ESHRE Campus

Early Pregnancy Winter Course

Recurrent Implantation Failure

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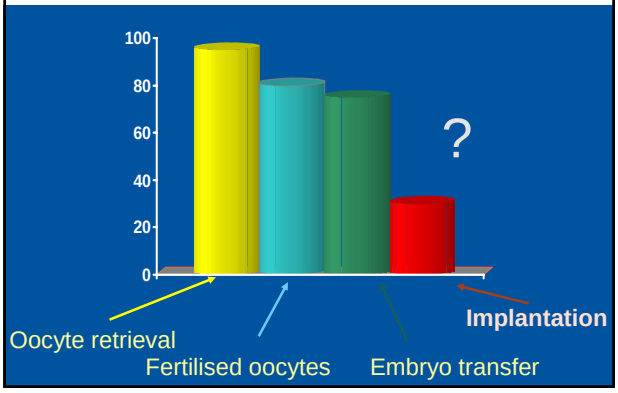
The Implantation Gap

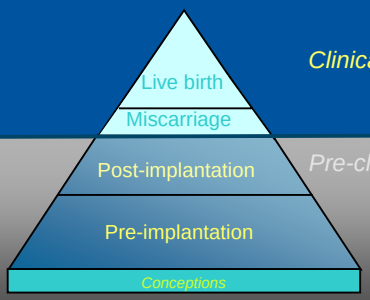


Lecture Overview

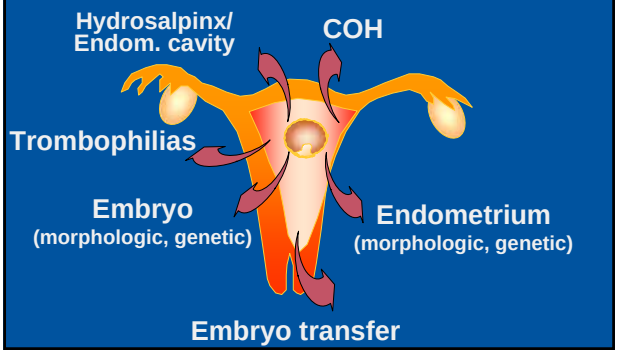
- Current approaches to diagnosis
- Current approaches to therapy
- Novel approaches

The Iceberg of Pregnancy Loss

(Macklon et al, Hum Reprod Update, 2002)



Causes of implantation failure



Current approaches to diagnosis

- •Inherited Thrombophilia
- •Aquired thrombophilia

Increased incidence in RIF
Qublan et al, Hum Reprod 2006

- •Thyroid abnormalities
- •Hydrosalpinges
- •Uterine anomaly
- •Infections

Dam et al Gyn Obstet Invest 2006

Pre-implantation genetic screening *Voullaire et al, Fertil Steril. 2007.*

Current approaches to diagnosis

Acquired and inherited thrombophilia: implication in recurrent IVF and embryo transfer failure

Hussein S.Qublan[1,7], Suhair S.Eid[2], Hani A.Ababneh[3], Zouhair O.Amarin[4], Aiman Z.Smadi[1], Farakaid F.Al-Khafaji[5] and Yousef S.Khader[6]

Table II. Frequency of thrombophilic factors in the study groups

Thrombophilic factors	Study group	Control group	
	Group A ($n = 90$)	Group B ($n = 90$)	Group C ($n = 100$)
Factor V Leiden			
Heterozygous	9 (10)	1 (1.1)	2 (2)
Homozygous	4 (4.4)	0	0
Methylenetetrahydrofolate reductase (C677T) mutation			
Heterozygous	7 (7.8)	8 (8.9)	9 (9)
Homozygous	13 (14.4)	3 (3.3)	2 (2)
Prothrombin G20210A gene			
Heterozygous	5 (5.6)	3 (3.3)	3 (3)
Homozygous	1 (1.1)	1 (1.1)	0
Protein C deficiency	2 (2.2)	1 (1.1)	0
Protein S deficiency	3 (3.3)	2 (2.2)	3 (3)
Antithrombin III deficiency	1 (1.1)	0	1 (1)
Lupus anticoagulant	8 (8.9)	2 (2.2)	2 (2)
Anticardiolipin	9 (10)	2 (2.2)	3 (3)
Combined thrombophilia	32 (35.6)	4 (4.4)	3 (3)

Current approaches to management

- Treatment of thrombophilias
- Empirical therapies
- Surgical interventions
- Assisted hatching/prolonged in-vitro culture
- Pre-implantation genetic screening

Boomsma and Macklon 2006

Aspirin: the evidence from RCTS

Study	n	Dose	Pregnancy Rate	*p*
Rubenstein 1999	298	100mg from CD 21	45% vs 28%	NS
Waldenström 2004	1380	75mg from ET	35% vs 30%	NS
Pakkila 2005	374	100mg from stim	25% vs 28%	NS
Duvan 2006	100	100mg from ET	24% vs 23%	NS

Aspirin: evidence in implantation failure

•RCT double blind, placebo controlled trial, 143 women

Aspirin (100 mg/day) + heparin (5000 IU b.d.) vs placebo

	Treatment	Control	OR	95% CI
Implantation rate	6.8%	8.5%	0.65	(0.33-1.28)
Miscarriage rate	21%	18%	1.2	(0.8-2.0)

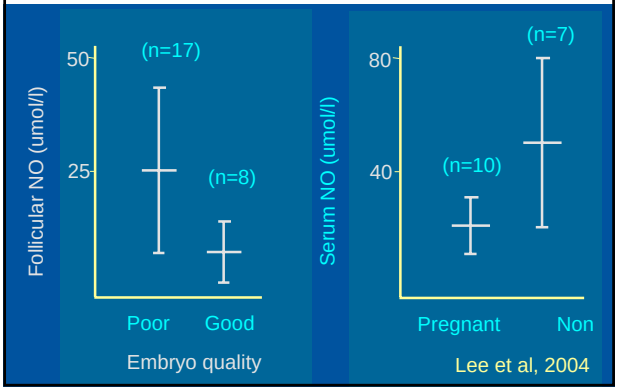
Stern et al, 2003

Nitric oxide donors: evidence

- Sildanefil from Day 3 improves uterine blood flow and endometrial development (Sher & Fisch 2000)
- RCT of NO donors (5mg NTG patch; 1 day prior to ET) Vs Placebo - Ohl et al 2002

	NO donor group (n = 70)	Placebo group (n = 68)
No of oocytes retrieved	9.5 ± 4.1	10.2 ± 5.0
No of 'good' quality embryos / trf	2.8 ± 0.7	2.8 ± 0.6
Pregnancy rate / transfer	28.6%	27.9%
Clinical pregnancy rate	22.9%	26.5%

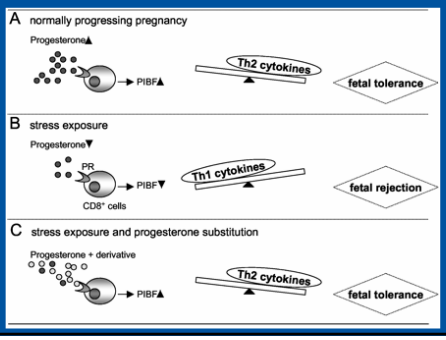
High NO levels increase fragmentation



Lee et al, 2004

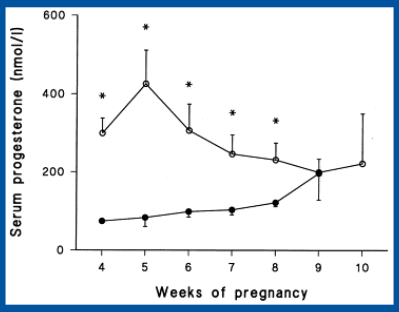
Progesterone treatment:rationale

Blois et al, J. Immunol 2004



Background levels of P4 in IVF

41 IVF pregnancies vs 43 spontaneous pregnancies



IVF pregnancy

Spontaneous pregnancy

*P<0.05

(Costea et al, 2000)

Progesterone supplements during early gestation: evidence

Impact on delivery rate after 3 weeks progesterone* after a positive hCG test

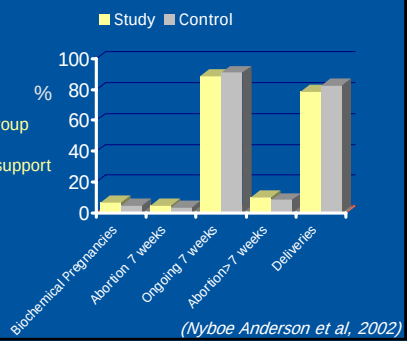
RCT

Two centre RCT

200 per matched group

Both groups luteal support

*600mg/day PV



(Nyboe Anderson et al, 2002)

The rationale for glucocorticoids

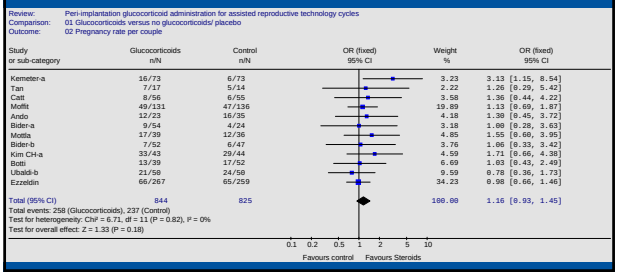
- Defect in cytokine network and excess of NK cell activity implicated in implantation failure (Ledee 2004,2005)
- Reduce the NK cell count (Pountain, 1993)
- Normalise the cytokine expression profile
- Suppression of endometrial inflammation (Hill 1990)

The data?
- Variations in results
- Inadequately powered studies

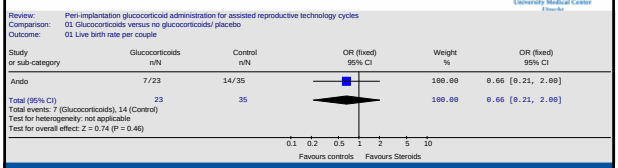
Results of meta-analysis

12 studies , 1669 patients

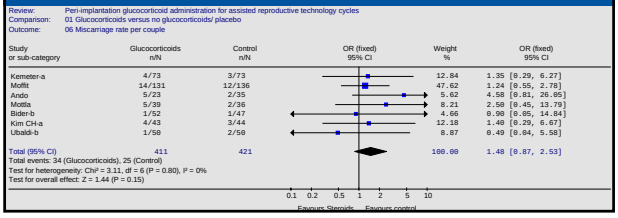
Pregnancy rate per couple



Live birth per couple



Miscarriage rate per couple

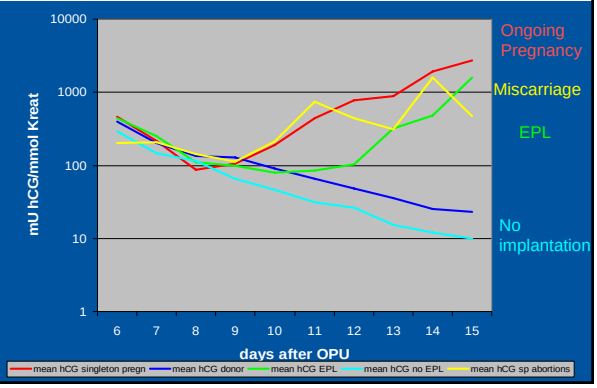


Can PGS reduce EPL?

Prospective matched controlled study in 74 women

Cut off level of hCG determined by oocyte donor curves

Urinary hCG concentrations and outcome



PGS reduces peri-implantation loss

Experimental approaches

- hrLIF
- NK cell tests
- IVIG infusion
- Allogenic lymphocyte therapy

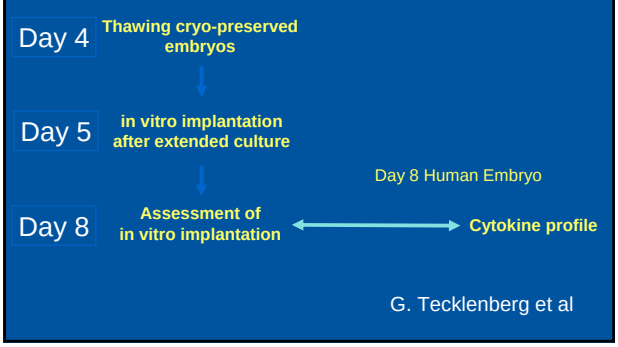
New approaches in Implantation Failure

•New approaches to understanding human implantation

•New approaches to studying the endometrial factor

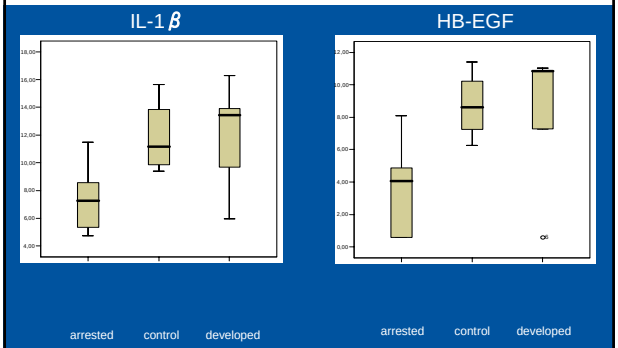
•New therapeutic approaches

Embryo-endometrial cross talk: in vitro model



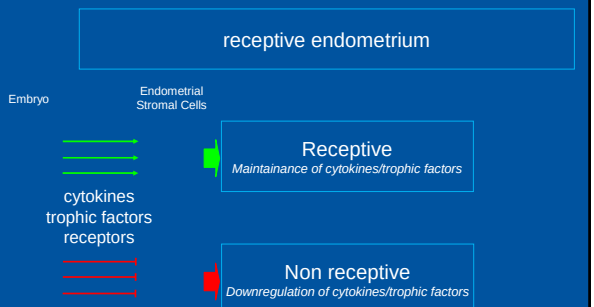
G. Tecklenberg et al

Significanty lower cytokine/trophic factor expression in arrested embryo implantation in vitro



Tecklenberg et al 2007

The embryo *dys*regulates the endometrial stromal cell response



Tecklenberg et al 2007

Ovarian Stimulation and the endometrium

- Ovarian stimulation affects endometrial receptivity
- Supraphysiological sex steroid levels as cause
- Evidence for action at level of gene expression

•hMG and GnRH agonist versus natural cycle	*Horjacas et al 2004*
•recFSH and GnRH antagonist/agonist and P4 versus natural cycle	*Mirkin et al 2004*
•recFSH and GnRH antagonist only versus natural cycle	*Macklon et al 2008*

Δ gene expression
=
Δ Endometrial receptivity?

Endometrial secretion aspiration

	aspiration (N=66)	control (N=66)	
Implantation rate	23 %	18 %	
Positive pregnancy test	36 %	33 %	
Pregnancy confirmed by ultrasound	33 %	30 %	NS

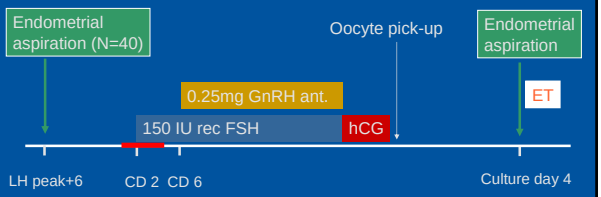
Van der Gaast *et al*. Reprod Biomed Online, 2002.

The intrauterine environment

Pro-inflammatory cytokines	IFN-γ IL-1, IL-12, IL-15, IL-17, TNFα
Anti-inflammatory cytokines	IL-5, IL-6, IL-10
Chemokines	CXCL 10, MCP-1, MIF, Eotaxin
Growth Factors	VEGF, HB-EGF
Signaling Factors	DKK-1

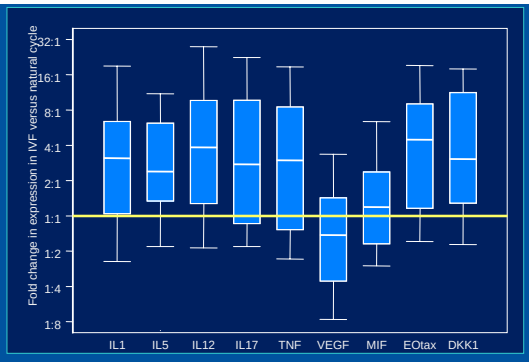
Impact of ovarian stimulation?

- 240 women undergoing first cycle IVF
- Exclusion criteria: >41 years of age



Boomsma et al

The impact of ovarian stimulation

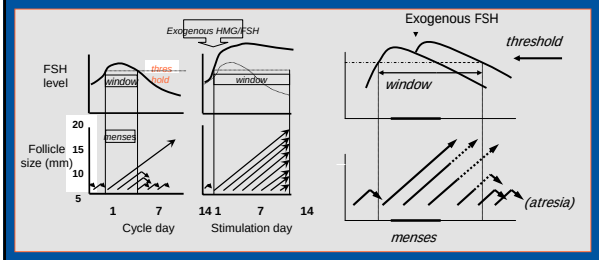


Boomsma et al 2007

Combined diagnostic techniques

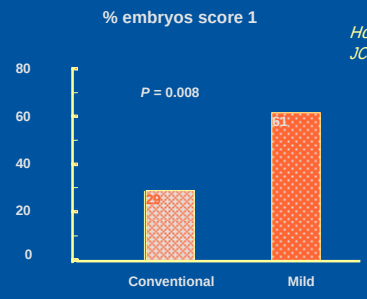
- Ledee et al J Reprod Immunol. 2007

Mild stimulation as a therapeutic option



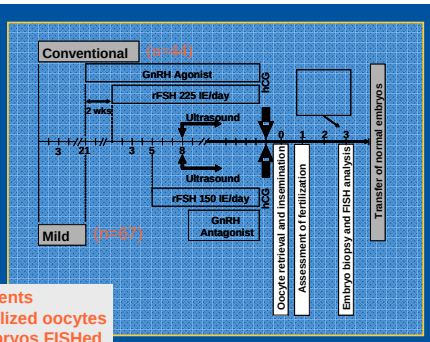
Macklon et al, Endocrine Reviews, April 2006

Mild Stimulation and Embryo Quality



Hohmann et al JCEM 2003

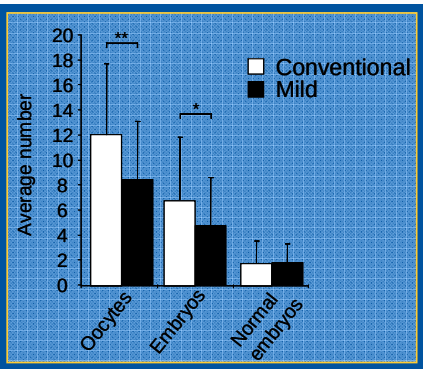
Effect of ovarian stimulation on embryo aneuploidy



111 patients
528 fertilized oocytes
302 embryos FISHed

Baart, Human Reproduction 2007

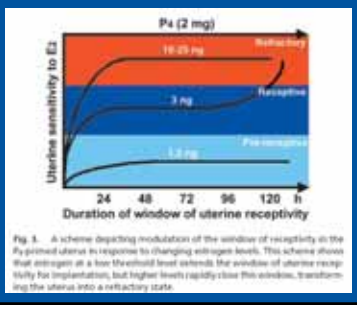
Chromosomally competent embryos generated after mild versus conventional stimulation



Baart, Human Reproduction 2007

Estrogen is a critical determinant that specifies the duration of the window of uterine receptivity for implantation

PNAS | March 4, 2003 | vol. 100 | no. 5 | 2963-2968



Conclusions

- Implantation failure remains the major challenge in IVF
- Multifactorial
- No effective evidence-based treatment
- Requires new approaches:
  - Careful phenotypic and genetic studies
  - Better understanding of human implantation
  - Rational therapies
  - Realistic expectations

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