Immunology
Potentially Hazardous Treatment
or
Your Best Chance of Success?

Debate

Presented by **Amin Gorgy**

Med Director
The Fertility & Gynaecology Academy in London

www.fertility-academy.co.uk

01 November 2014

- INFERTILITY TREATMENTS
- REPRODUCTIVE IMMUNOLOGY
- GYNAECOLOGY CARE

The Fertility & Gynaecology Academy

Thanks to The Organizers of The Fertility Shaw particularly Jonathan Scott

It is an honour to debate

the Value of Immune Supportive Therapy in Recurrent Miscarriage

with Prof Lesly Regan

Prof Regan and I are both believers of Reproductive Immunology

- Prof Regan and her group were behind the evidence of treating Anitphospholipid Antibodies with Aspirin and Heparin:

Ref:

- Unexplained Recurrent Pregnancy Loss; Saravelos & Regan, 2014
- Recurrent Miscarriage; Rai & Regan, Lancet 2006
- Impaired Expression of Endo Markers ; .. Regan, .. , Mol Hum Rep 2006
- Recurrent Miscarriage: Pathology & Outcome; & Regan, C O Ob/Gyn2005
- Heparin & Aspirin Attenuate placental Apoptosis, Am J Ob/Gyn 2005
- Thrombophilia & Pregnancy Loss; J Reprod Immunology 2002
- Antiphospholipid antibodies & Infertility; Hum Fertil 2002

Prof Regan: Other Areas of Reproductive Immunology

Ref:

- Maternal Activation of Killer-cell Immunoglobulin-like Receptors (KIRs) Protect Against Human Reproductive Failure Mediated by Fetal HLA-C2; J Clin Inest 2010
- Natural Selection of Human Embryo: Impaired Decidualization of Endometrium Disables Embryo-Maternal Interactions and Causes Recurrent Pregnancy Loss (PloS One 2010)

Immune Supportive Therapy: is it the treatment for **Unexplained** Recurrent Miscarriage and Repeated Implantation Failure?

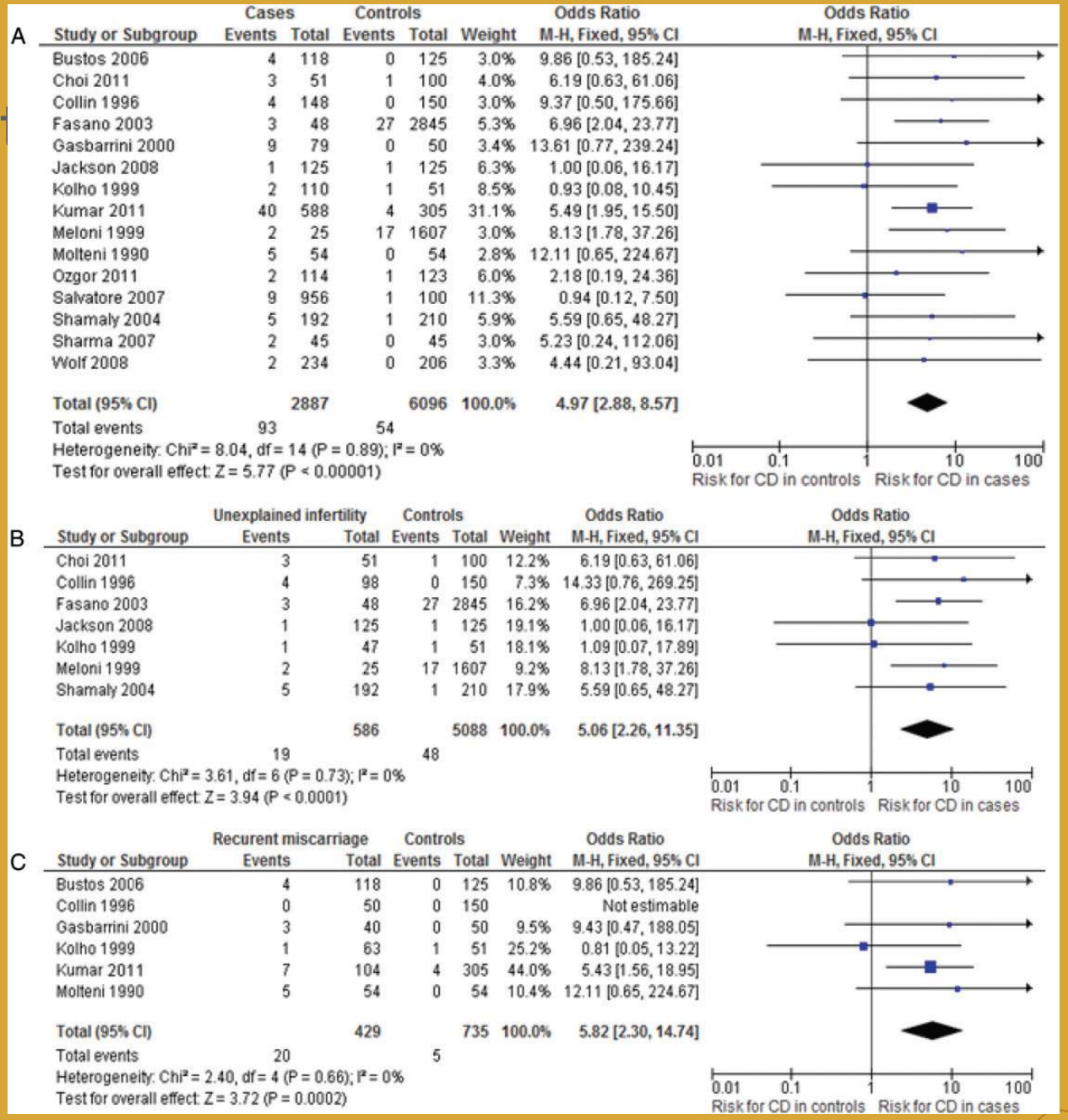
Does It Increase You Chances of Having A Baby?

Celiac Disease and Reproductive Diorders Meta-Analysis

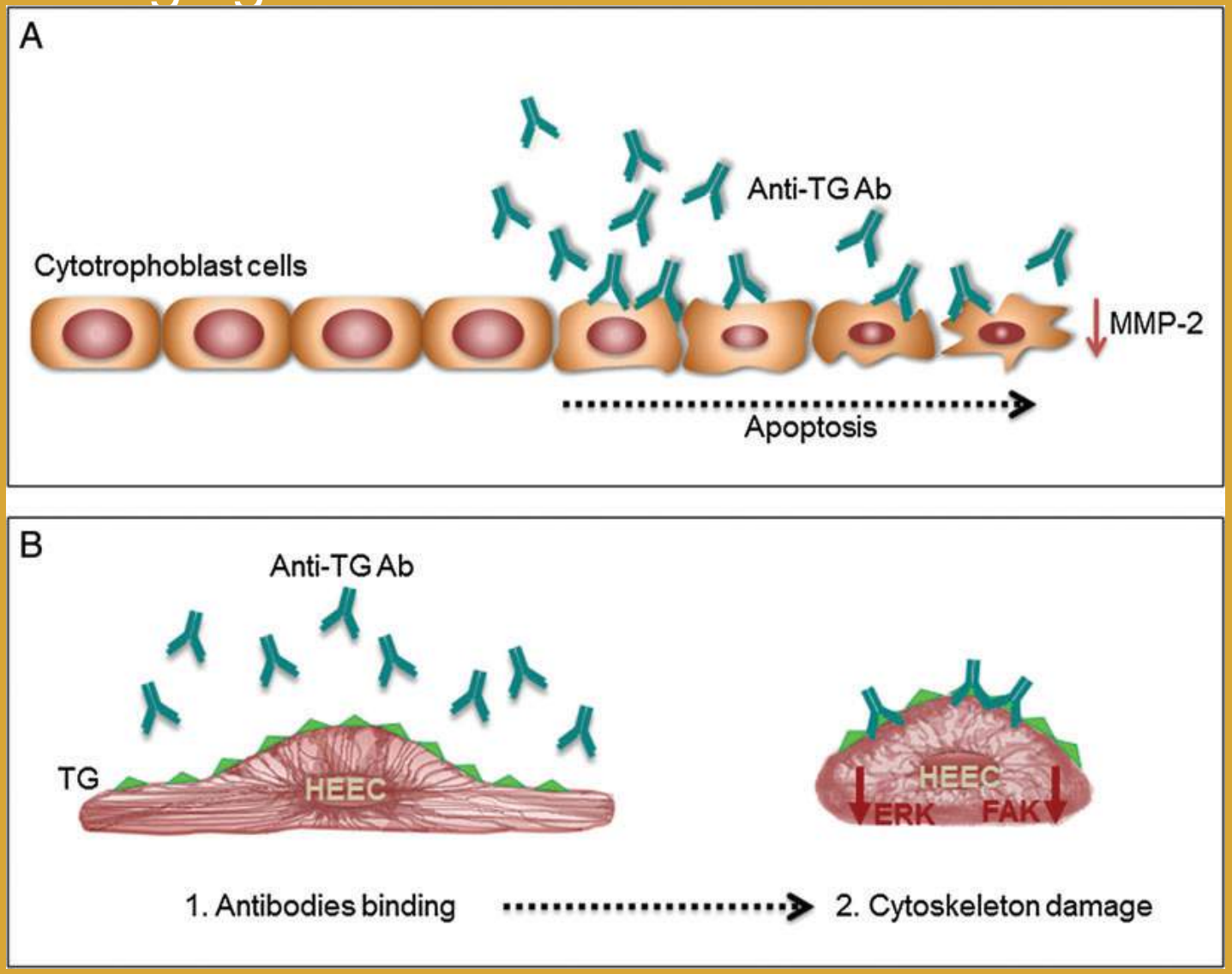
Human Reproduction Update; Aug 2014

Chiara Tersigni et al,
Rome, Italy

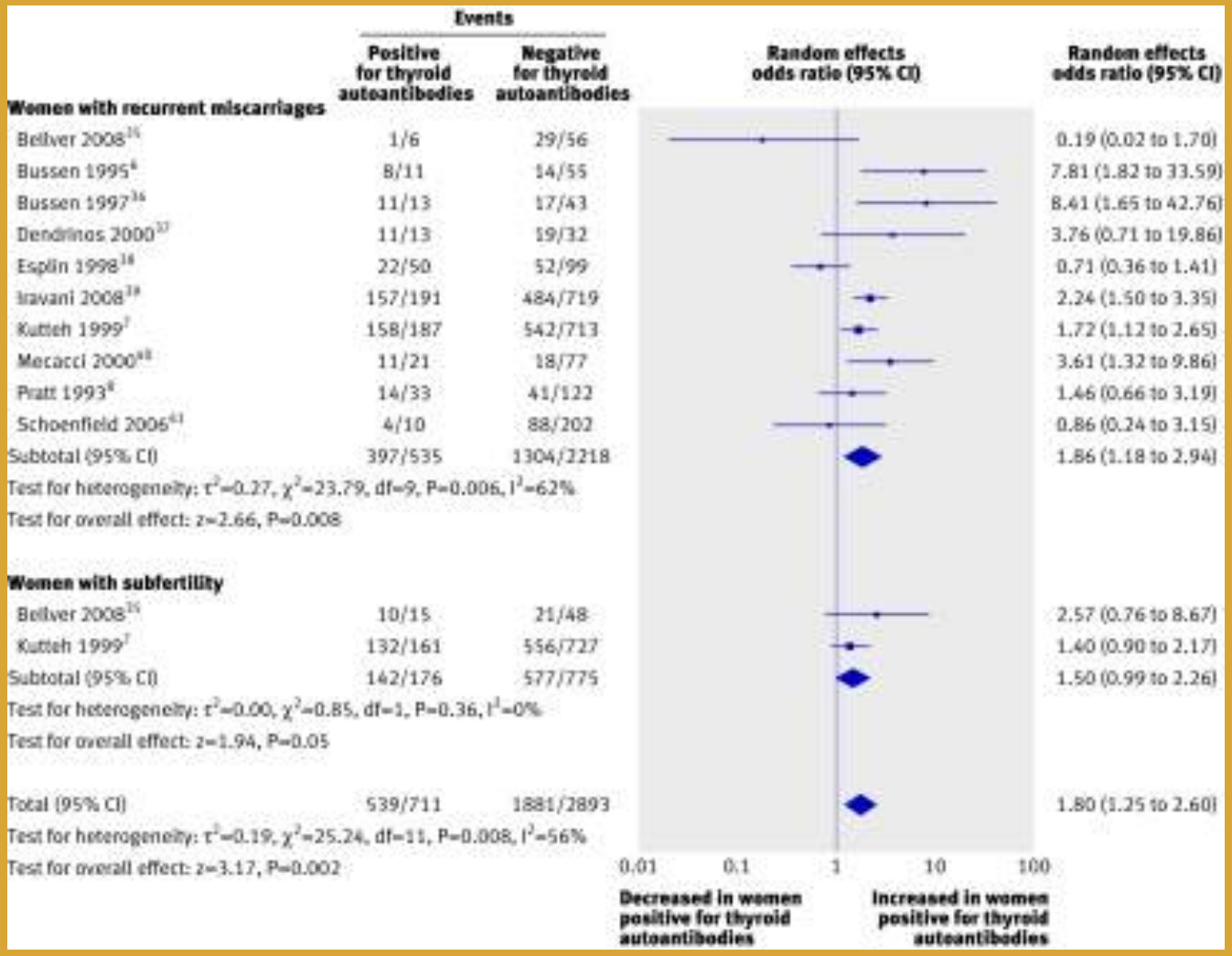
Crit


A
Cases
Controls
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Bustos 2006 4 118 0 125 3.0% 9.86 [0.53, 185.24]
Choi 2011 3 51 1 100 4.0% 6.19 [0.63, 61.06]
Collin 1996 4 148 0 150 3.0% 9.37 [0.50, 175.66]
Fasano 2003 3 48 27 2845 5.3% 6.96 [2.04, 23.77]
Gasbarrini 2000 9 79 0 50 3.4% 13.61 [0.77, 239.24]
Jackson 2008 1 125 1 125 6.3% 1.00 [0.06, 16.17]
Kolho 1999 2 110 1 51 8.5% 0.93 [0.08, 10.45]
Kumar 2011 40 588 4 305 31.1% 5.49 [1.95, 15.50]
Meloni 1999 2 25 17 1607 3.0% 8.13 [1.78, 37.26]
Molteni 1990 5 54 0 54 2.8% 12.11 [0.65, 224.67]
Ozgor 2011 2 114 1 123 6.0% 2.18 [0.19, 24.36]
Salvatore 2007 9 956 1 100 11.3% 0.94 [0.12, 7.50]
Shamaly 2004 5 192 1 210 5.9% 5.59 [0.65, 48.27]
Sharma 2007 2 45 0 45 3.0% 5.23 [0.24, 112.06]
Wolf 2008 2 234 0 206 3.3% 4.44 [0.21, 93.04]
Total (95% CI) 2887 6096 100.0% 4.97 [2.88, 8.57]
Total events 93 54
Heterogeneity: Chi² = 8.04, df = 14 (P = 0.89); I² = 0%
Test for overall effect: Z = 5.77 (P < 0.00001)
0.01 0.1 1 10 100
Risk for CD in controls Risk for CD in cases
B
Unexplained infertility
Controls
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Choi 2011 3 51 1 100 12.2% 6.19 [0.63, 61.06]
Collin 1996 4 98 0 150 7.3% 14.33 [0.76, 269.25]
Fasano 2003 3 48 27 2845 16.2% 6.96 [2.04, 23.77]
Jackson 2008 1 125 1 125 19.1% 1.00 [0.06, 16.17]
Kolho 1999 1 47 1 51 18.1% 1.09 [0.07, 17.89]
Meloni 1999 2 25 17 1607 9.2% 8.13 [1.78, 37.26]
Shamaly 2004 5 192 1 210 17.9% 5.59 [0.65, 48.27]
Total (95% CI) 586 5088 100.0% 5.06 [2.26, 11.35]
Total events 19 48
Heterogeneity: Chi² = 3.61, df = 6 (P = 0.73); I² = 0%
Test for overall effect: Z = 3.94 (P < 0.0001)
0.01 0.1 1 10 100
Risk for CD in controls Risk for CD in cases
C
Recurent miscarriage
Controls
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Bustos 2006 4 118 0 125 10.8% 9.86 [0.53, 185.24]
Collin 1996 0 50 0 150 Not estimable
Gasbarrini 2000 3 40 0 50 9.5% 9.43 [0.47, 188.05]
Kolho 1999 1 63 1 51 25.2% 0.81 [0.05, 13.22]
Kumar 2011 7 104 4 305 44.0% 5.43 [1.56, 18.95]
Molteni 1990 5 54 0 54 10.4% 12.11 [0.65, 224.67]
Total (95% CI) 429 735 100.0% 5.82 [2.30, 14.74]
Total events 20 5
Heterogeneity: Chi² = 2.40, df = 4 (P = 0.66); I² = 0%
Test for overall effect: Z = 3.72 (P = 0.0002)
0.01 0.1 1 10 100
Risk for CD in controls Risk for CD in cases

Damaging Effects of Antibodies



Thyroid Antibodies & Miscarriage in Case-Controlled Studies



Antibodies

Double Stranded DNA

Single Stranded DNA

Polynucleotide

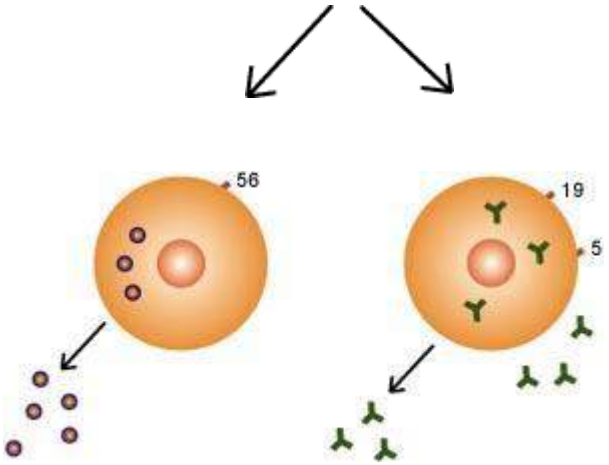
Histone

→ Inflammation Around the Placenta

Natural Killer Cells

The Immune System
has 30 Different Kinds of Lymphocytes

Two Types Can
Damage Pregnancies

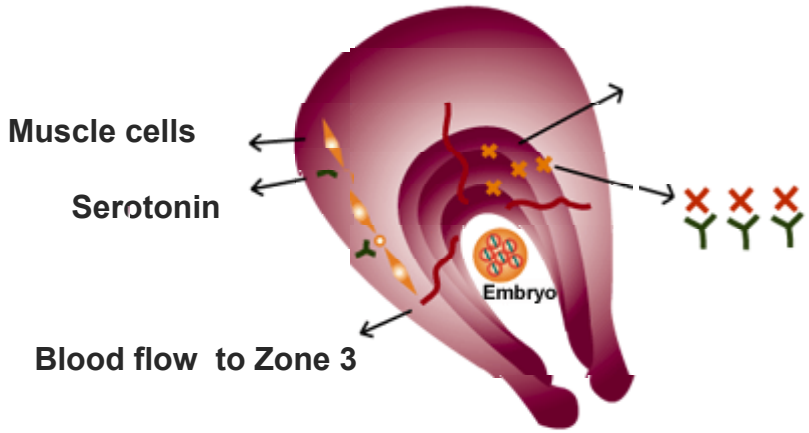


Antibodies to Hormones

Tumour Necrosis Factor Alpha (TNFa)

Antibodies to Neurotransmitters

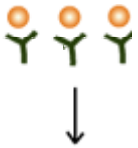
Antibodies to Neurotransmitters



Zones 1, 2 & 3 of endometrium on day of ovulation

Endorphins & enkaphlins are involved in the modeling of the 3 layers of endometrium

Antibodies to these lead to a thin "teflon" endometrium without a blood supply



Serotonin needed to change muscle cells of uterus to accommodate a pregnancy

Antibodies to serotonin leads to a uterus that does not accommodate a pregnancy

Natural Killer (NK) Cells in Miscarriage and Implantation Failure

Increased blood NK cells in Rec M/C & Implantation Failure:

- Aoki et al 1995
- Fukui et at 1999
- Emmer et al 2000
- Matsubayashi et al 2001
- Coulam & Roussev (1) 2003
- Coulam & Roussev (2) 2003
- Thum et al 2004
- Skakar et al 2003

Increased uterine NK cells in M/C & Implantation Failure:

- S Quenby 1999,2005 & 6
- Clifford et al 1999
- Tuckerman et al 2007
- Laird et al 2005

Uterine NK cells are different from Blood NK cells

Uterine NK cells:

- CD 56 (bright)
- Mainly produce cytokines
- Recruited in two waves to the uterus; ovulation & at 2 weeks after the missed period.

Blood NK cells:

- Mainly CD 56(dim) and some CD 56 (bright)
- Mainly cytotoxic (cytolytic)
- Home to inflammation sites: decidua & other sites (men)
- Argued to be stress related and so is the blood pressure.
- Chronic stress → ↑ NK cells

Effect of increased NK ells and Treatment

Pathology:

- NK cells release cytokines → inflammatory reaction
- Defective angiogenesis → early onset of maternal circulation → Excessive placental oxidative stress (S Quenby)

Treatment:

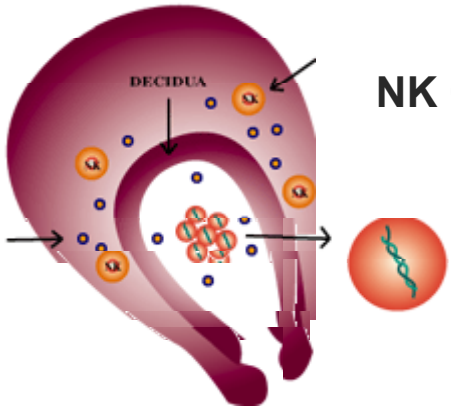
- Prednisolone reduces the u-NK cell population and activity
- Prednisolone reduces endometrial spiral artery development in RM patients.
- Prednisolone increased LB rate from 40 to 60% (S Quenby)
- Heparin and Aspirin attenuate placental apoptosis (L Regan)
- Add Pred to Aspiri & Hep: ↑LB (70.3 vs 29.7%) (Gomaa 2014)
- IVIg reduces NK cell population and activity

Effect of Elevated TH1 Cytokines

- ↑ TH1 (TNFα & IFN γ) and TH17 (IL-17) in blood and decidua in patients with infertility & RM. (Piccinni 2005).
- ↑ TH1 (TNFα & IFN γ) causes trophoblast apoptosis &defective angiogenesis.
- They cause activation of complement and coagulation. (Clark 2008, Knackstedt 2001)
- Peripheral blood cells over producing TNFα enter the implantation site blood pools. (Boomsma 2009)
- ↑ TH1/TH2 ratio is more important
- Levels can be adjusted & effect counteracted with: TNA α antagonists (Humira), IVIG, Aspirin & Heparin, Steroids

Before Implantation

TNF Alpha

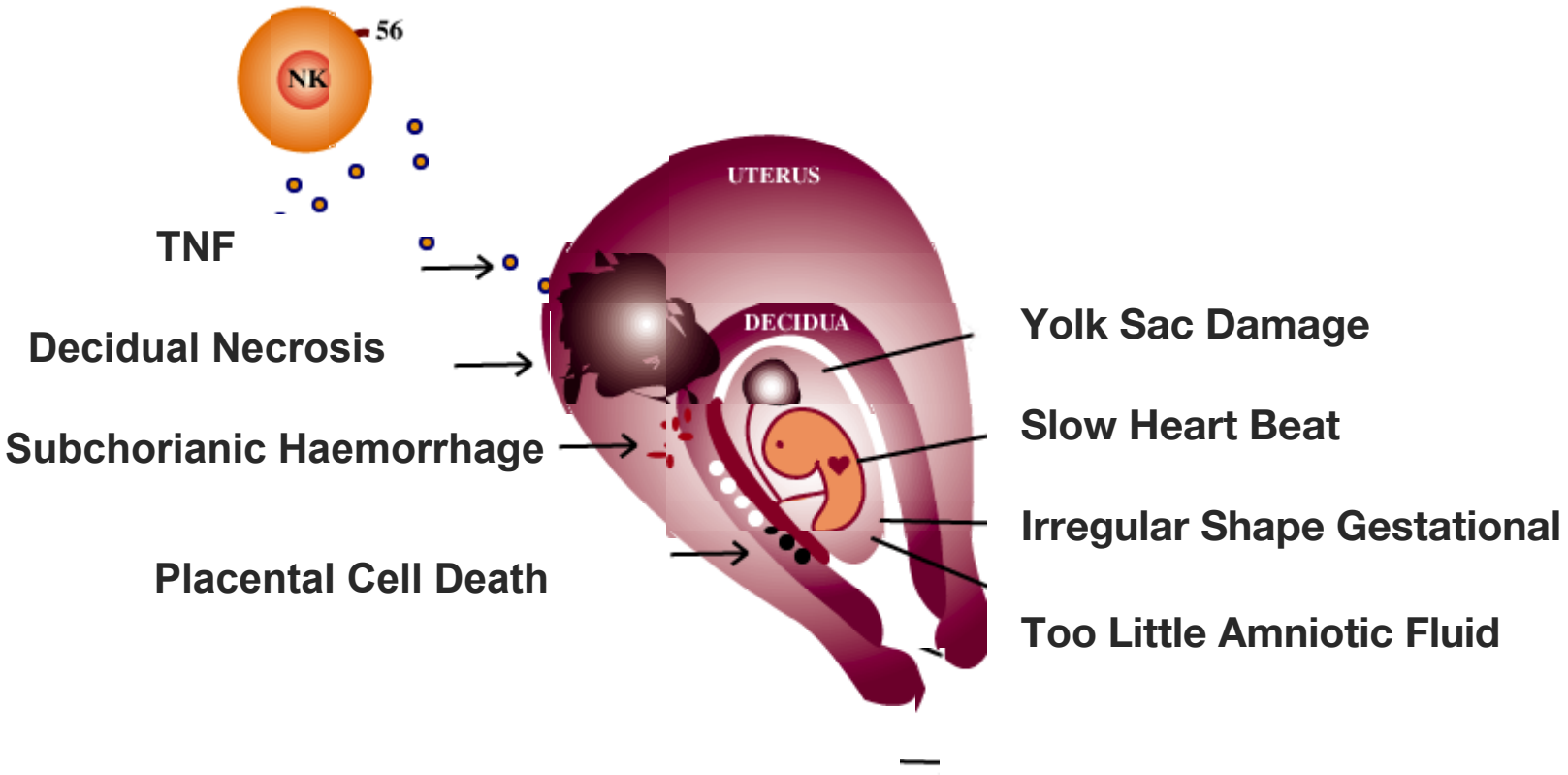


NK Cells Resident in uterus

Causes Apoptosis of the DNA in the Embryo Leading to Spot Welding of the DNA

↓

Embryo Grows Slowly and Dies.
Embryo Never Attaches.
Placental Tissue Grows With No Embryo Seen.


56
NK
TNF
Decidual Necrosis
Subchorianic Haemorrhage
Placental Cell Death
UTERUS
DECIDUA
Yolk Sac Damage
Slow Heart Beat
Irregular Shape Gestational
Too Little Amniotic Fluid

What is needed for a therapy to work?

- There must be an abnormal physiology
- This abnormality should be checked by a test
- The therapy must work on this pathology
- The outcome should be better after giving the therapy to the right cohort of patients
- Success should be judged by the outcome: in our case Live Birth

Aspirin For Recurrent Miscarriage in Antiphopholipid Syndrome Vs Unexplained
(Raj Rai & Lesley Regan, Lancet 368, 2006)

	Level of evidence	References
Intervention of benefit		
Aspirin+heparin for antiphospholipid syndrome	Ib	99
Psychological support	III	146–148
Metformin for women with insulin resistance	III	153
Heparin for women with thrombophilic defects	IV	160
Intervention of no benefit		
Progesterone supplementation after positive pregnancy test	I	150
Intravenous immunoglobulin/glucocorticosteroids	Ia	93,161
Aspirin for "unexplained" reccurent miscarriage	IIa	155,156
Embryo aneuploidy screening	IIa	165

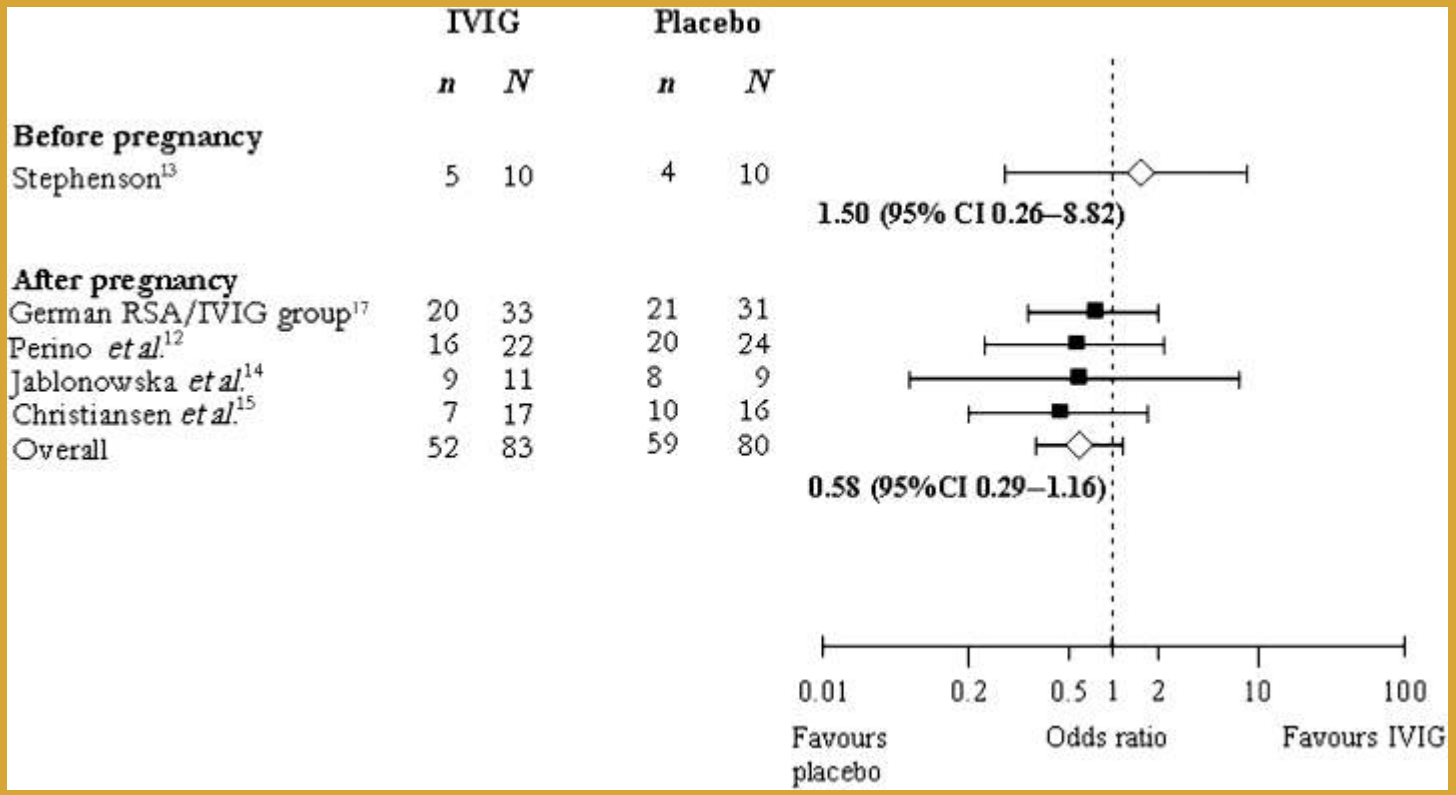
What does IVIg do?

- Reduces NK cell cytotoxicity (killing activity)
- Reduces expression of pro-inflammatory T cell cytokines
- Increases the activity of T regulatory cells (Immune Tolerance)
- Suppresses B cell production of antibodies
- Contains antibodies to antibodies
- Actions on Fc receptors including binding of complement

C Coulam, O Christiansen, Hutton, Clark and others

Use of intravenous immunoglobulin for treatment of recurrent miscarriage: a systematic review, Hutton et al 2006

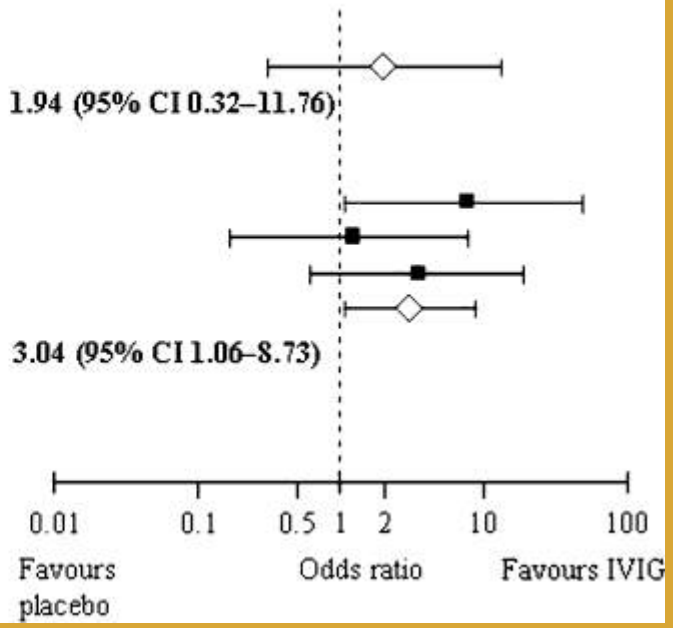
live birth rates among all cases of primary recurrent miscarriage, stratified by treatment start time



Use of intravenous immunoglobulin for treatment of recurrent miscarriage: a systematic review, Hutton et al 2006

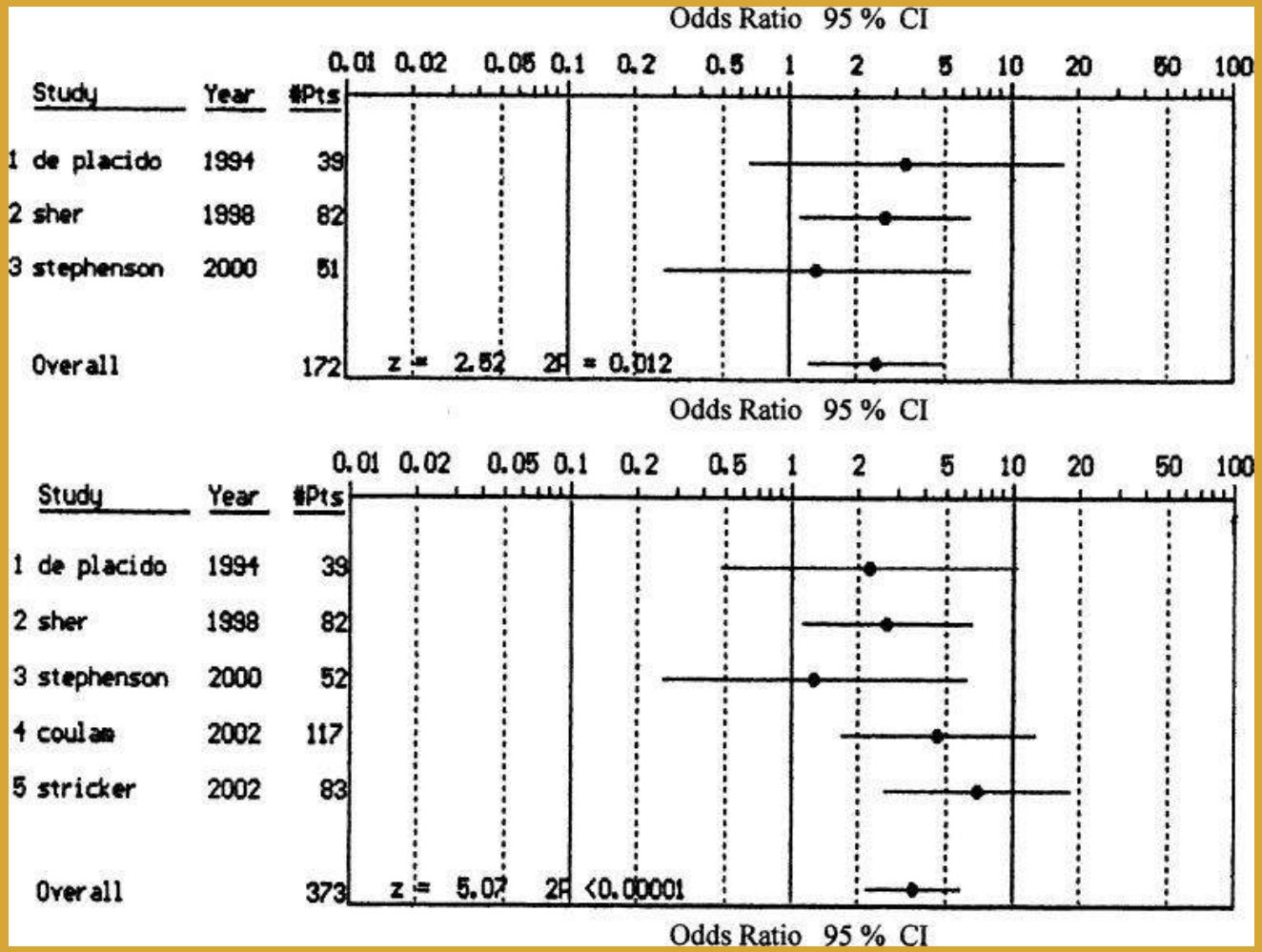
Cases of secondary recurrent miscarriage, stratified by treatment start time.

	IVIG		Placebo	
	n	*N*	*n*	*N*
Before pregnancy				
Stephenson[13]	7	10	6	11
After pregnancy				
Christiansen *et al.*[10]	9	14	2	10
Jablonowska *et al.*[14]	8	11	7	10
Christiansen *et al.*[15]	6	12	3	13
Overall	23	37	12	33



Is intravenous immunoglobulins (IVIG) efficacious in early pregnancy failure? A critical review and meta-analysis for patients who fail in vitro fertilization and embryo transfer (IVF)

David A. Clark, Carolyn B. Coulam, and Raphael B. Stricker; 2006



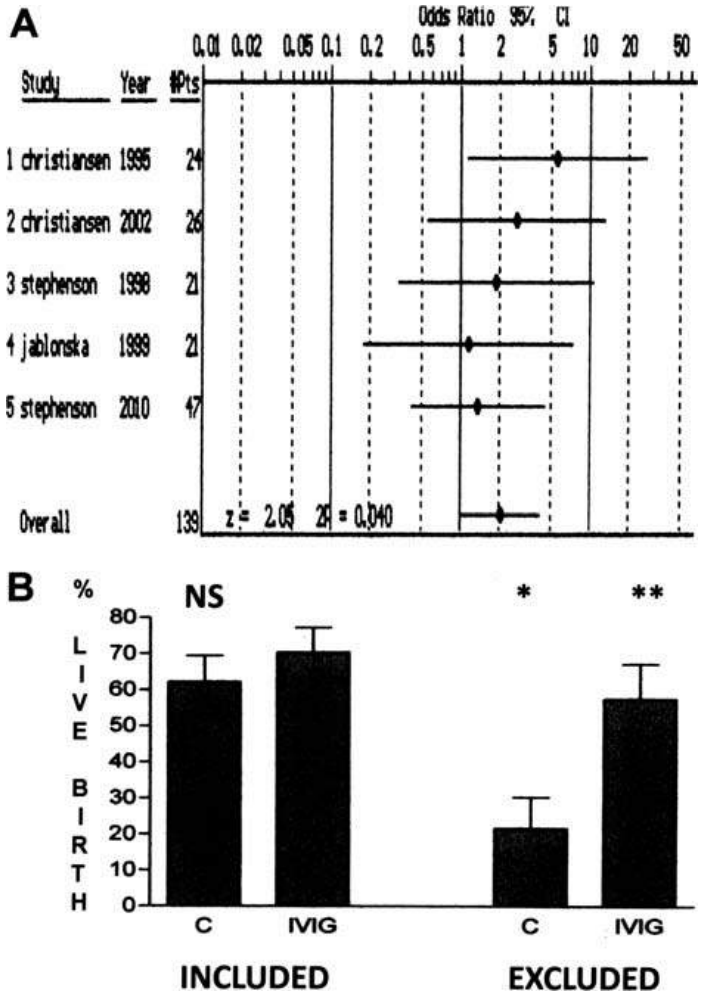
Double-blind randomized controlled trial (RCT) of intravenous immunoglobulin (IVIG) in idiopathic secondary recurrent miscarriage and conclude ‘no benefit was found’. Stephenson et al. (2010)

Methodological Flaws:

- The planned sample size was not achieved. No Conclusion
- Heterogeneous group of patients. Idiopathic
- Using Gamimune: ? Less potent (Clark et al 2006)
- Exclusion of patients with immune issues
- Exclusion from the meta-analysis two trials by Christiansen et al (1995 & 2002) because they included patients with immune abnormalities!!!
- Adding these two trial will make the meta analysis significant in favour of IVIg.

Intravenous immunoglobulin and idiopathic secondary recurrent miscarriage: methodological problems

David Clark letter, Hum Repro 2011



Is intravenous immunoglobulins (IVIG) efficacious in early pregnancy failure? A critical review and meta-analysis for patients who fail in vitro fertilization and embryo transfer (IVF)

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Table IV.

Classification of Outcome of Controlled Trials of IVIG in Reproductive Failure

	Pre-ovulatory IVIG start		IVIG started post-pregnancy	
Outcome	**RSA trials**	**IVF failure trials**	**RSA trials**	**IVF failure trials**
Positive[a]	Coulam [95] (48)	Sher [82] (10)	None	None
	Kiprov [35] (49)	de Placido [39] (9)		
	Stricker [47] (50)	Stricker [61] Table III		
		Coulam [107] Table II		
Negative	Stephenson [39] (51)	Stephenson [51] (4)	German Grp [64] (52)	None
			Christiansen [34] (53)	
			Christiansen [58] (54)	
			Perino [46] (55)	
			Jablonowska [41] (56)	

Debate: Should Immunotherapy be Used? Intravenous Immunoglobulin: Yes. Carolyn Coulam 2014

Trial	n	IVIg start	Selection	LB (p< 0.05)
Moraru et al 2012	157	Before pre	Immune test	Yes
Coulam et al 1995	95	Before pre	Ob history	Yes
Kiprov et al 1996	35	Before pre	Immune test	Yes
Stricker et al 2000	47	Before pre	Immune test	Yes
Stevenson et al 98	39	Before pre	Ob History	No
Mueller-Eckhart 94	64	After pre	Ob History	No
Christiansen 2002	34	After pre	Ob History	No
Christiansen 1995	58	After pre	Ob History	No
Perino et al 1997	46	After pre	Ob History	No
Jablonowska 1999	41	After pre	Ob History	No

Side Effects of IVIg Therapy

- Temporary headache
- Temporary high blood pressure
- Nausea and sometimes vomiting
- Rash
- Back pain
- Fever, chills
- Tiredness and physical weakness
- Flue-like symptoms

Rare & Isolated Cases:

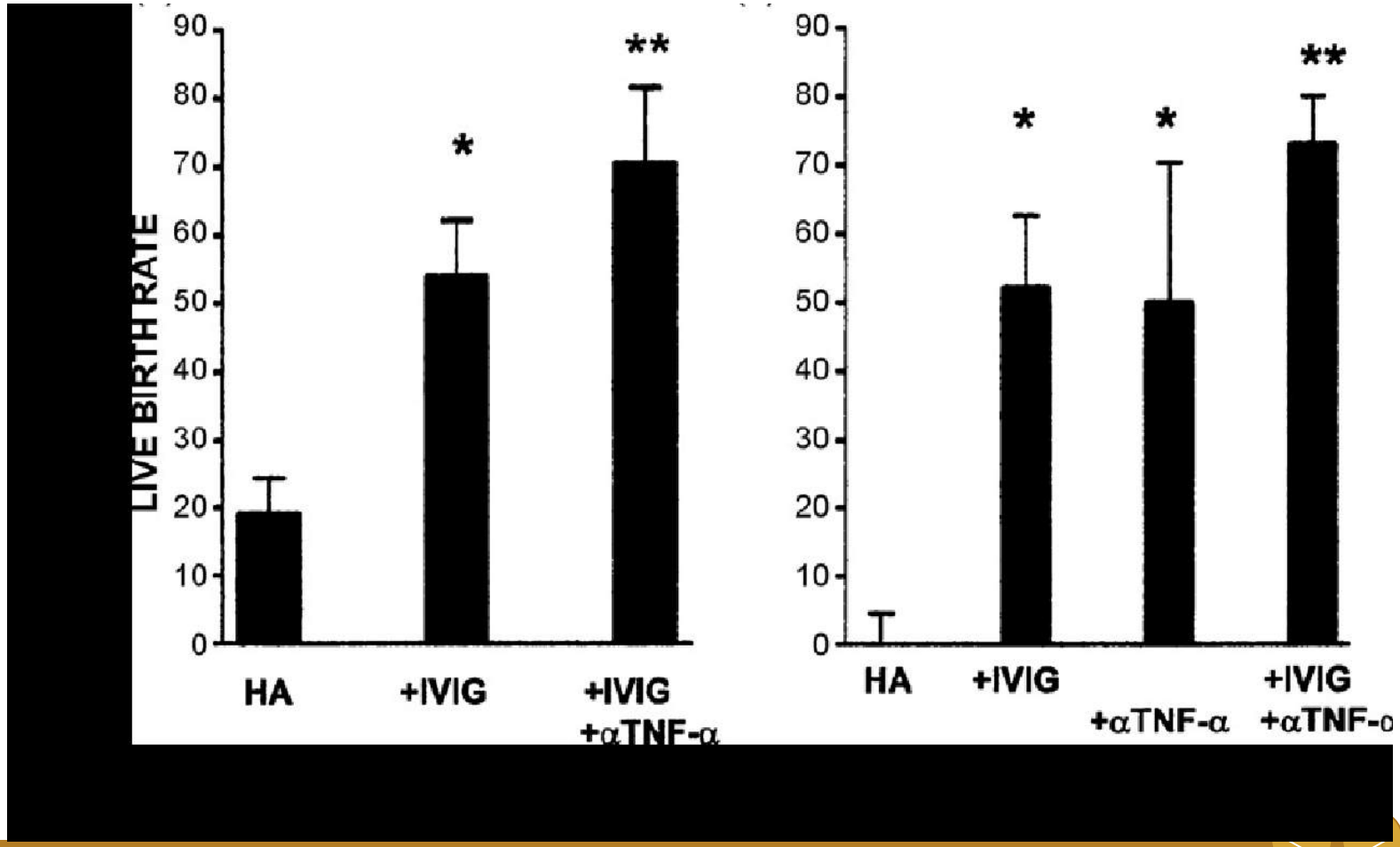
Transient skin reaction, temporary aseptic meningitis, sever hypersensitivity, blood clots & embolism, transient haemolysis

Treatment with Adalimumab (Humira) and IVIg Improves Pregnancy Rates in Women Undergoing IVF

Winger et al 2008

- IVIg significantly improved LB rate in patients with elevated NK cell cytotoxicity and elevated TH1/TH2 cytokine ratio.
- Adding Humira to IVIg improved the LB rate further.
- Patients with border line elevated TH1/TH2 cytokine ratio were given IVIg only
- Patients with remarkably high TH1/TH2 cytokine ratio were given Humira in addition to the IVIg

Treatment with tumour necrosis factor inhibitors and intravenous immunoglobulin improves live birth rates in women with recurrent spontaneous abortion (Winger & Reed 2008) and in Infertile IVF Patients (Winger et al 2009)



Side Effects of Anti-TNFα Therapy: Current Knowledge. (Antoni & Braun 2002)

- Flare of dormant TB: TB gold quantiferon test.
- Other sever infections: No
- Lymphoma: No
- No increased development of:

ANAs, Lupus like syndrome,
infusion reaction, allergic reactions,
neurological disorders

Regulatory T-Cells and Immune Tolerance in Pregnancy: A New Target for Fertility Treatment

Leigh Guerin, …., & Sarah Robertson 2009

- T-reg cells are a sub-type of lymphocytes
- Important role in Immune Tolerance
- Protective in:
  - Auto-immune disease (Sagaguchi 2005)
  - Transplantation tolerance (Waldmann et al 2004)
  - Inflammatory diseases (Wahl et al 2004)

Through:

- Inhibit cytokine production
- Suppress antibody production
- Inhibit cytotoxic function of NK cells
- Inhibits antigen presenting cells; DCs & macrophages

Immune Tolerance Prevents Immune Rejection of the Foetus Sarah Robertson group 2009

- T-reg cells increase in early pregnancy and decline prior to labour
- They even increase prior to pregnancy following intercourse
- Miscarriage is associated with low blood and endometrial levels
- Recurrent miscarriage is associated with low blood levels
- Unexplained infertility is associated with low endometrial levels

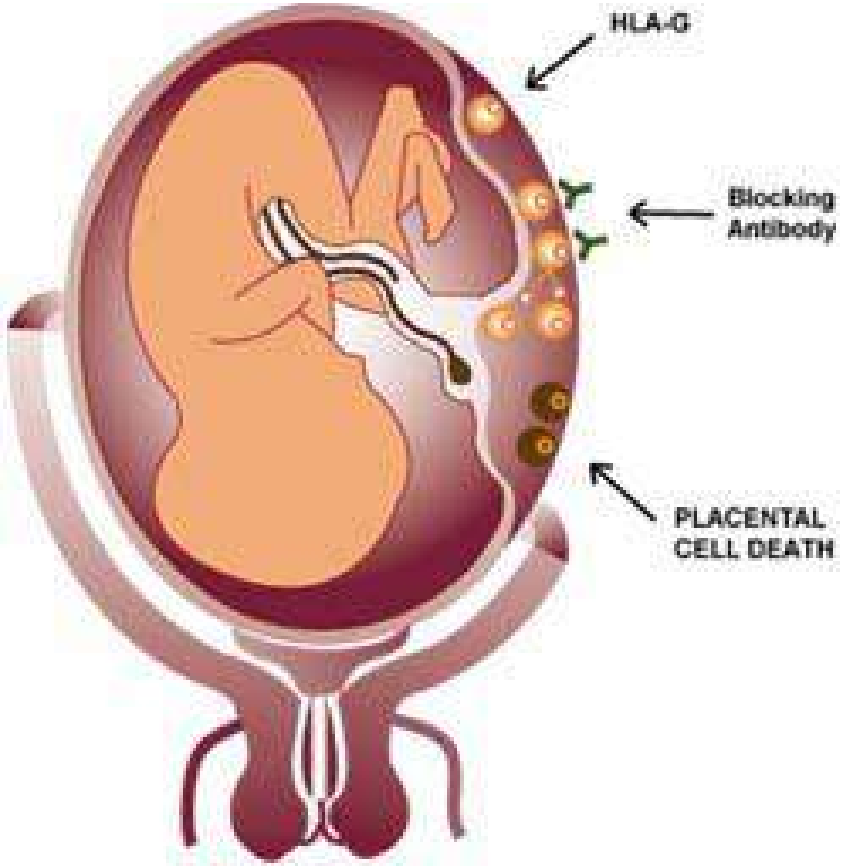
Possible therapy to induce T-reg cells:

Lymphocyte Immune Therapy

G-CSF

Paternal Leukocyte Antibodies

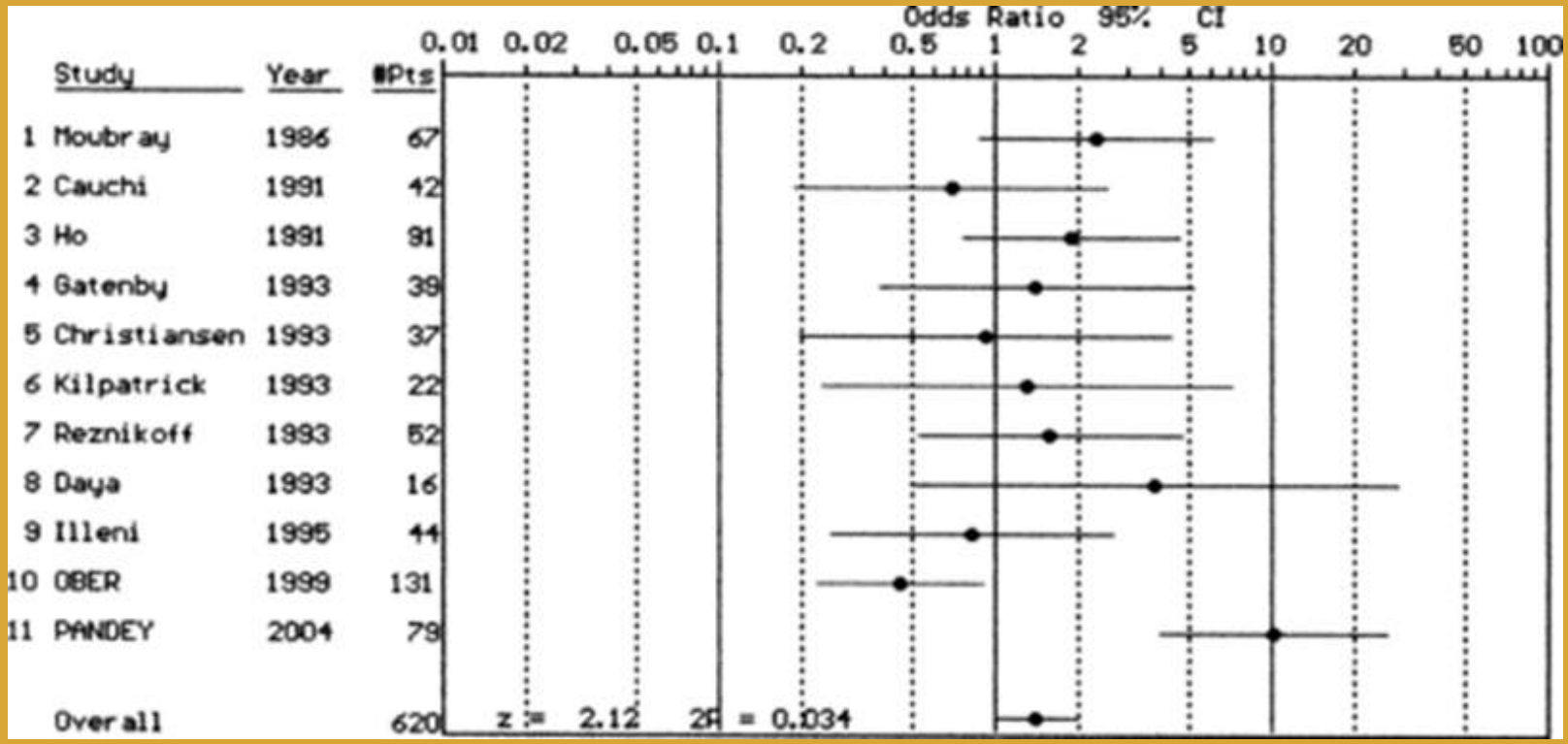
- **HLA-G:** Message sent from father to stimulate blocking antibody.
- **Blocking Antibody:** Protects and stimulates the growth of placental cells.
- **Placental Cell Death:** Consequences of low blocking antibody.



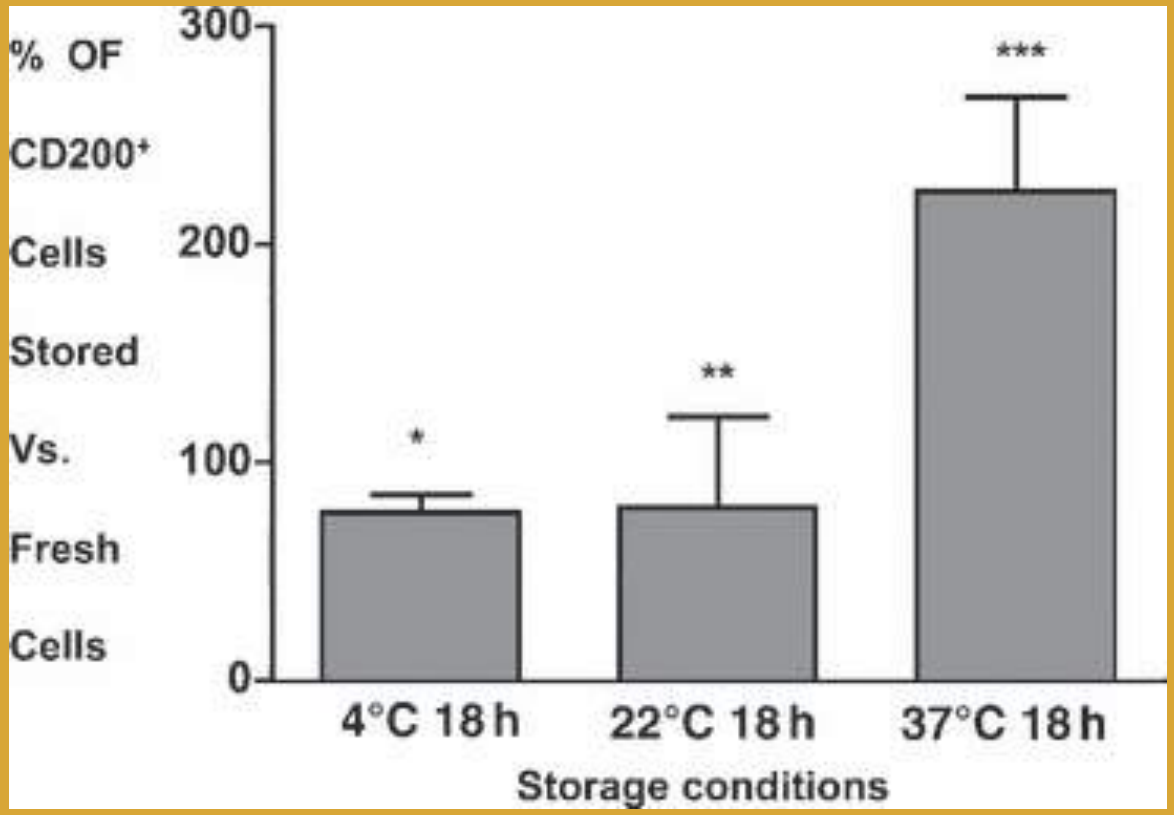
Lymphocyte Immune Therapy

- First used to induce immune tolerance in Kidney transplant
- RCT by Mowbray published 1985
- Ober's trial 1999: -ve outcome
- Media attention, FDA allowed LIT only in Research Setup
- Pandy & Agrawal 2004: extremely +ve effect
- Meta-analysis : +ve outcome even including Ober trial
- LIT success is related to the dose of CD 200 marker in LIT product
- CD 200 is significantly reduced with storing the sample at 4^0 C overnight (Ober) and increase at 37^0 C (Pandy & Agrawal)

Lymphocyte Immune Therapy; Meat-Analysis



Effect of LIT Product storage Overnight



Transfusion-related Risks of Intradermal Allogeneic Lymphocyte Immunotherapy. (Kling et al 2006)

- Infection risk is minor
- Transplant rejection later in life is a minor risk
- Post-transfusion purpura was suspected once but not verified
- Anaphylaxis was not promoted.
- Malignancy risk was not increased
- Fetal/newborn alloimmune disease (sever haemolytic disease, thrombocytopenia, neutropenia): not observed.

In Conclusion:

Acute side effects are comparable to those reported after intradermal vaccination for infectious disease.

Specific risks for anaphylaxis, autoimmune or graft versus host disease were not detected.

Granulocyte-Colon Stimulating Factor (G-CSF) for Patients with Recurrent Miscarriage and Implantation Failure

- G-CSF increased LB from 13% (placebo) to 37.7% in patients with RMC (Betina Toth, Heidleburg & Wolfgang Wurfel, Munich groups 2013)
- G-CSF improved pregnancy rate from 20% to 43% in patients with repeated implantation failure (Wurfel 2000, 3)
- Inspired by the paper of Hiby, Regan, .. & Moffett 2008, Wurfel group in Munich found high incidence (78%) of missing KIRs (2DS1, 2DS5 & 3DS1) in patients with Repeated Implantation Failure
- Treating this group with G-CSF increased pregnancy rate to 73.8% in D5 & 42% in D2 ET. (Wolfgang Wurfel 2010)

Use of G-CSF for Treatment of Unexplained Recurrent Miscarriage: a Randomized Controlled Trial. (Scrapellini & Sbracia 2009)

- G-CSF group: 82% LB Vs 48.5% in Placebo group Significant Difference: p = 0.006, OR 5.1 (95% CI 1.5-18.4)
- Higher levels of β-hCG: a +ve effect on trophoblast growth and placental metabolism (McCraken et al 1996 & 99)
- G-CSF induces TH2 response (Pan et al 2011)
- G-CSF inhibits NK cells (Schlahsa et al 2011)
- G-CSF induces immune tolerance

Side Effects of G-CSF Therapy

- The Germans reported side effects in 10% of their 78 patients (127 cycles)
  - Irritation at injection site
  - Slight leukocytosis
  - Rise in temperature $<38^0C$
  - Mild bone pain
  - Hyperemesis gravidarum

- G-CSF treatment during pregnancy for chronic neutropenia had no adverse effect on the pregnancy or the foetus, 125 cases. (Okasaki et al 2002)

Combined Immune Therapy

- Adding Heparin to Aspirin improves LB in patients with APLA from 44 to 80%. (Kutteh 1996, Rai, Dave & Regan 1997)
- Adding Prednisolone to Aspirin and heparin improved the on-going pregnancy rate beyond 20 ws to 70.3 Vs 9.2% in patients with unexplained RM (RCT); Gomma et al 2014
- Adding IVIg to Aspirin & Heparin for patients with APLA made the therapy successful for Implantation Failure as well as RM (Coulam 2012)
- Adding IVIg to Aspirin & Heparin improved the outcome for patients with Thyroid Abs and Implantation Failure. (Sher 1998)
- In patient with 1ry RMC adding IVIg to HA increase LB:19 to 55%. Adding LIT increased LB to 70% (Winger et al 2007)
- In patients with RMC adding IVIG to HA increase LB:19 to 54%. Adding TNFα antagonist increased LB to 70% (Winger et al 2007)

Immune Supportive Therapy:
Is it the treatment for Patients with
Immune System Imbalance
and Recurrent Miscarriage or
Repeated Implantation Failure?

Does It Increase You Chances of Having A Baby?

YES

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Prof Sir Magdi Yacoub once said

I am grateful for those who agreed with my ideas as they made me work more

But I am most grateful for those who disagreed with my ideas as they made me work harder to find the truth

Debate: Should Immunotherapy be Used? Intravenous Immunoglobulin: Yes. Carolyn Coulam 2014

Study	No. Trials	No. Patients	OR (95% CI) Overall	OR (95% CI) 1ry MC	OR (95% CI) 2ry MC
Hutton et al 2007	8	442	1.28 (0.78-2.10)	0.66 (0.35-1.20)	2.71 1.09-6.77)*
Daya et al 1998	6	240	1.08 (0.63-1.86)	1.04 (0.54-2.01)	1.18 (0.43-3.21)
Ata et al 2011	6	272	0.92 (0.55-1.54)	0.67 (0.32-1.39)	1.15 (0.47-2.84)
Clark et al 2011	5	210			2.1 (1.06-4.49)*
Li et al 2013	10	8207	1.62 (1.24-2.1)*		

Thromboelastogram

- Identifies a group of women with history of RMC and a tendency toward thrombosis. (Rai et al 2003)
- To detect haemostatic abnormalities that otherwise are not identified by conventional clotting tests. (Carrington Sacks & Regan 2005)
- Treated with Aspirin.
- Only done at St Mary's Hospital.
- No further trials

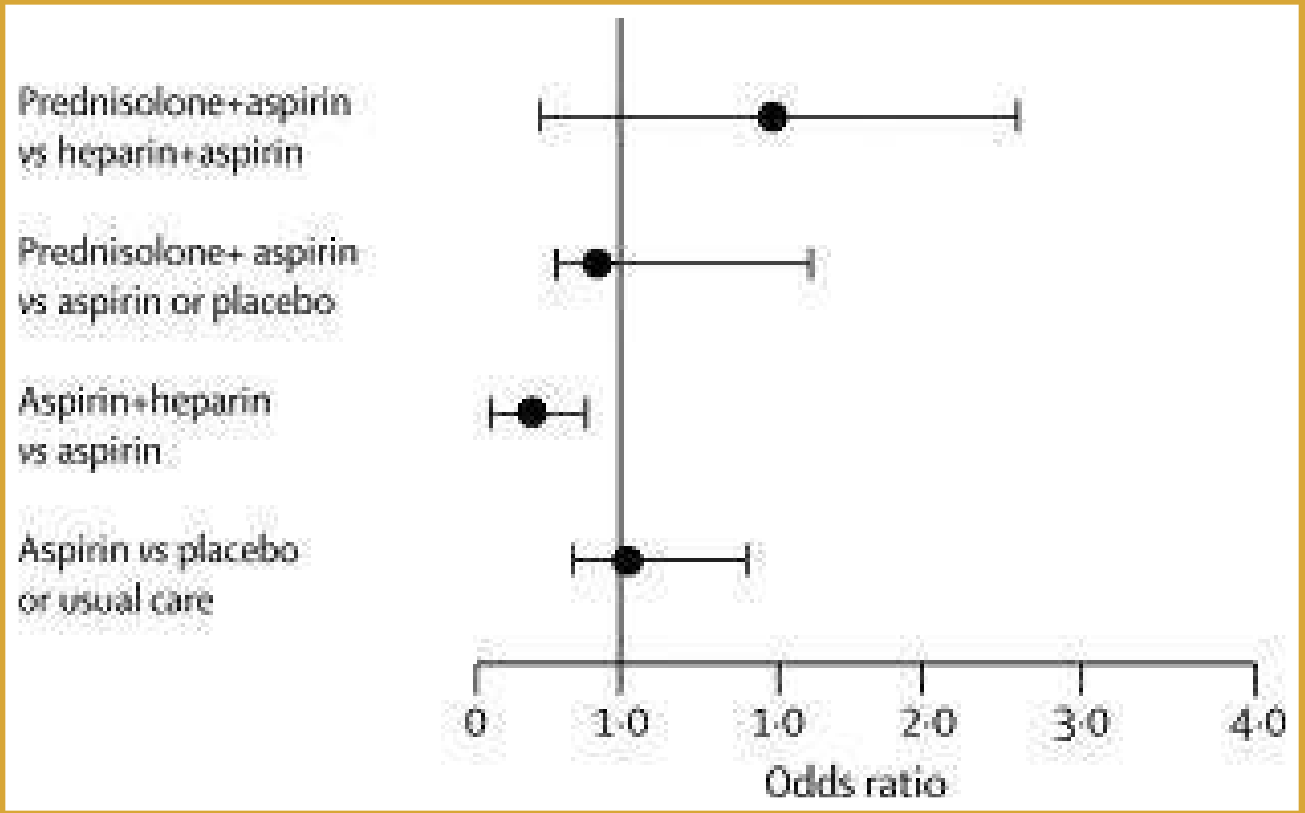
- The other reference: LA and TEG are apparently not interchangeable as predictors of hypercoagulability state. (Confino et al 1989)

With the exception of aspirin and heparin for prevention of recurrent miscarriage in women with the antiphospholipid syndrome, no other suggested therapies for this heterogenous group of patients have been evaluated in randomized controlled trials.

(Recurrent miscarriage: pathophysiology & outcome, Carrington, Sacks & Regan; Curr Opin Obstet Gynaecol, 17 (^), 2005

# of Women with Antiphospholipid Syndrome and RM

Recurrent miscarriage; Raj Rai & Lesley Regan, The Lancet, 368, 2006



Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia : a multinational open-label randomised trial
(TIPPS: thrombophilia in pregnancy study 2014)

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.

Prof Regan
is one of the high academic calibres in UK
a good book writer
and a capable TV presenter

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I am a Clinician

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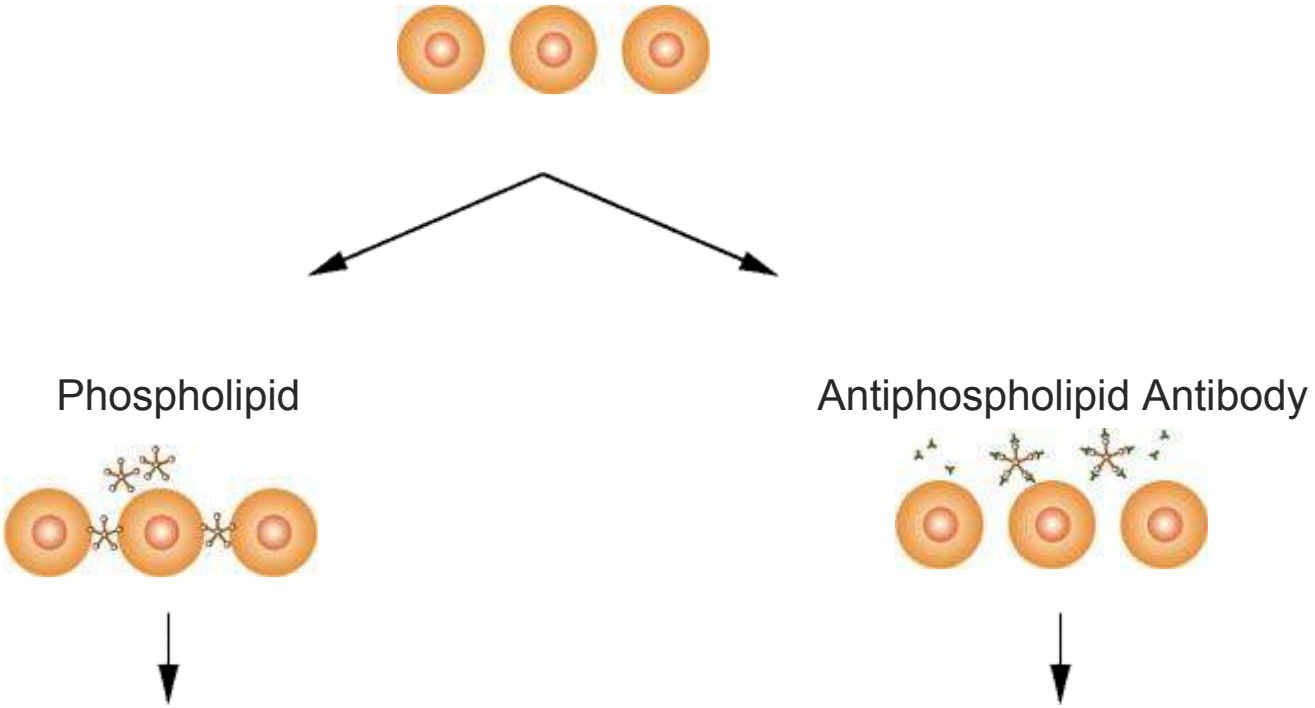
I am a Clinician

With vision

Cytotrophoblast Placental Cell
Function: Attaches Placenta to Uterus



Cytokines levels in Recurrent Miscarriage , Infertility and Implantation Failure

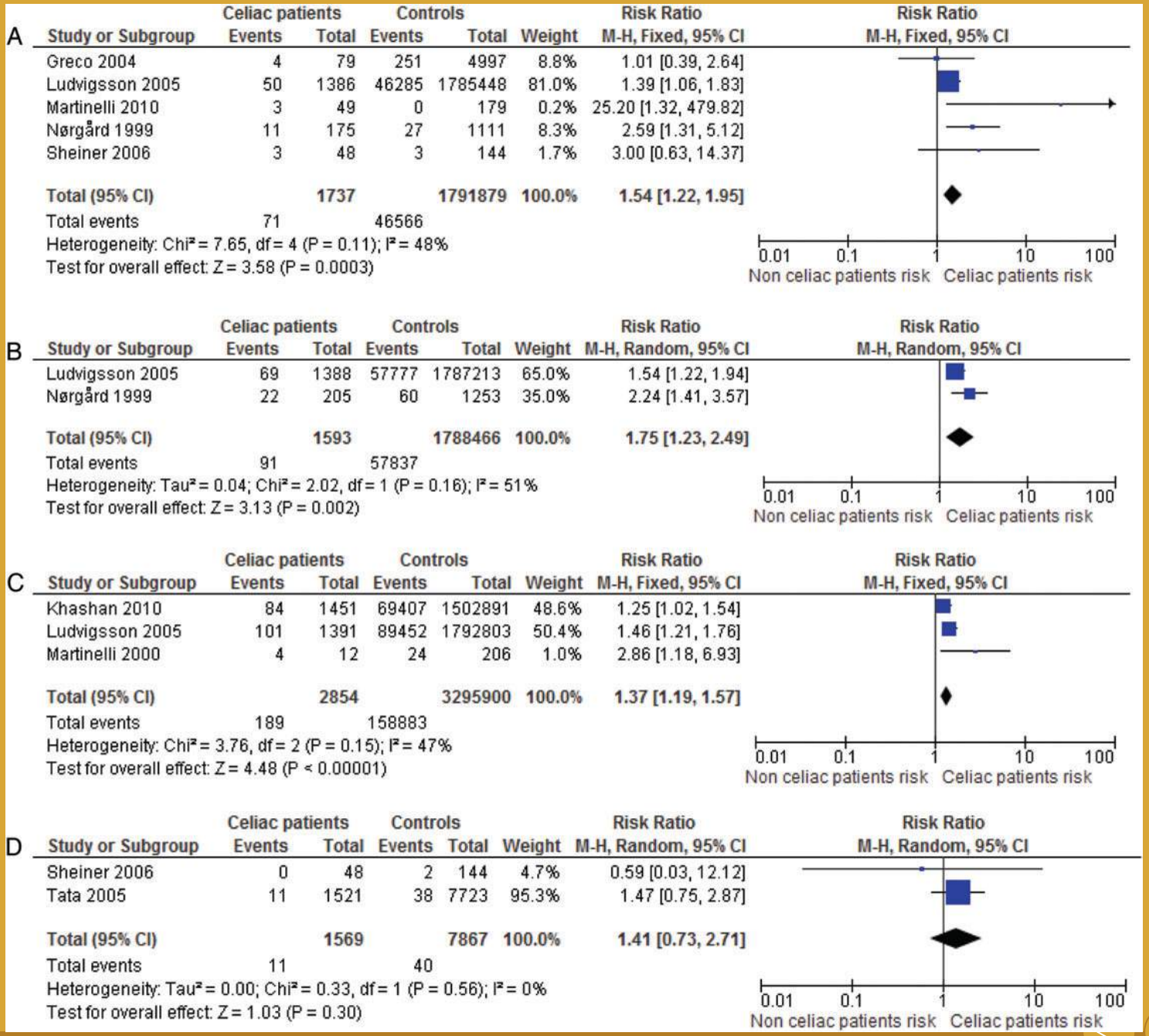
Cytokine Levels:

- Increased TH1 (TNFα & IFN γ) level
- Increased TH1/TH2 ratio (TNFα & IFN γ / IL-10)
- Increased level of TH17 (IL-17)
- ? Increased TH 17 / T reg cells ratio

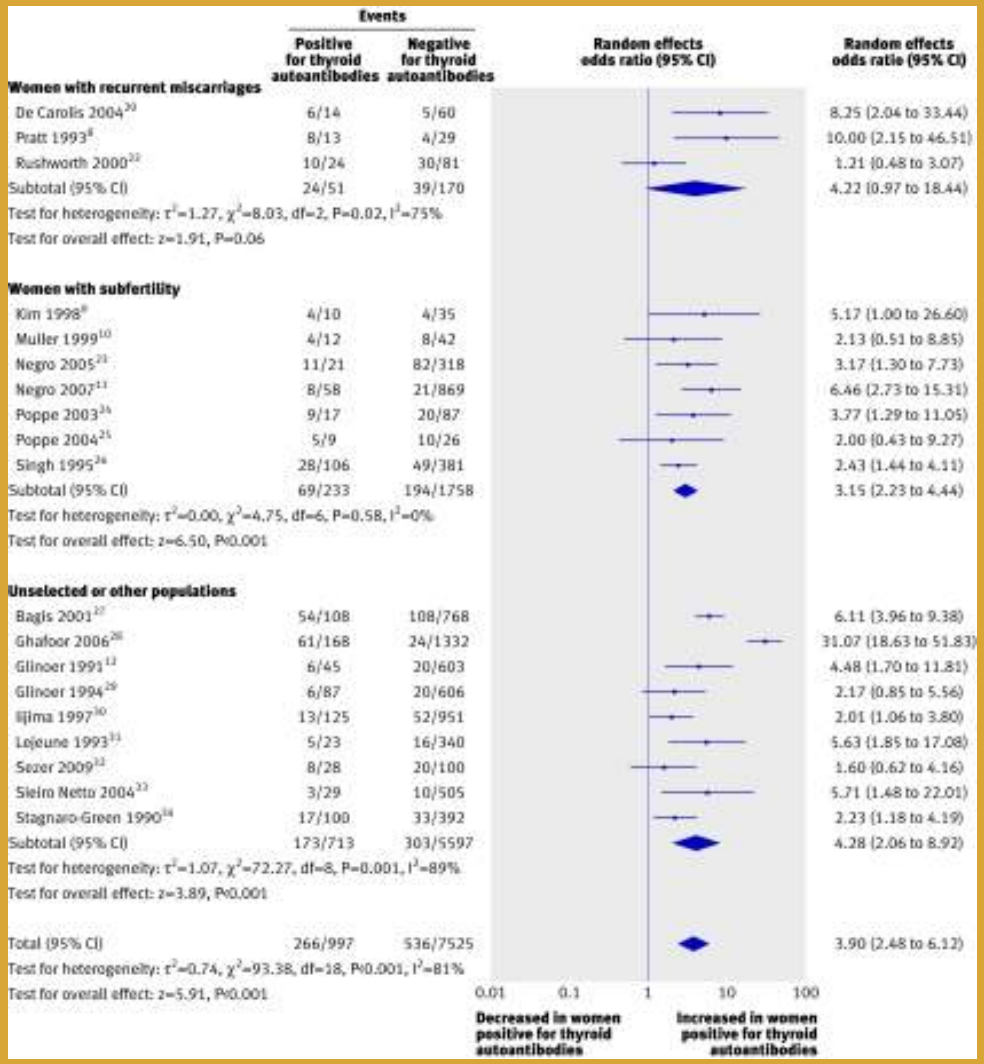
Inflammatory pathway:
Vascular damage and cell apoptosis.

Management:

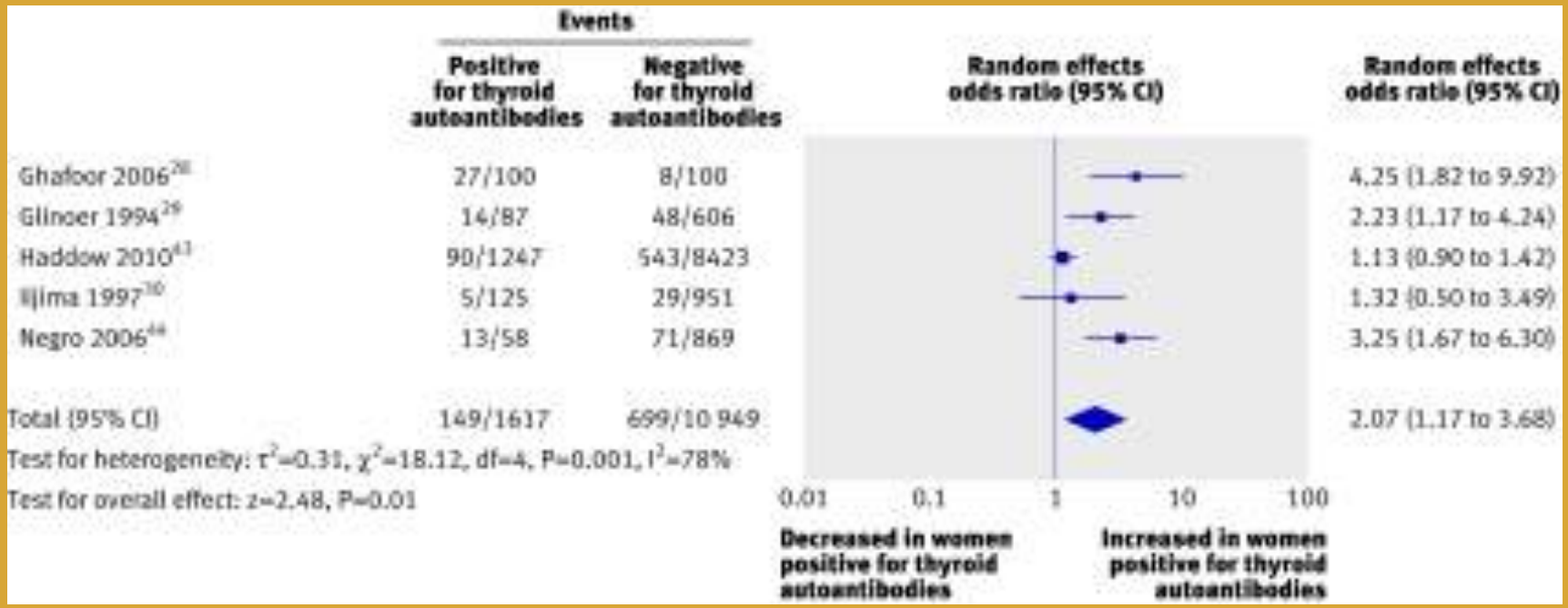
- TNA α antagonists (Humira)
- IVIG
- Aspirin & Heparin
- Steroids


A
Celiac patients
Controls
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Greco 2004 4 79 251 4997 8.8% 1.01 [0.39, 2.64]
Ludvigsson 2005 50 1386 46285 1785448 81.0% 1.39 [1.06, 1.83]
Martinelli 2010 3 49 0 179 0.2% 25.20 [1.32, 479.82]
Nørgård 1999 11 175 27 1111 8.3% 2.59 [1.31, 5.12]
Sheiner 2006 3 48 3 144 1.7% 3.00 [0.63, 14.37]
Total (95% CI) 1737 1791879 100.0% 1.54 [1.22, 1.95]
Total events 71 46566
Heterogeneity: Chi² = 7.65, df = 4 (P = 0.11); I² = 48%
Test for overall effect: Z = 3.58 (P = 0.0003)
0.01 0.1 1 10 100
Non celiac patients risk Celiac patients risk
B
Celiac patients
Controls
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Ludvigsson 2005 69 1388 57777 1787213 65.0% 1.54 [1.22, 1.94]
Nørgård 1999 22 205 60 1253 35.0% 2.24 [1.41, 3.57]
Total (95% CI) 1593 1788466 100.0% 1.75 [1.23, 2.49]
Total events 91 57837
Heterogeneity: Tau² = 0.04; Chi² = 2.02, df = 1 (P = 0.16); I² = 51%
Test for overall effect: Z = 3.13 (P = 0.002)
0.01 0.1 1 10 100
Non celiac patients risk Celiac patients risk
C
Celiac patients
Controls
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Khashan 2010 84 1451 69407 1502891 48.6% 1.25 [1.02, 1.54]
Ludvigsson 2005 101 1391 89452 1792803 50.4% 1.46 [1.21, 1.76]
Martinelli 2000 4 12 24 206 1.0% 2.86 [1.18, 6.93]
Total (95% CI) 2854 3295900 100.0% 1.37 [1.19, 1.57]
Total events 189 158883
Heterogeneity: Chi² = 3.76, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 4.48 (P < 0.00001)
0.01 0.1 1 10 100
Non celiac patients risk Celiac patients risk
D
Celiac patients
Controls
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Sheiner 2006 0 48 2 144 4.7% 0.59 [0.03, 12.12]
Tata 2005 11 1521 38 7723 95.3% 1.47 [0.75, 2.87]
Total (95% CI) 1569 7867 100.0% 1.41 [0.73, 2.71]
Total events 11 40
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)
0.01 0.1 1 10 100
Non celiac patients risk Celiac patients risk

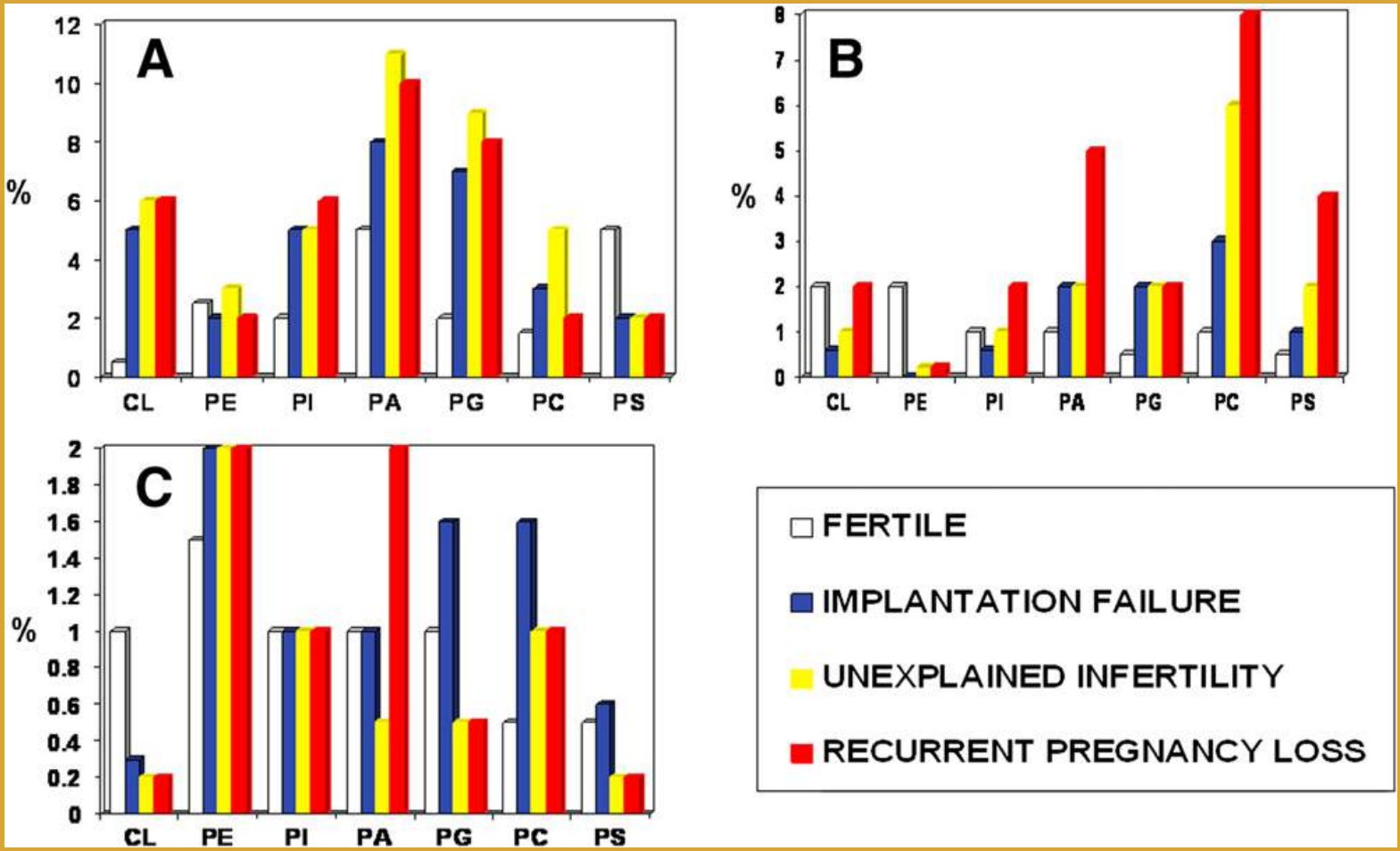
Thyroid Antibodies & Miscarriage in Cohort Studies



Thyroid Antibodies & Pre-Term Birth



Prevalence of Antiphospholipid Antibodies Among Wonen Experiencing Unexplained Infertility, Recurrent Implantation Failure & Recurrent Miscarriage

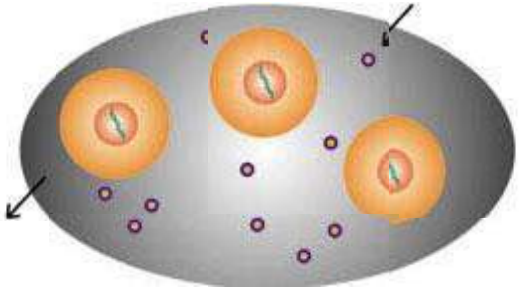


At Ovulation or Recovery of Eggs

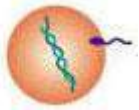
TNF

DNA in

Eggs



Ovary



Damages DNA in Eggs by Apoptosis - Spot Welds the DNA so that it Divides Poorly

↓

Embryos Show Cellular Division, Fragmentation of Cells, Inclusions in Cells. This Causes Failed IVF, Implantation Failure & Ovarian Failure

Pregnancy in Rheumatology Patients Exposed to Anti-tumour Necrosis Factor (TNF)-α Therapy (No evidence of embryotoxicity or teratogenecity)

C. H. Roux; O. Brocq; V. Breuil; C. Albert; L. Euller-Ziegler 2007

TNF-α-exposed Psoriatic Arthritis (PsA), Juvenile Idiopathic Arthritis (JIA) and Rheumatoid Arthritis (RA)

Medscape® www.medscape.com

Authors	Disease	Anti-TNF-α	Exposure	Number of pregnancies	Live births	Miscarriages	Therapeutic terminations	Malformations
Joven *et al.* [12]	PsA	Eta	First month	1	1			
Carter *et al.* [19]	PsA	Eta	Throughout pregnancy	1				VATER association
Joven *et al.* [12]	PsA	Inf	First month	1	1			
Dechant *et al.* [18]	PsA	Inf	Conception	1				
Joven *et al.* [12]	JIA	Eta	9 weeks	1	1			
Katz *et al.* [11]	JIA	Inf	Conception/T1	2				
Joven *et al.* [12]	JIA	Inf	First month	1	1			
Koskvik *et al.* [8]	JIA+RA	Eta	Conception/3 weeks	5	3	2		
Hyrich *et al.* [20]	Rheumatic	Eta	Conception	16	13	6 (3 MTX,	3	
	diseases (mostly RA)	Inf		3		1 LFN)		
		Ada		3				

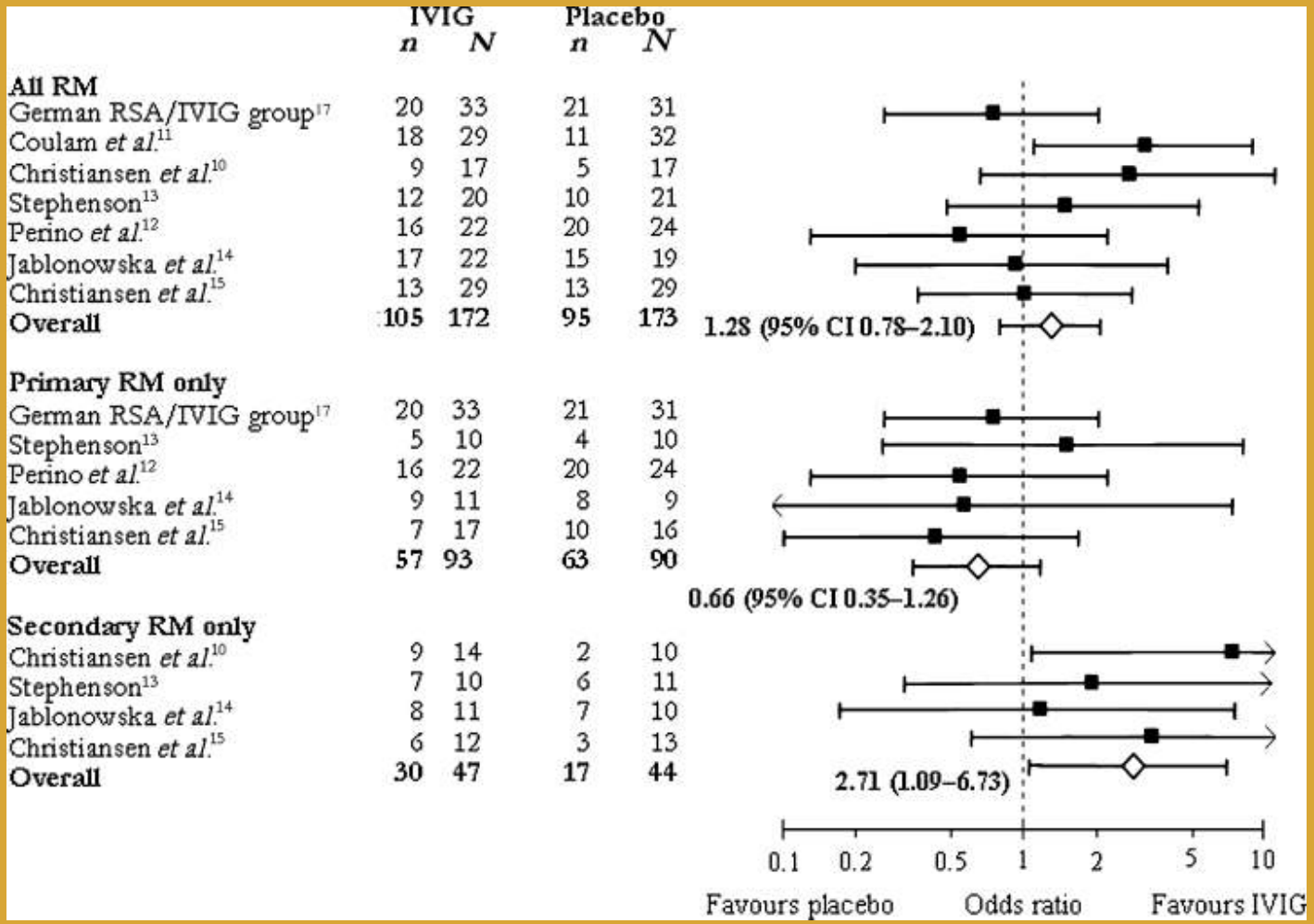
Eta, Etanercept; Inf, Infliximab; Ada, Adalimumab; MTX, Methotrexate; LFN, Leflunomide; T1, First trimester.

Do we expect the IVIg to help if the patient does not have any of these issues?

Do we expect it to work if the patient miscarries because of chromosomal abnormality or for another unknown reason?

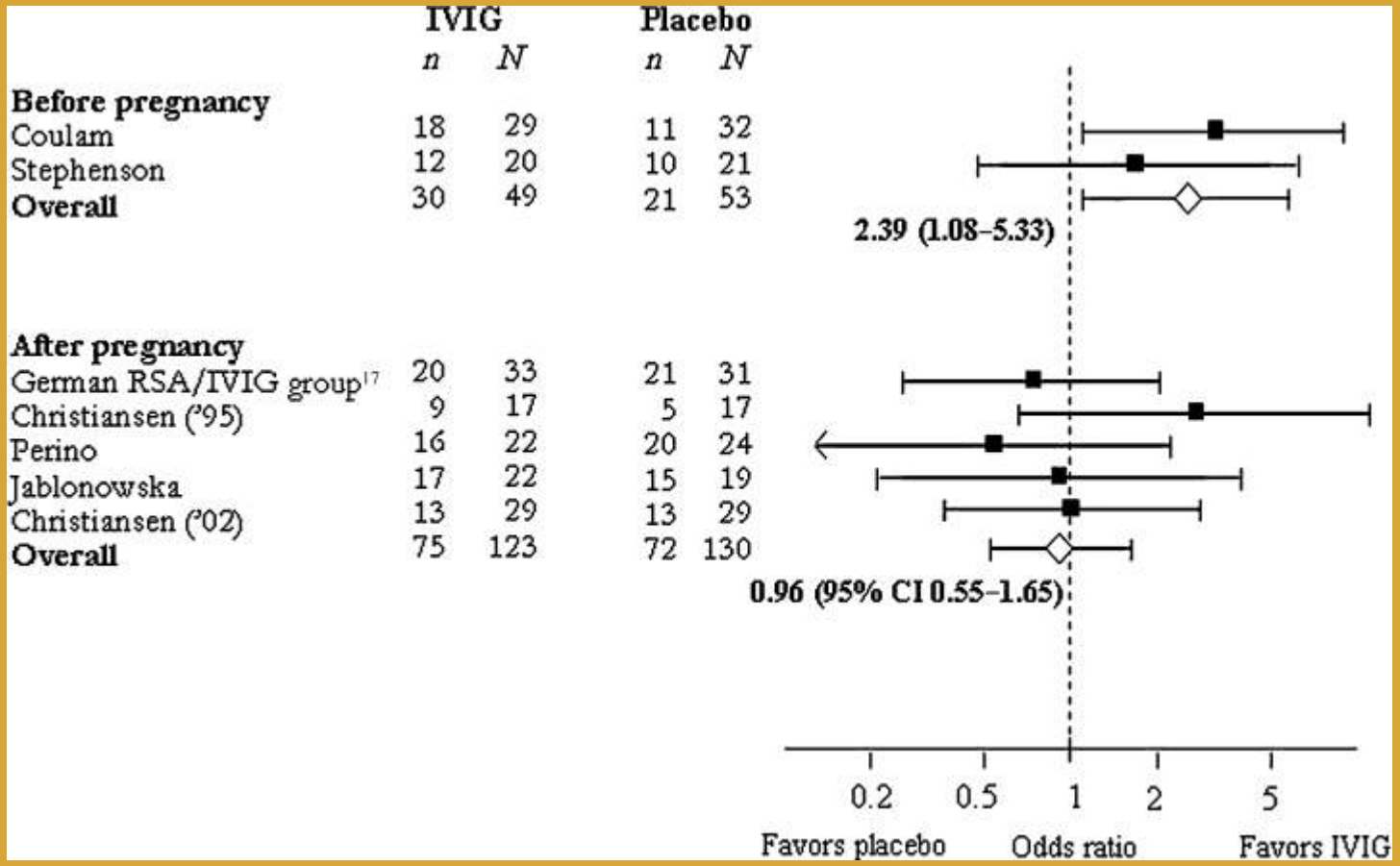
Use of intravenous immunoglobulin for treatment of recurrent miscarriage: a systematic review, Hutton et al 2006

live birth rates among categories of recurrent miscarriage



Use of intravenous immunoglobulin for treatment of recurrent miscarriage: a systematic review, Hutton et al 2006

live birth rates among all types of recurrent miscarriage, stratified by treatment start time



Pregnancy in Rheumatology Patients Exposed to Anti-tumour Necrosis Factor (TNF)-α Therapy (No evidence of embryotoxicity or teratogenecity)

C. H. Roux; O. Brocq; V. Breuil; C. Albert; L. Euller-Ziegler 2007

TNF-α-exposed RA Pregnancies

Medscape® www.medscape.com

Authors	Anti-TNF	Exposure	Number of pregnancies	Live births	Miscarriages	Therapeutic terminations	Malformations
Chambers *et al.* [6, 7]	Eta	T1	29	7	3	1	Trisomy 18 with miscarriage
Sills *et al.* [9]	Eta	Conception	1	1			
Chakravarty *et al.* [10]	Eta		15	6	1 (MTX)	1	
Joven *et al.* [12]	Eta	5–14 weeks	4	1		1	
Rump *et al.* [15]	Eta	Throughout pregnancy	1	1			
		First month	1	1			
Feyertag *et al.* [16]	Eta	Throughout pregnancy	1	1			
Our cases 2	Eta	Conception/T1	1			1	
3	Eta	Conception	1	1			
Chambers *et al.* [6, 7]	Inf	T1	4	2	1	1	
Chakravarty *et al.* [10]	Inf		2	1			
Katz *et al.* [11]	Inf	Conception/T1	8				Intestinal malrotation (LFN)
Joven *et al.* [12]	Inf	First month	2	1	1		
Kinder *et al.* [14]	Inf	Conception/first month	1		1 (MTX)		
Joven *et al.* [12]	Ada	6.5 months	1				
Our case 1	Ada	Conception/T1	1			1	

Eta, Etanercept; Inf, Infliximab; Ada, Adalimumab; MTX, Methotrexate; LNF, Leflunomide; T1, First trimester.

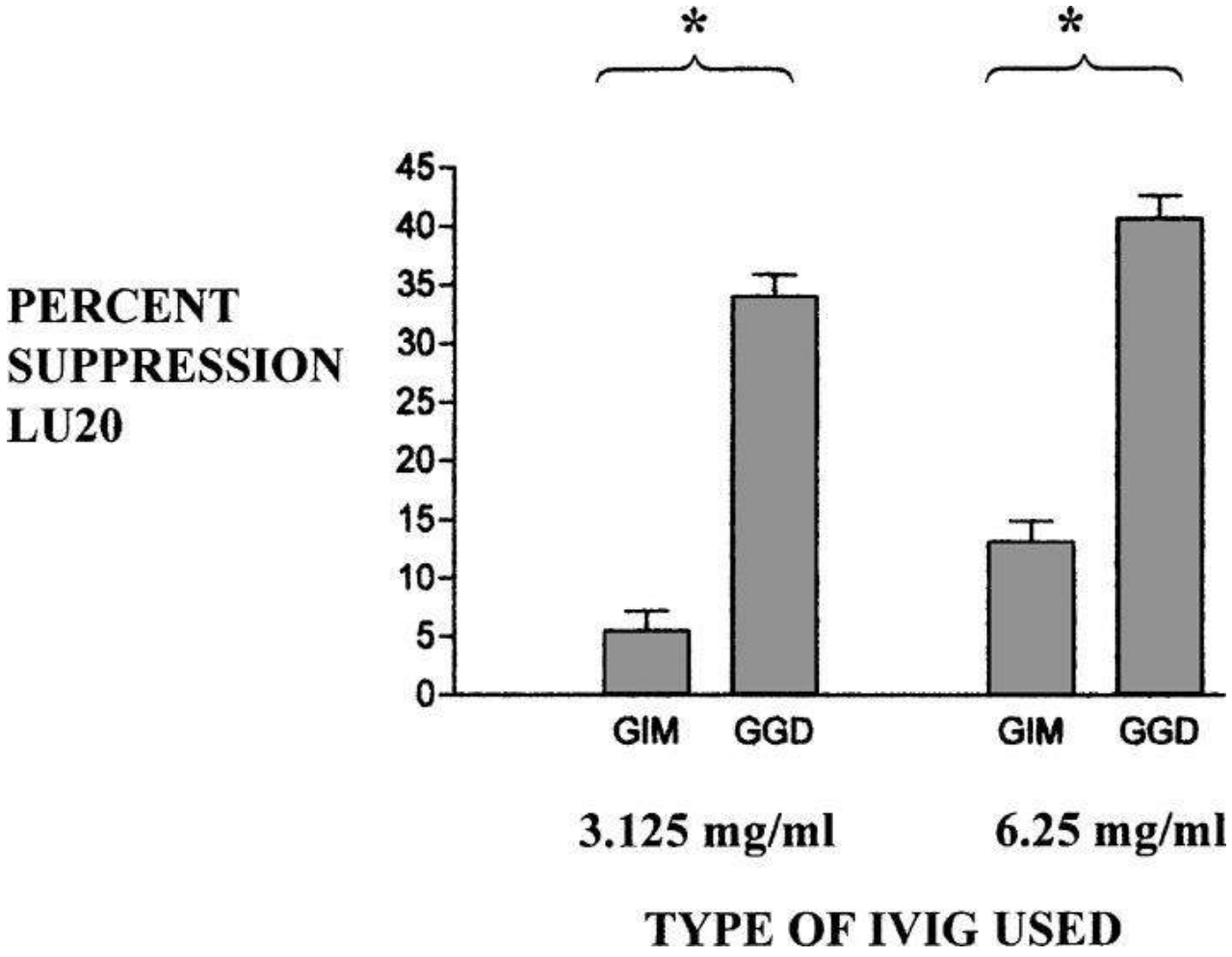
Immune Supportive Therapy for Recurrent Miscarriage & Repeated Implantation Failure

Is it for unexplained miscarriage and infertility?

Why is it controversial?

Is intravenous immunoglobulins (IVIG) efficacious in early pregnancy failure? A critical review and meta-analysis for patients who fail in vitro fertilization and embryo transfer (IVF)

David A. Clark,, Carolyn B. Coulam, Raphael B. Stricker (2006)



Lymphocyte Immune Therapy

Recurrent Miscarriage Immunology Trialist Group 1994;

- Live birth difference 8-10% (1.16 & 1.21),. Not great.
- Lower outcome in older women with > 5 miscarriages
- Higher LB in women with or converted to leukocyte Ab +ve
- Minimal side effects and no increased risk on the foetus

Allogeneic Leukocyte Immunization after Five or More

Miscarriages. Carp et al 1997

- Seroconverted 1ry RMC: 31% benefit & LB risk 2.04
- Seroconverted 3ry RMC: 50% benefit & LB risk 2.92
- Paternal leukocyte antibody test might not be perfect
- Sero-conversion : better outcome and longer effect