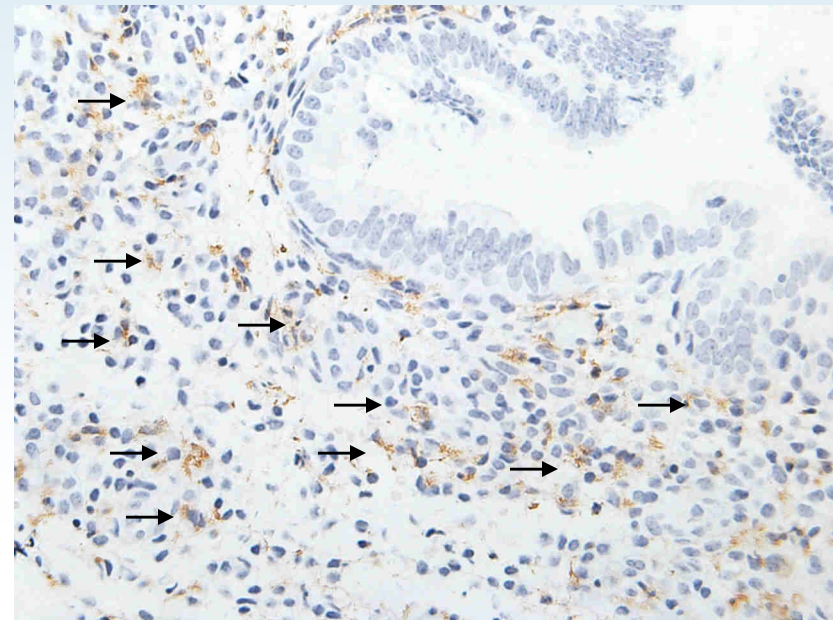
**Figure 2** Meta-analysis of live birth rates in randomized placebo-controlled trials of IVIG for idiopathic secondary recurrent miscarriage. \* $P = 0.503$ .

<sup>†</sup>Test for heterogeneity:  $\chi^2(2) = 0.17$ ,  $P = 0.918$ .

# Uterine Natural Killer cells in womb lining



patient with two normal deliveries

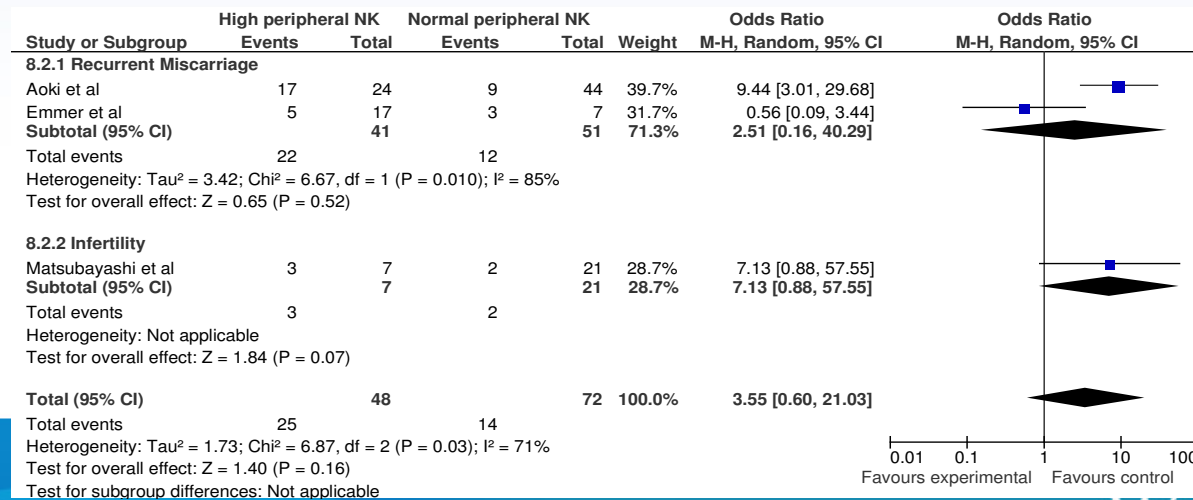
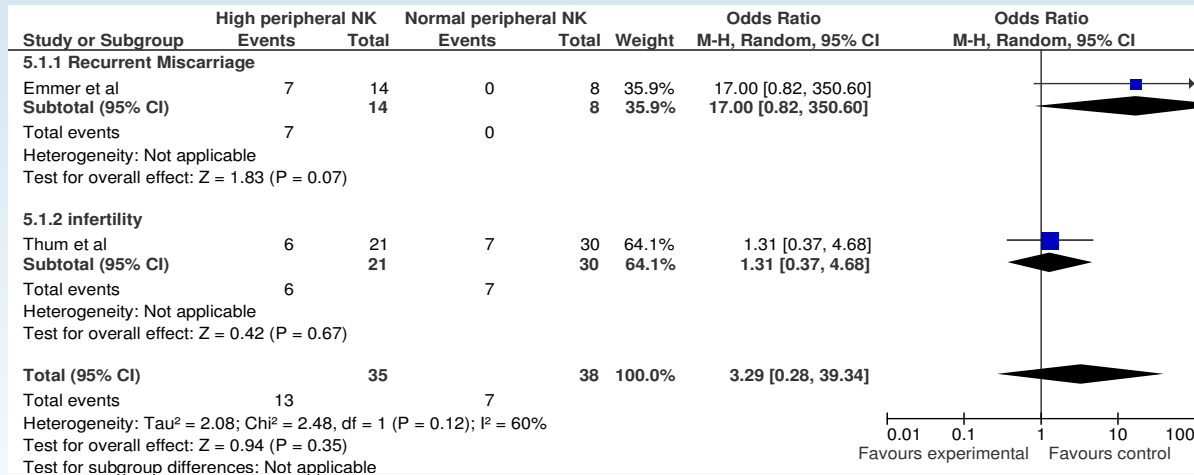


Patient who had ten miscarriages

uNK cells more numerous in RM

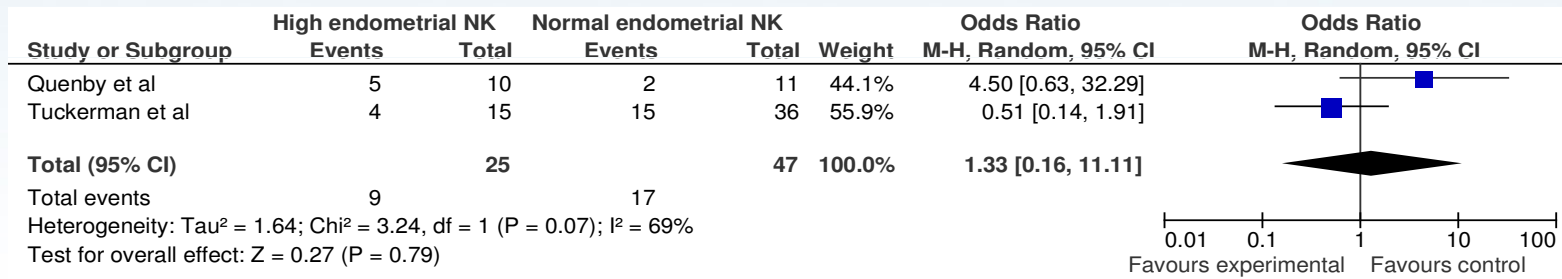
Quenby et al, 1999,2005; Clifford et al, 1999, Tuckerman et al., 2007

# Predict outcome?

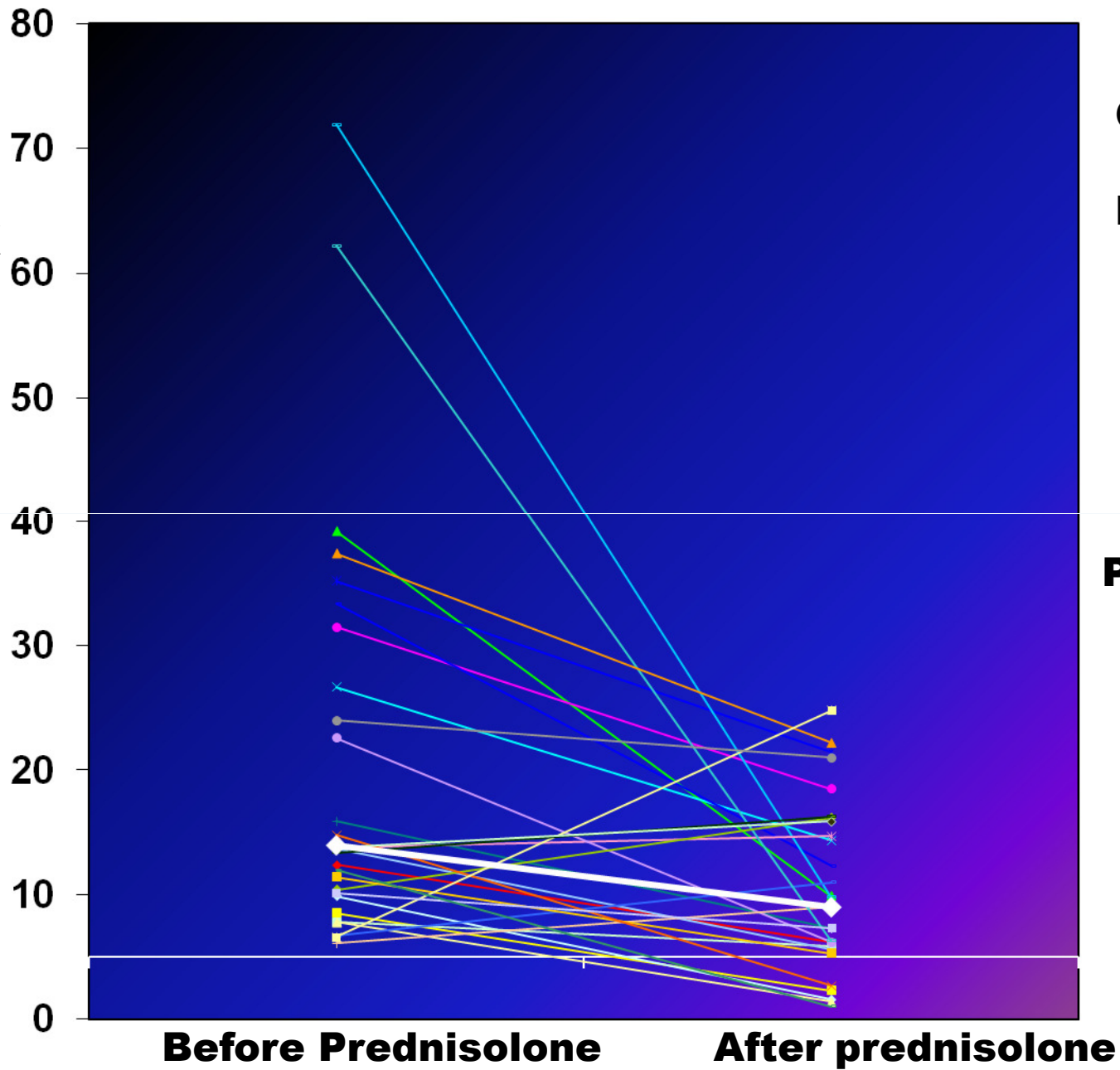




# Predict outcome?



**% uNK  
cells**



Quenby et al.,  
2005  
Fert & Steril

**P=0.0009**

**Normal  
range**

WICK

# Success in control group

Author	date	patients	control	Live birth rate
Kutteh	1996	APS	aspirin	44%
Rai	1997	APS	aspirin	42%
Farquharson	2002	APS	aspirin	72%
Laskin	2009	RM -all	aspirin	78%
Cochrane heparin	2009	idiopathic	Aspirin placebo	82% 81%
Kaandorp	2010	idiopathic	Aspirin placebo	67% 62%
Clark	2010	idiopathic	Intensive care	80%
El-Zibdeh	2005	idiopathic	placebo	70%
Cochrane IVIG	2010	Idiopathic	control	60%
Stephenson	2010	secondary	placebo	62%
Quenby	2010	Endometrial raised NK cell	placebo	50%

# Live birth rates

	weeks	general pop	0 previous miscarriages	1 previous miscarriage	2 previous miscarriages	3 previous miscarriages	4 Previous miscarriages	previous live birth
Biochemical	<5	75%						
Clinical	5-10	88%	94%	86%	77%	72%	58%	95%
First trimester	10-12	97%						
reference		Bottomley 2009	Bhattacharya et al., 2010	Bhattacharya et al., 2010	Bhattacharya et al., 2010	Bhattacharya et al., 2010	Bhattacharya et al., 2010	Bhattacharya et al., 2008

# Conclusions

- New treatments are need prevent recurrent miscarriage
- Role of Heparin is limited
- Aspirin may cause harm
- Progesterone needs a further trial
- Need to identify high risk groups suitable for appropriate therapies