

Investigation and Current Management of Recurrent IVF Failure

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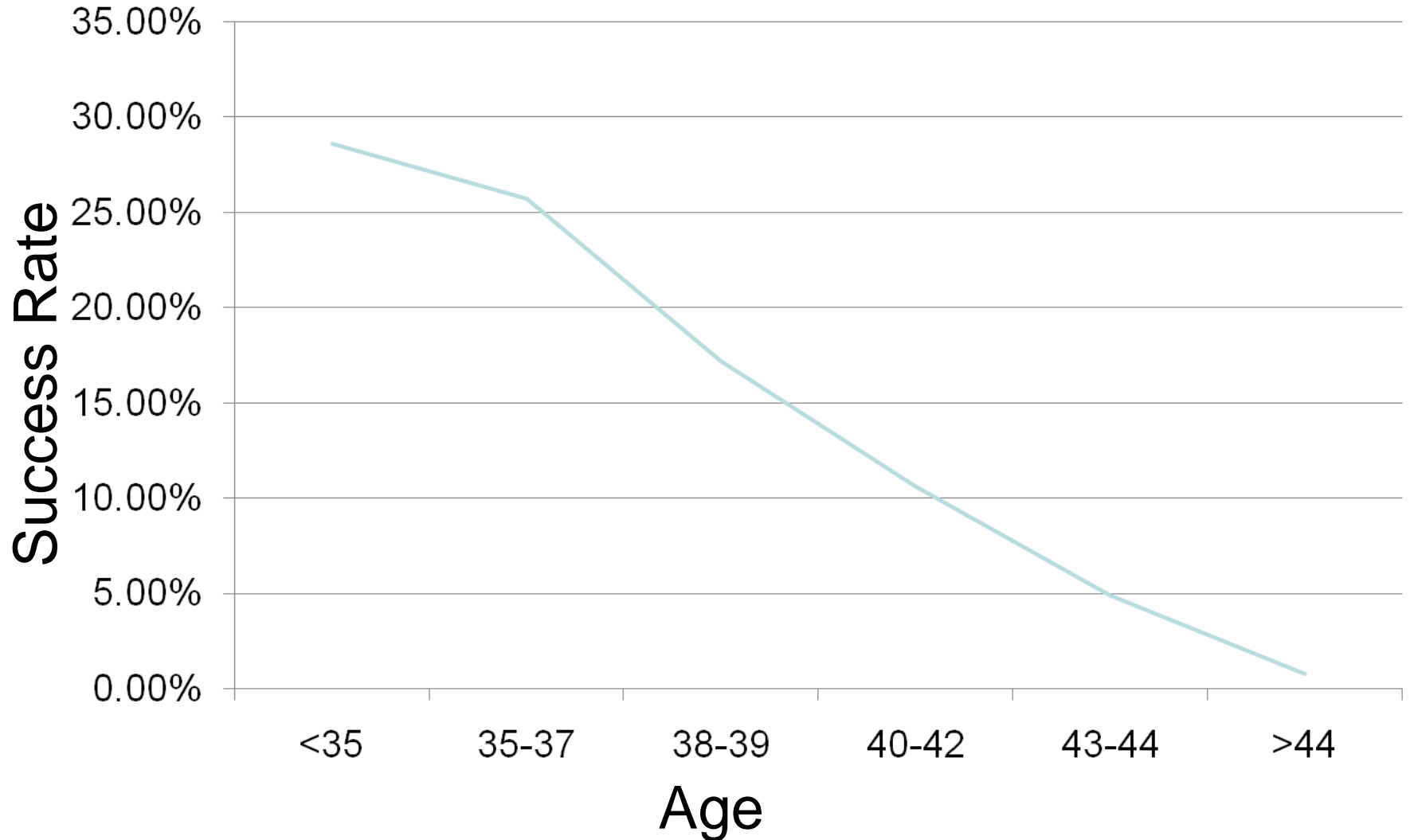
Definiton

- No agreed definition
 - one to seven failed implantations?
- ≥ 3 failed implantations

Background Issues

- Maternal Age

HFEA Figures 2006



Natural (and soft) cycle IVF

HFEA 2006

- (4/28) for women aged under 35
- (0/29) for women aged between 35-37
- (1/14) for women aged between 38-39
- (0/25) for women aged between 40-42
- (0/6) for women aged between 43-44
- (1/9) for women aged over 44

Background Issues

- Maternal Age
- Indication for Art
 - Endometriosis

Endometriosis

- Ovarian damage
 - Disease
 - Iatrogenic
- Oocyte quality
- Adenomyosis

Endometriosis

Meta analysis

Stage	LBR	No of Cycles	p
Control	18.7%	528	
Stage I / II	20%	101	
Stage III / IV	11.4%	403	0.0002

Kuivasaari P; Hum Reprod 2005

Background Issues

- Maternal Age
- Indication for Art
 - Endometriosis
 - Tubal disease

Tubal Disease

- Degree?
 - Filmy adhesions
 - Bilateral hydrosalpinges
 - Infection
 - Endometritis
 - PID
 - “Toxic contents”

Hydrosalpinges

	Bilateral Salpingectomy	No surgery	p
Live birth rate	31 (29.5%)	14 (17.5%)	0.083

Strandell A; Hum Reprod 1999

Cochrane Report:

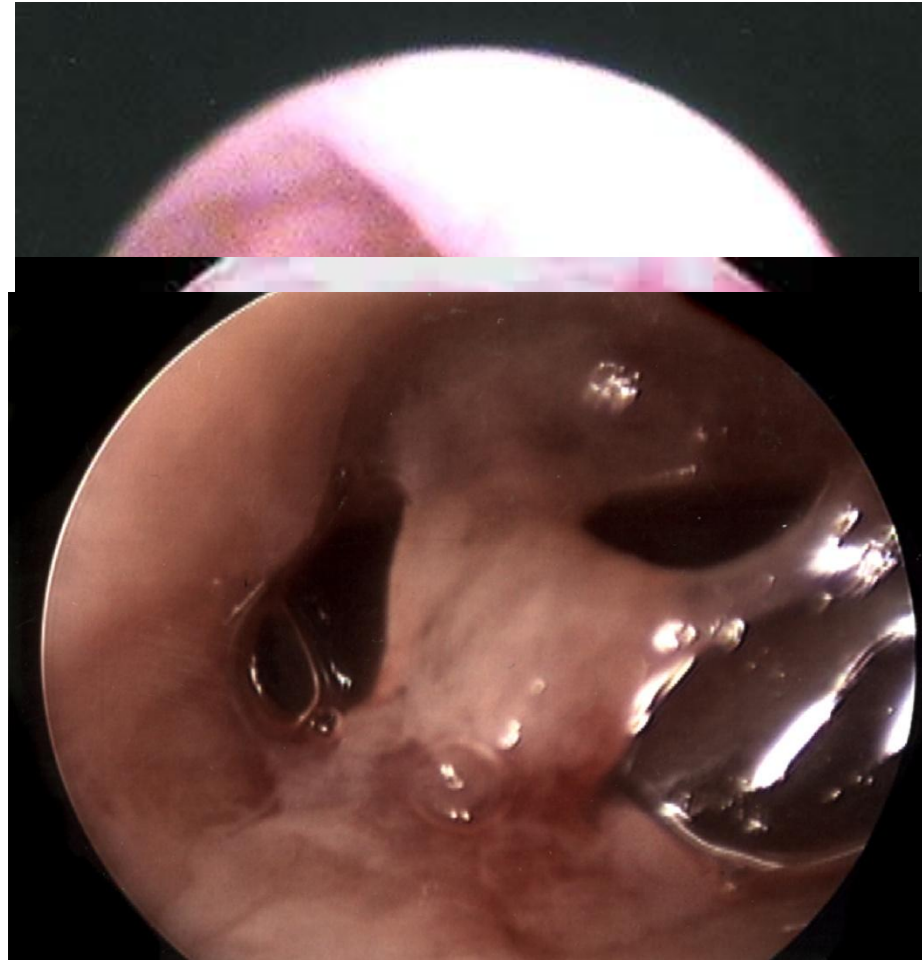
Surgical treatment for tubal disease in women due to undergo IVF

Johnson N et al 2010

- 5 randomised controlled trials
 - 646 women
- Laparoscopic salpingectomy:
 - OR ongoing pregnancy 2.14 (95%CI 1.23 to 3.73)
- Laparoscopic occlusion:
 - OR ongoing pregnancy 7.24 (95%CI 0.87 to 59.57)

Background Issues

- Maternal Age
- Indication for Art
 - Endometriosis
 - Tubal disease
 - Uterine pathology
 - Septate / bicornuate
 - Synechiae
 - Fibroids and polyps:
 - Where?
 - What size?



Hysteroscopy - Uterine Synechiae

Embryo issues

- Embryo quality



Embryo Quality & Implantation

	Two grade A embryos (%)	One grade A + one poor embryo (%)	Two poor embryos (%)
Transfers (<i>n</i>)	104	65	52
Miscarriage			
Ongoing pregnancy			
Singleton			
Twin			

Eric Van Royen Hum Reprod 1999

Embryo Quality & Implantation

	Two grade A embryos (%)	One grade A + one poor embryo (%)	Two poor embryos (%)
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Singleton	28 (43)	30 (79)	12 (100)
Twin	37 (57)		

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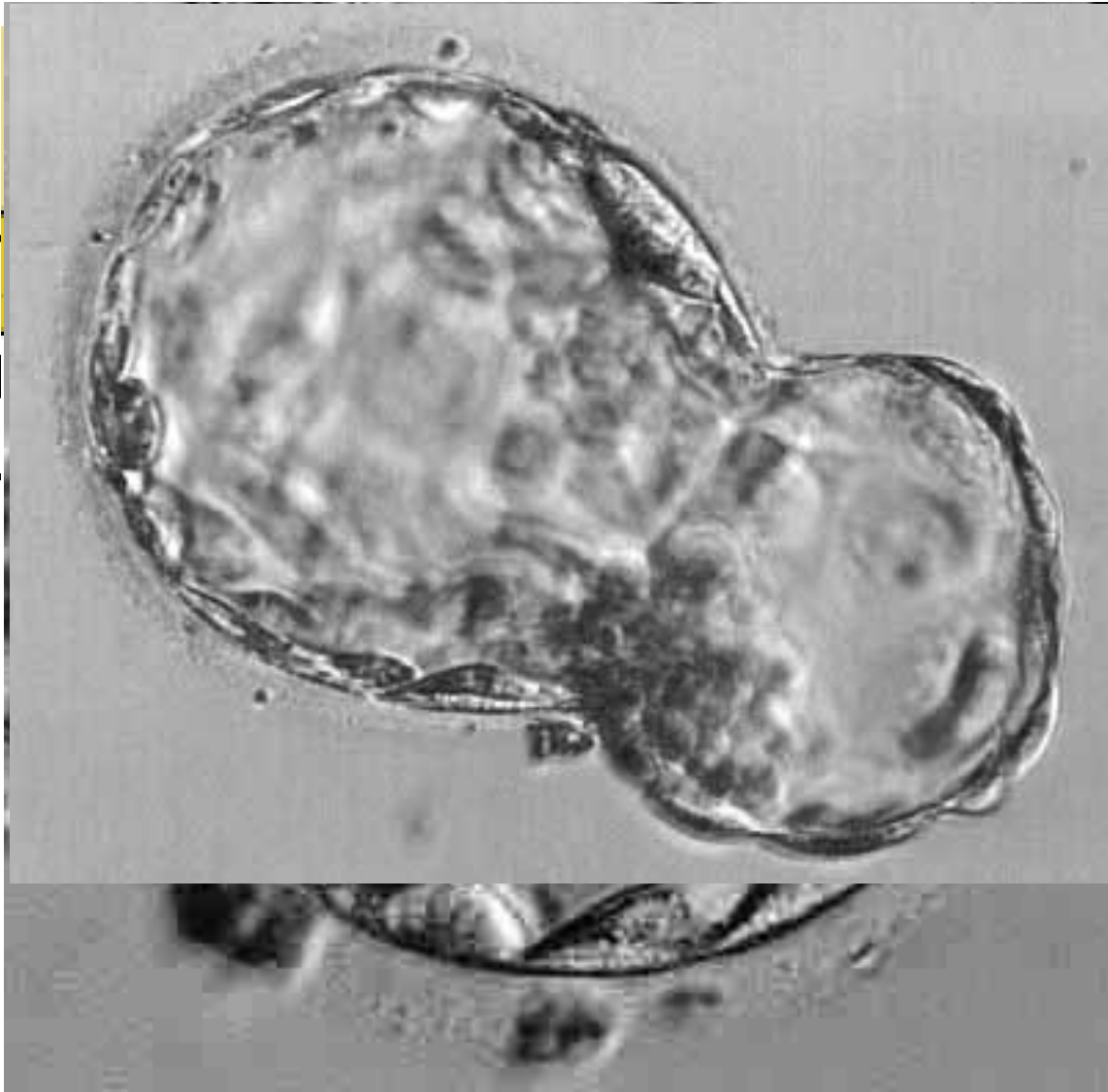
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Eric Van Royen Hum Reprod 1999

Blastocyst Culture

- Embry
- Redu
- Embry



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Blastocyst Culture

- **Blastocyst transfer for multiple prior IVF failure: a five year descriptive study.** Walsh AP, et al Ir Med J 2009
 - 392 couples
 - Average 4.5 failed IVF cycles
 - Mean age 36.0 (+/- 3.9) yrs
 - Average number of oocytes 9.1 (+/- 5.4)
 - Fertilisation rate 59.5%
 - No blastocysts in 99 cases (25.3%)
 - Clinical pregnancy in 50.0% of transfers.

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Let's say.....

- Pregnancy rate IVF: 39%
- 392 women mean age 36
 - 153 pregnant; 239 not pregnant
- BC figures:
 - 25% no ET = 98
 - Adjusted figures:
 - 153 pregnant / 141 not pregnant (population = 294)
 - $153/294 = \mathbf{52\%}$ / $141/294 = \mathbf{48\%}$

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Walsh AP, et al Ir Med J 2009

Blastocyst Culture

- Is it high quality embryos?
or
- Is it elimination of failures?

Preimplantation Genetic Screening (PGS)

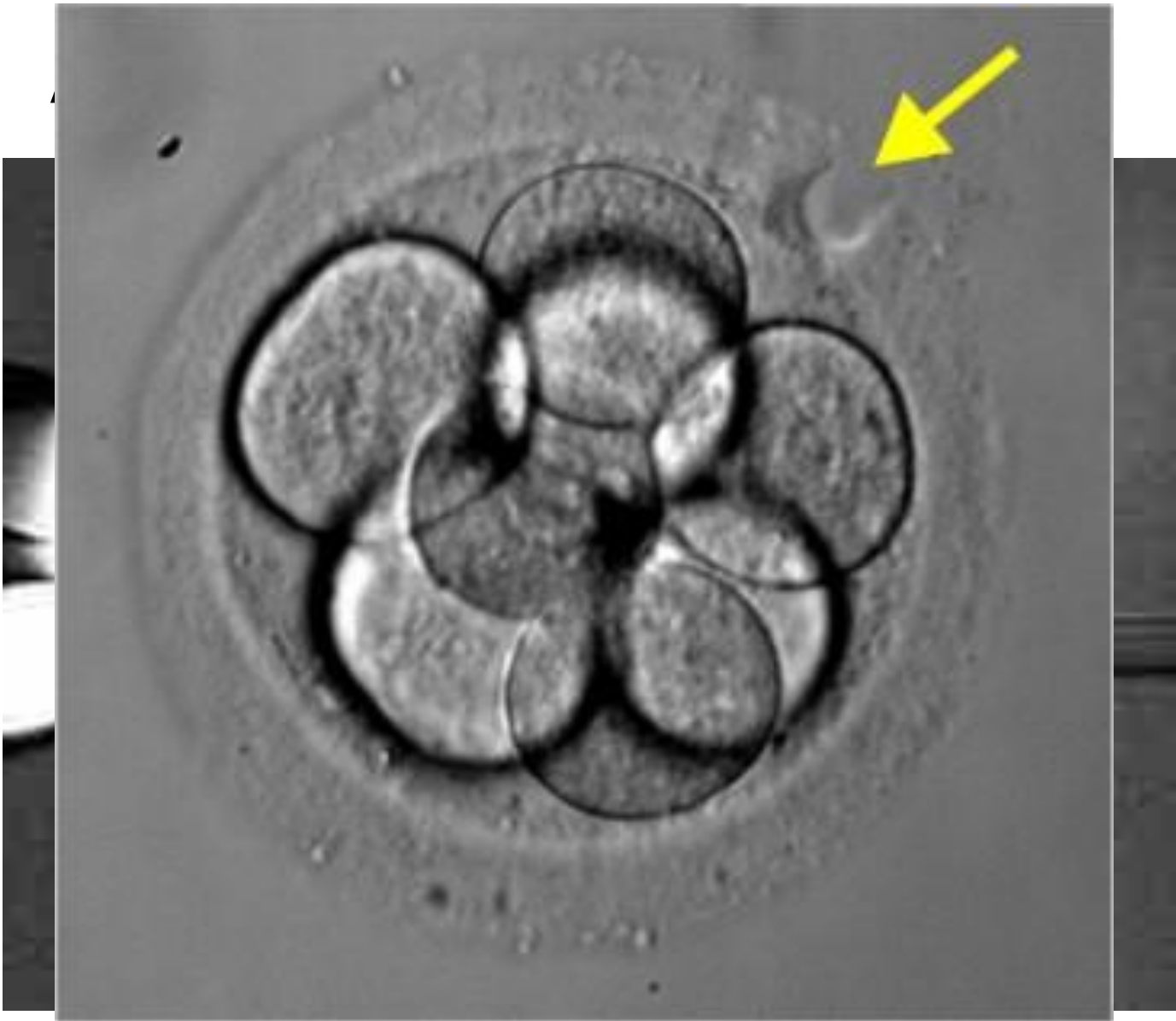
- High % chromosomal abnormalities
- Screen embryos
 - Culture
 - Biopsy
 - FISH or whatever
 - Select normal embryos
- Transfer

PGS

- Prospectively randomized controlled trial of PGS in IVF/ICSI patients with poor implantation

Blockeel C Reprod Biomed 2008

- 200 patients recurrent failed implantation
- 139 underwent ovarian stimulation / 72 had PGS
- Chrs X, Y, 13, 16, 18, 21 & 22 with FISH in day-3
- Implantation rate: study group (21.4%) / control group (25.3%)
- Clinical pregnancy rate 25.0% in study group versus 40.3% in control group ($p > 0.5$)
- PGS does not increase the implantation rates in women with repeated implantation failure.



Assisted Hatching

- **Laser assisted zona thinning technique has no beneficial effect on the ART outcomes of two different maternal age groups.**

Kutlu P J Assist Reprod Genet. 2010

- 252 couples
- Group 1: <35 years; group 2: ≥35 years
- Randomised: assisted zona thinning vs control
- CPRs: 57% and 56% group 1 (p = 0.86)
43% and 38% group 2 (p = 0.59)

Killer Cells

- CD
- End
 - M
 - A
 - V
- Per
- >12



site

ailure

NK Cells and Outcome

- **Simple enumerations of peripheral blood natural killer (CD56+ NK) cells, B cells & T cells have no predictive value in IVF treatment outcome.**

Thum MY et al Hum Reprod 2005

- ‘....There were no significant differences with regard the mean values of absolute lymphocyte count, T cell count, B cell count and NK cell count (... Total, dim and bright...) between the pregnant and non-pregnant groups and also between the ongoing pregnancy and miscarriage groups....’

IVIIG

Treatment of repeated unexplained IVF failure with IVIIG: a randomized, placebo-controlled Canadian trial

Stephenson MD 2000 Hum Reprod

- live-birth rates:
 - 4/26 (15%) IVIG group
 - 3/25 (12%) saline controls group

IVIG

Is IVIG efficacious in early pregnancy failure? A critical review and meta-analysis for patients who fail IVF

Clark DA J Assist Reprod Gen 2006

- Meta analysis of 3 papers (selection justification?)
- ‘..... a significant increase in the live birth rate per woman.....’

Treatment with adalimumab (Humira) and IVIG improves pregnancy rates in women undergoing IVF

Winger EE et al Am J Reprod Med 2009

- 75 women with elevated NK cells:
 - IVIG & Humira 59%(50/85),
 - IVIG 47%(21/45),
 - Humira 31%(4/13)
 - No treatment 0%(0/9)

CD3⁻ CD56⁺ CD16⁺ NK Cells and Improvement of Pregnancy Outcome in IVF/ICSI Failure After Additional IVIG-Treatment

Lothar Heilmann, Am J Reprod Immunol. 2010

- 188 women; IVIG if NK >12%
- Live birth: 42% treated vs 34.9% untreated

Immunological testing and interventions for reproductive failure

SAC, RCOG 2008

- **Opinion**

‘...there is little evidence to support any particular test or immunomodulatory treatment in the investigation and treatment of couples with reproductive failure. These tests and treatments should be restricted to those entered into formal research studies.’

Antiphosphopipid Antibodies

- Approximately 20 antibodies
- Anticardiolipin and lupus anticoagulant have clinical significance in recurrent miscarriage
- APL abs and IVF success a meta-analysis
Hornstein et al Fertil Steril 2000
 - APA +ve 57% CPR
 - APA –ve 49.2% CPR

Heparin

A randomized, double-blind, placebo-controlled trial of heparin and aspirin for women with IVF implantation failure and antiphospholipid or antinuclear antibodies.

Stern C et al Fertil Steril 2003

- Subcutaneous heparin & aspirin from ET (158 transfers) or placebo (142 transfers)
- No significant difference in pregnancy rates or implantation rates

Antiphospholipid antibodies and infertility.

Backos M Hum Fertil 2002

- ‘....prospective studies examining the effect of aPL on the outcome of IVF-ET demonstrate that these antibodies do not significantly affect either the implantation or ongoing pregnancy rates.....’
- ‘....Hence routine screening for aPL among women undergoing IVF-ET is not warranted and therapeutic interventions should be used only in well designed randomized controlled trials.’

Glucocorticoids?

Cochrane Review: Peri-implantation glucocorticoid administration for ART cycles

Boomsma et al 2007

- 13 RCTs; 1759 couples
- Pregnancy rates:
 - OR = 1.15 (95% CI 0.93-1.43)

Vasodilators

- To improve endometrial thickness....

NO donors for patients undergoing IVF. A prospective double-blind randomised, placebo controlled trial. Ohl J et al Hum Reprod 2002

- Nitroglycerine: 138 patients; randomised double blind trial; Patches from ET⁻¹
- No difference in any outcome parameter

Vasodilators

- **Viagra**

- Type 5 phosphodiesterase inhibitor
- Thickens endometrium

- **Thin endometrium in ART**

Senturk LM et al Curr Opin Obstet Gynecol. 2008

‘...Various recent modalities proposed for the treatment of thin endometrium seem to be useless and inefficient from an evidence-based medicine point of view...’

Conclusions

1. Review the case for pre-existing pathology and optimise health
2. Blastocyst culture?
3. Probably avoid medical approaches?
4. Support the couple.....