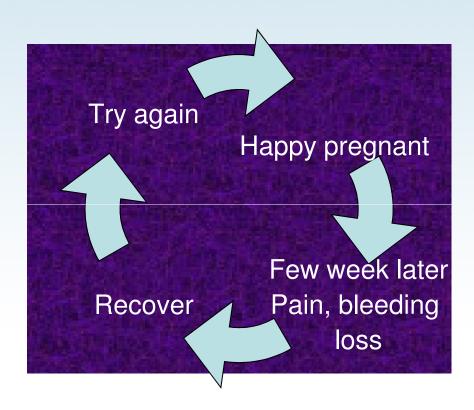
The evidence for early pregnancy support and treatment intervention

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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

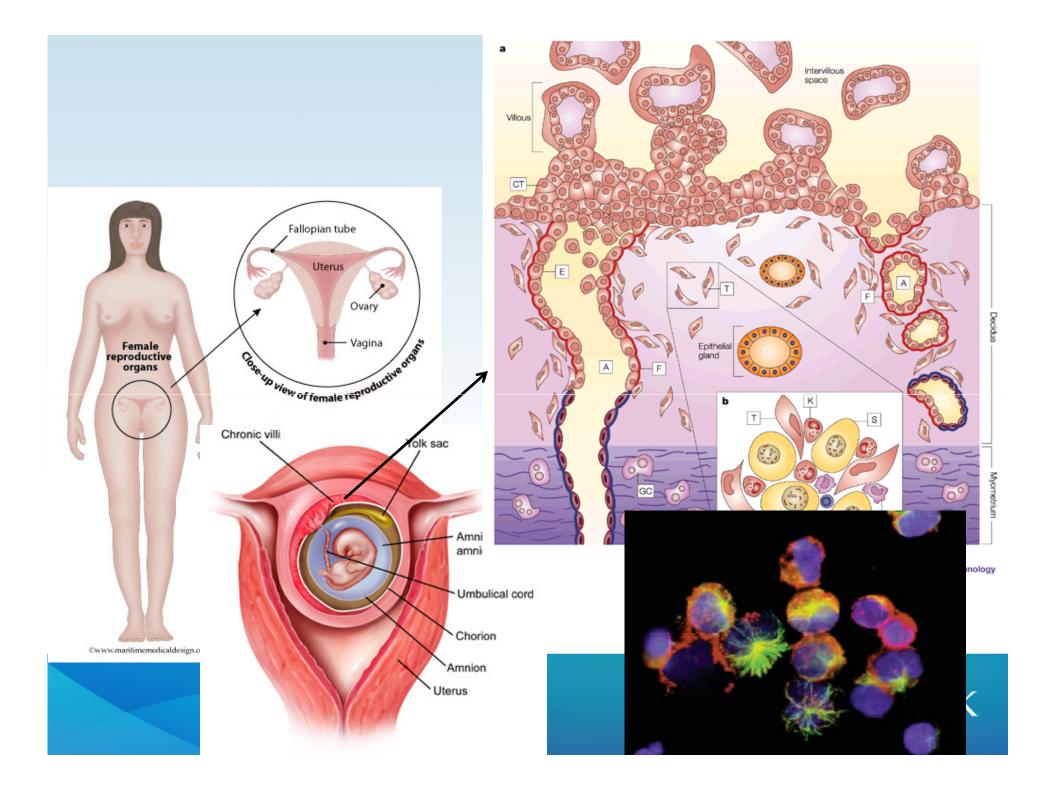
- Definition RM: 3 consecutive pregnancy losses before the 20th weeks
- Sporadic miscarriage rate is 15%
- RM rate $0.15^3 = 0.3-0.4\%$.
- The actual prevalence of RM is 1-3%



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





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 I Pregnancy loss.

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

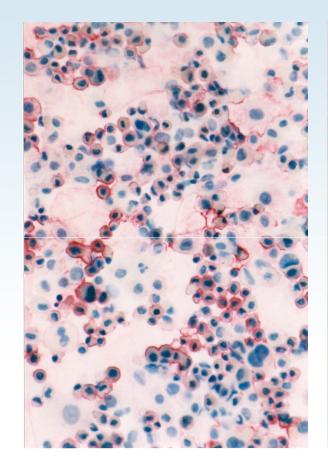
Comparison: 3 Heparin (LMW and unfractionated) and aspirin versus aspirin or IVIG

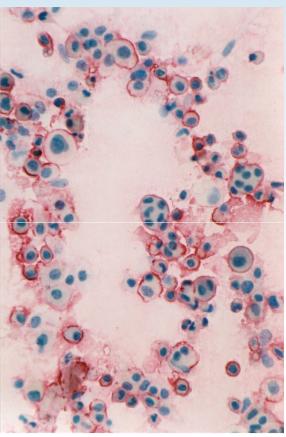
Outcome: | Pregnancy loss

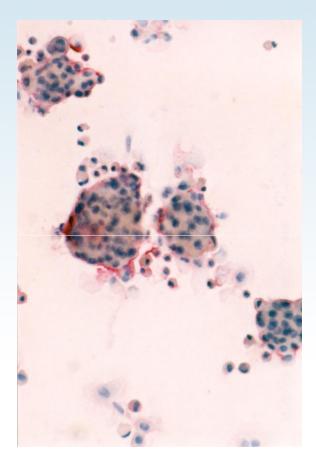
Study or subgroup	Heparin/aspirin	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Random,95% CI		M-H,Random,95% CI
Heparin (LMW) and aspirin w	ersus aspirin alone				
Farquharson 2002	11/51	13/47	-	100.0 %	0.78 [0.39, 1.57]
Subtotal (95% CI)	51	47	-	100.0 %	0.78 [0.39, 1.57]
Total events: 11 (Heparin/aspirir	n), 13 (Control)				
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70	(P = 0.49)				
2 Heparin (LMW) and aspirin w	ersus IVIG				
Triolo 2003	3/19	9/21	-	100.0 %	0.37 [0.12, 1.16]
Subtotal (95% CI)	19	21	-	100.0 %	0.37 [0.12, 1.16]
Total events 3 (Heparin/aspirin)	, 9 (Control)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 1.70$	(P = 0.089)				
B Heparin (unfractionated) and	aspirin versus aspirin				
Kutteh 1996a	5/25	14/25	-	27.0 %	0.36 [0.15, 0.84]
Rai 1997	13/45	26/45	-	73.0 %	0.50 [0.30, 0.84]
Subtotal (95% CI)	70	70	•	100.0 %	0.46 [0.29, 0.71]
Total events: 18 (Heparin/aspirir	n), 40 (Control)				
Heterogeneity: Tau ² = 0.0; Chi ²	= 0.44, df = 1 (P = 0.5	1); I ² =0.0%			
Test for overall effect: Z = 3.45	(P = 0.00057)				

HEPARIN ON TROPHOBLAST

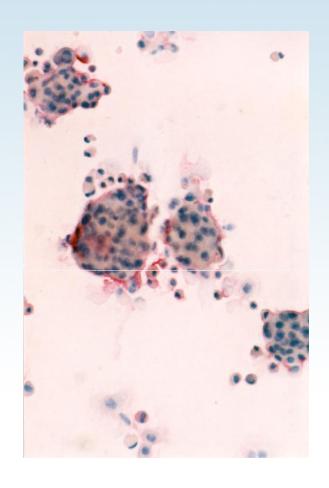


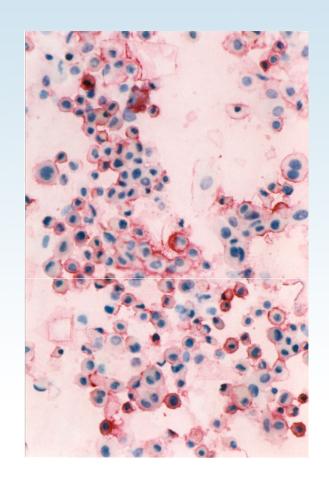












ID2 48hrs

Inflammation and APS

ACA activate compliment

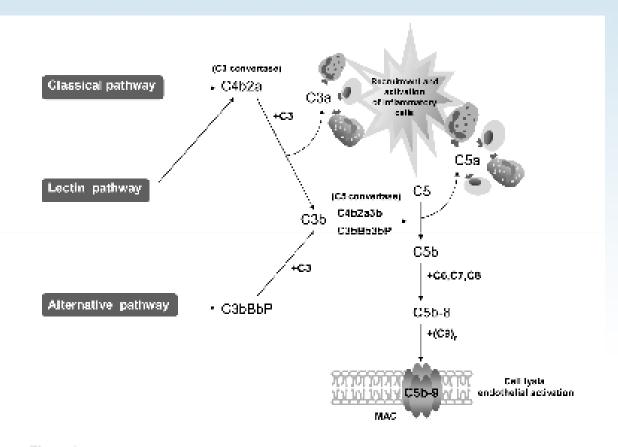
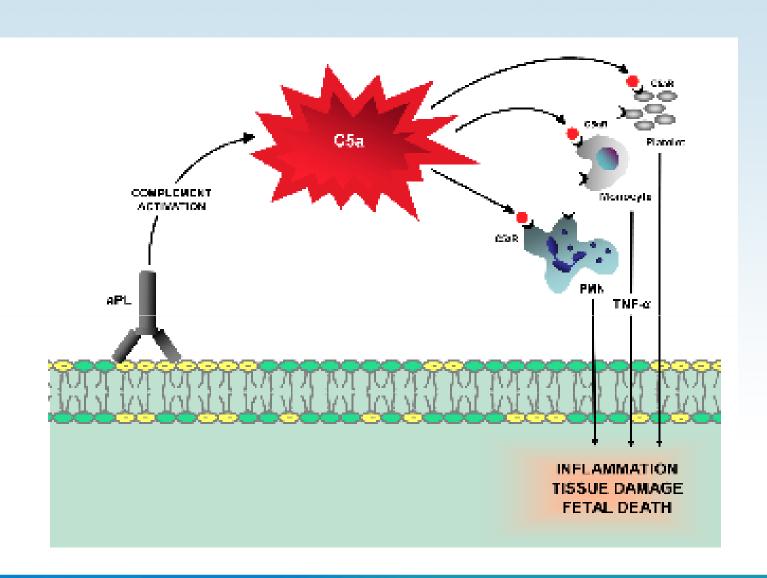
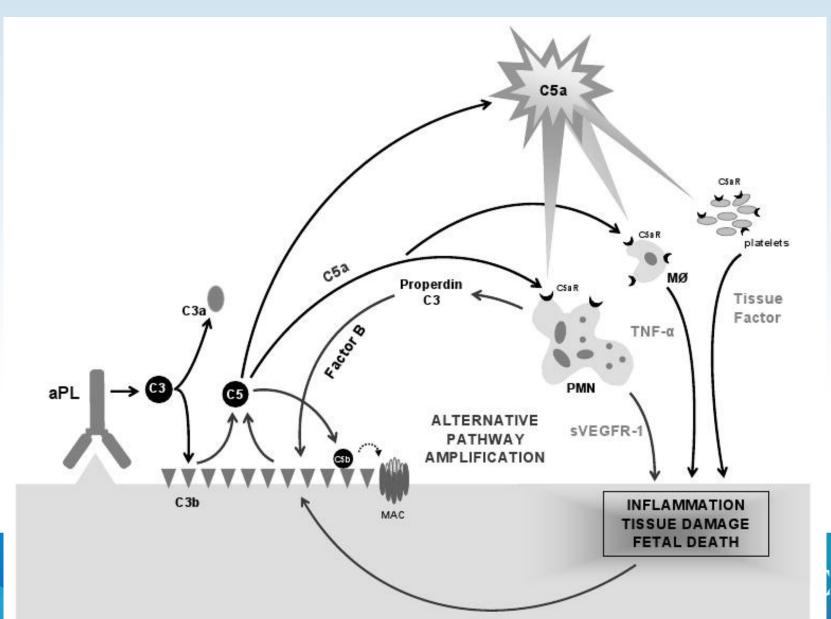


Figure 1.

Complement cascade. Schematic diagram of the three complement activation pathways and the products they generate. From Hughes Syndrome, 2nd 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	+	-	-
Hirodin	+	-	-

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



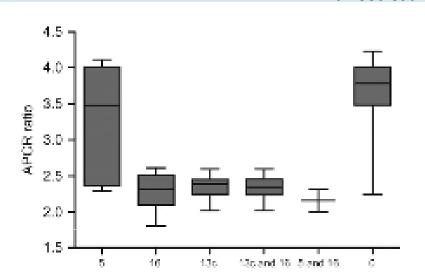
Trophoblast surface

- 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





All the little beautiful and	-	Marine Marine 1	(mercentuse).	AND DESCRIPTION OF THE PARTY.	and the second	a CONTRACTOR STATE	and the second second

Polymorphism	Study group (n =51) Number (%)	Parous 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)	$P \le 0.0273$
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)	$P \le 0.0001$

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

Review: Progestogen for preventing miscarriage

Comparison: I Progestogen versus placebo/no treatment

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

Study or subgroup	Progestogen	Placebo	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto,Fixed,95% CI		Peto,Fixed,95% CI
El-Zibdeh 2005	11/82	14/48	-	46.9 %	0.37 [0.15, 0.90]
Goldzieher 1964	1/6	4/10		8.5 %	0.36 [0.04, 2.99]
Le Vine 1964	4/15	8/15	-	18.4 %	0.34 [0.08, 1.44]
Swyer 1953	7/27	9/20		26.1 %	0.44 [0.13, 1.46]
Total (95% CI)	130	93	•	100.0 %	0.38 [0.20, 0.70]
Total events: 23 (Progesto	ogen), 35 (Placebo)				
Heterogeneity: Chi ² = 0.0	08, $df = 3 (P = 0.99); I^2 =$:0.0%			
Test for overall effect: Z :	= 3.10 (P = 0.0020)				
			0.01 0.1 1 10 100		
		Favo	urs progestogen Favours placebo		

Sub clinical hyopthyroidism

Reid et al., 2010

Analysis I.3. Comparison I Levothyroxine versus no treatment, Outcome 3 Miscarriage (first trimester).

Review: Interventions for clinical and subclinical hypothyroidism in pregnancy

Comparison: I Levothyroxine versus no treatment

Outcome: 3 Miscarriage (first trimester)

Study or subgroup	Levothyroxine n/N	No treatment n/N			Kisk Ratio red,95% CI		Weight	Risk Ratio M-H,Fixed,95% CI
Negro 2006	2/57	8/58		-			100.0 %	0.25 [0.06, 1.15]
Total (95% CI)	57	58		-			100.0 %	0.25 [0.06, 1.15]
Total events: 2 (Levothyro	oxine), 8 (No treatment)							
Heterogeneity: not applic	able							
Test for overall effect: Z :	= 1.78 (P = 0.075)							
			0.01	0.1	1 10	100		
		Favo	ours levot	nyroxine	Favours r	no treatmer	nt	



Immunotherapy

Porter et al 2010 Cochrane



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

Review: Immunotherapy for recurrent miscarriage

Comparison: 3 Trophoblast membrane immunization

Outcome: I Live birth rate

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto,Fixed,95% CI		Peto,Fixed,95% CI
Johnson 1991	8/17	14/20		100.0 %	0.40 [0.11, 1.45]
Total (95% CI)	17	20		100.0 %	0.40 [0.11, 1.45]
Total events: 8 (Treatment	t), 14 (Control)				
Heterogeneity: not applic	able				
Test for overall effect: Z =	= 1.40 (P = 0.16)				
			0.1 0.2 0.5 1 2 5 10		

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

Review: Immunotherapy for recurrent miscarriage

Comparison: 4 Intravenous immune globulin

Outcome: I Live birth rate

Study or subgroup	Treatment	Control	Peto Odds Ratio	Peto Odds Ratio
	n/N	n/N	Peto,Fixed,95% CI	Peto,Fixed,95% CI
Cauchi 1991	0/1	0/1		0.0 [0.0, 0.0]
Christiansen 1995	8/14	2/8	-	3.45 [0.63, 18.95]
Christiansen 2002	13/29	13/29	+	1.00 [0.36, 2.79]
Coulam 1995	10/21	7/19	-	1.54 [0.45, 5.31]
German RSA/IVIG 1994	20/33	21/31	-	0.74 [0.27, 2.03]
Jablonowska 1999	17/22	15/19	-	0.91 [0.21, 3.93]
Perino 1997	16/22	20/24	-	0.54 [0.14, 2.18]
Stephenson 1998	8/17	7/13	_	0.77 [0.19, 3.18]
Total (95% CI)	159	144	+	0.98 [0.61, 1.58]
Total events 92 (Treatment), 85 (C	Control)			
Heterogeneity: $Chi^2 = 3.72$, $df = 6$	$(P = 0.71); I^2 = 0.0\%$			
Test for overall effect: $Z = 0.08$ (P :	= 0.94)			
			001 01 1 10 100	



Cochrane Porter 2010

 "A specific assay to diagnose immunemediated 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

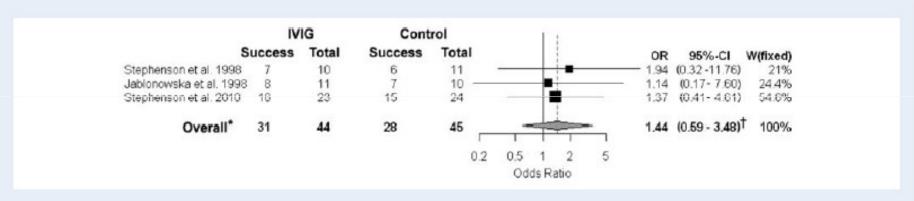
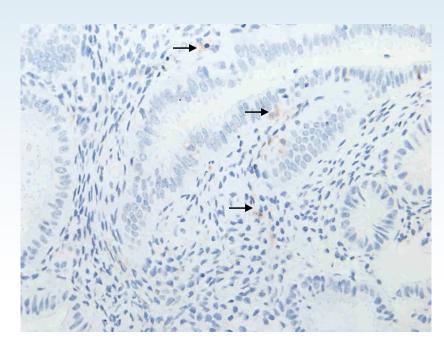


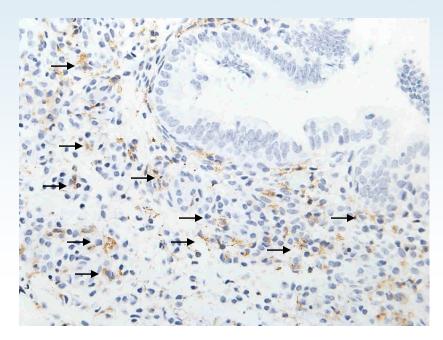
Figure 2 Meta-analysis of live birth rates in randomized placebo-controlled trials of IVIG for idiopathic secondary recurrent miscarriage. *P = 0.503. †Test for heterogeneity: $\chi^2(2) = 0.17$, P = 0.918.



Uterine Natural Killer cells in womb lining



patient with two normal deliveries



Patient who had ten miscarriages

uNK cells more numerous in RM

WARWICK

Predict outcome?

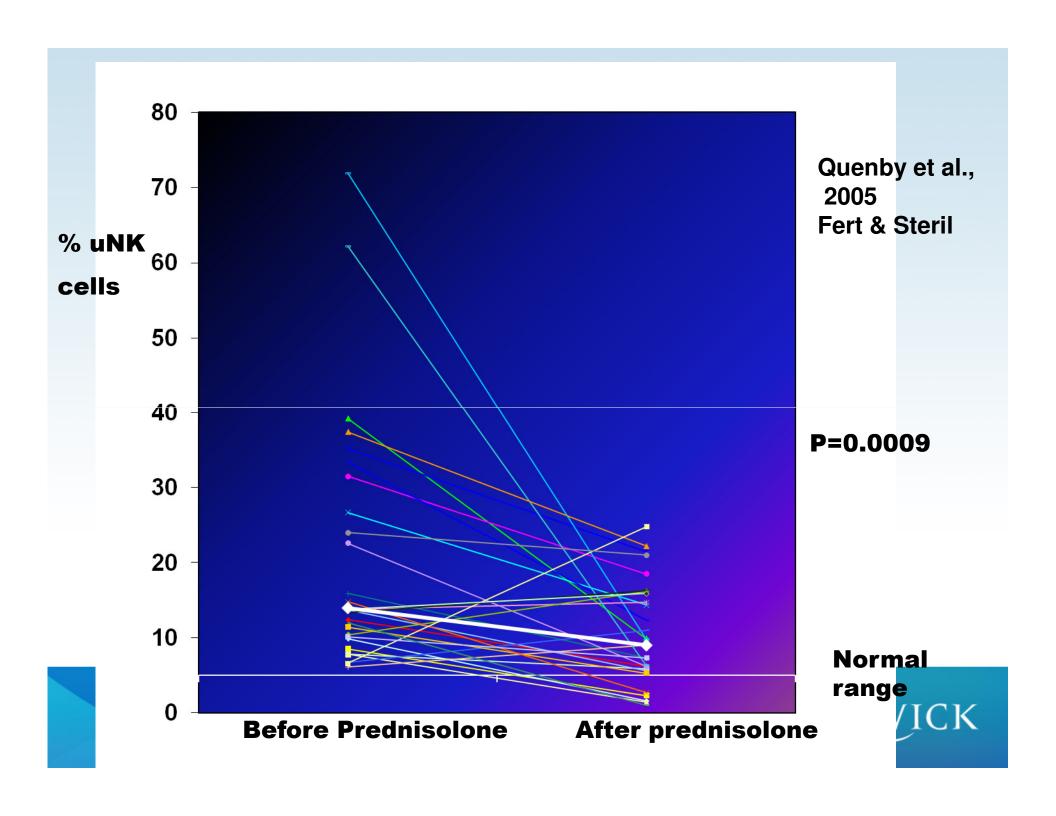
	High periphe	ral NK	Normal peripher	al NK		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	I M-H, Random, 95% CI
5.1.1 Recurrent Miscar	riage						
Emmer et al Subtotal (95% CI)	7	14 14	0	8 8	35.9% 35.9 %	17.00 [0.82, 350.60] 17.00 [0.82, 350.60]	
Total events	7		0				
Heterogeneity: Not appli	cable						
Test for overall effect: Z	= 1.83 (P = 0.0	07)					
5.1.2 infertility							
Thum et al	6	21	7	30	64.1%	1.31 [0.37, 4.68]	-
Subtotal (95% CI)		21		30	64.1%	1.31 [0.37, 4.68]	
Total events	6		7				
Heterogeneity: Not appli	cable						
Test for overall effect: Z	= 0.42 (P = 0.0)	67)					
Total (95% CI)		35		38	100.0%	3.29 [0.28, 39.34]	
Total events	13		7				
Heterogeneity: Tau ² = 2.	.08; Chi ² = 2.4	8, df = 1 (P = 0.12); I ² = 60%				0.01 0.1 1 10 100
Test for overall effect: Z	= 0.94 (P = 0.3	35)				Fa	avours experimental Favours control
Test for subgroup differe	ences: Not app	licable				1 6	avodio experimentali il avodio control

	High periphe	ral NK	Normal peripher	al NK		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95%	CI M-H, Rand	dom, 95% CI
8.2.1 Recurrent Misca	arriage							
Aoki et al	17	24	9	44	39.7%	9.44 [3.01, 29.68	3]	
Emmer et al	5	17	3	7	31.7%	0.56 [0.09, 3.44		
Subtotal (95% CI)		41		51	71.3%	2.51 [0.16, 40.29		
Total events	22		12					
Heterogeneity: Tau ² =	3.42; Chi ² = 6.6	7, df = 1 (1)	$P = 0.010$; $I^2 = 85$	%				
Test for overall effect:	Z = 0.65 (P = 0.9)	52)						
8.2.2 Infertility								
Matsubayashi et al	3	7 7	2	21	28.7%	7.13 [0.88, 57.55		
Subtotal (95% CI)		7		21	28.7%	7.13 [0.88, 57.55	5]	
Total events	3		2					
Heterogeneity: Not app	olicable							
Test for overall effect:	Z = 1.84 (P = 0.0)	07)						
Total (95% CI)		48		72	100.0%	3.55 [0.60, 21.03	-	
Total events	25		14					
Heterogeneity: Tau ² =	1.73: Chi ² = 6.8	7. df = 2 (P = 0.03); I ² = 71%	'			 	
Test for overall effect:	,	,	,,				_ 0.01 0.1	1 10 100
Test for subgroup diffe	`	,				I	Favours experimental	Favours control
reaction subgroup diffe	TOTIOGO. INOT APP	iioabic						

Predict outcome?

	High endomet	rial NK	Normal endometrial NK			Odds Ratio		Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% (CI	M-H, R	andom	, 95% C	
Quenby et al	5	10	2	11	44.1%	4.50 [0.63, 32.29]			+		
Tuckerman et al	4	15	15	36	55.9%	0.51 [0.14, 1.91]			-		
Total (95% CI)		25		47	100.0%	1.33 [0.16, 11.11]		-			
Total events	9		17								
Heterogeneity: Tau ² =	Heterogeneity: $Tau^2 = 1.64$; $Chi^2 = 3.24$, $df = 1$ ($P = 0.07$); $I^2 = 69\%$						0.01	0.1	+	10	100
Test for overall effect:	Z = 0.27 (P = 0.79)	9)				F		xperimen	ıtal Fa	avours co	





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	O previous miscar- riages	1 previous miscar- riage	previous miscar- riages	3 previous miscar- riages	4 Previous miscar- riages	previous live birth
Biochem- ical	<5	75%						
Clinical	5-10	88%	94%	86%	77%	72%	58%	95%
First trimester	10-12	97%						
reference		Bottomley 2009	Bhattachary a et al., 2010	Bhattachary a et al., 2010	Bhattacharya et al., 2010	Bhattacharya et al., 2010	Bhattacharya et al., 2010	Bhattachary a 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

