Prof. Abha Majumdar

Director, Center of IVF and Human Reproduction
Sir Ganga Ram Hospital, New Delhi, INDIA

GRIPMER

'**President's Medal**' for best medical graduate 1970-75
Awarded by DMA on Dr. B.C Roy's birthday' for outstanding contribution towards medicine,1999
'**Vikas Ratan Award**' by Nations economic development & growth society 2002
'**Chitsa Ratan Award**' by International Study Circle in 2007
'Life time Medical excellence award' Obs & Gyne by Hippocrates foundation 2014
'**Abdul Kalam gold medal**' by Global Economic Prog & Research Association 2015
Rashtriya Gaurav Gold Medal award', October 2017 by GEPRA
'Distinguished teacher of excellence award' for PG medical education by national board of examinations and ANBAI in 2017
'**Inspiring Gynecologist of India',** by the Economic Times on doctors day 2018
Course director for post doctoral **Fellowship in Reproductive Medicine** by NBE since 2007 and by FOGSI for basic & advanced infertility training since 2008.
Member of Editorial board of '**IVF Worldwide',** peer reviewer for '**Journal of Human Reproductive Sciences',** Member of advisory board for '**Journal of Fertility Science & Research'** and consultant advisor for queries to NDTV.com
Field of interest: Infertility, ART, Reproductive endocrinology, Endoscopic surgery for pelvic resurrection.

Director

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SGRH
IVF SIR GANGARAM HOSPITAL

Single oocyte
Single embry
Single h

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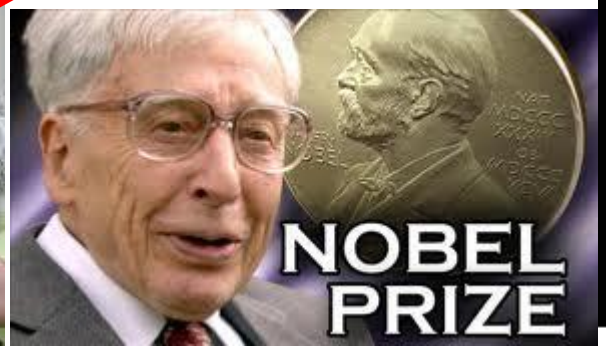
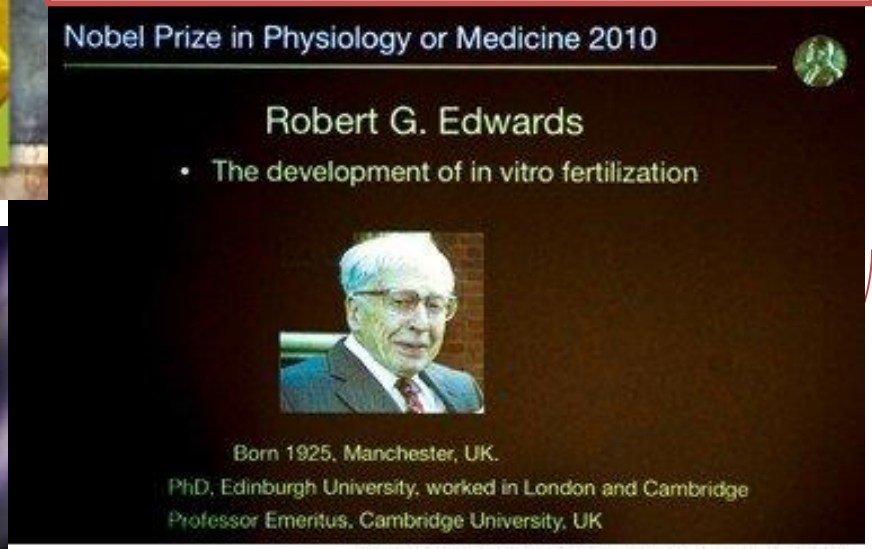
Of t… …ners, the
…gist Robert G.
…ongest to be
…His award for medicine
… 32 years after he figured out how
…o create the beginnings of human life
outside the uterus through in vitro
fertilization.

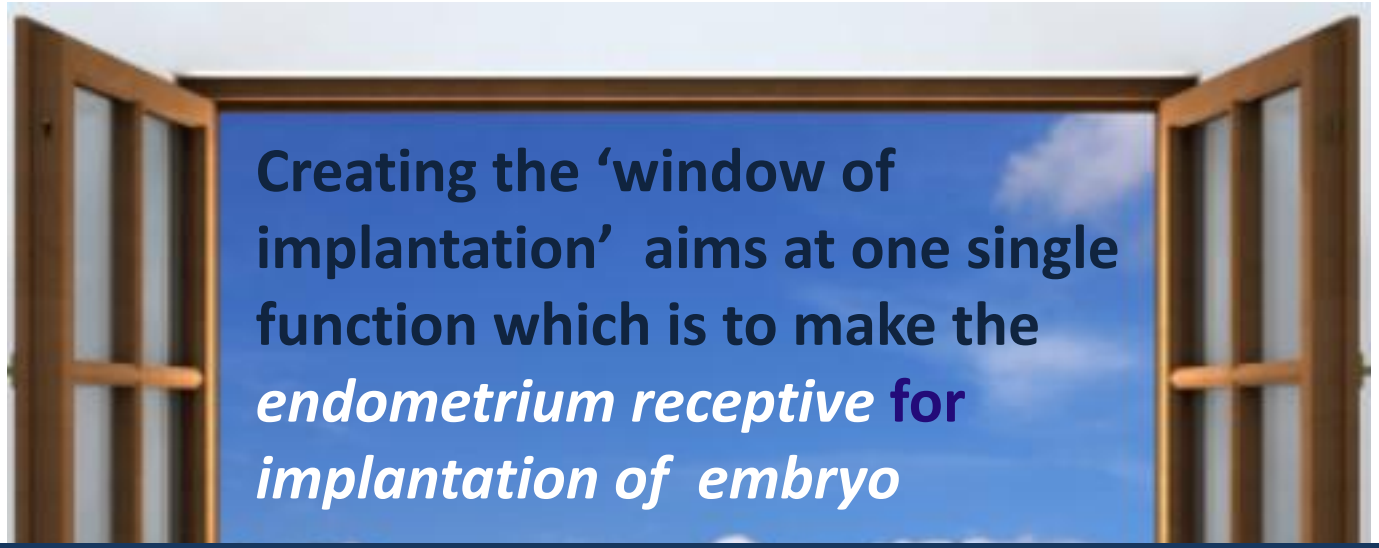
EMBRYO IMPLANTATION





Jonathan Nackstrand, AFP/Getty Images

Every single menstrual cycle aims at endometrial growth & receptivity which is a steroid dependent phenomenon & is targeted to create a 'window of implantation' which spans from day 20 to 24 of a 28 day cycle.

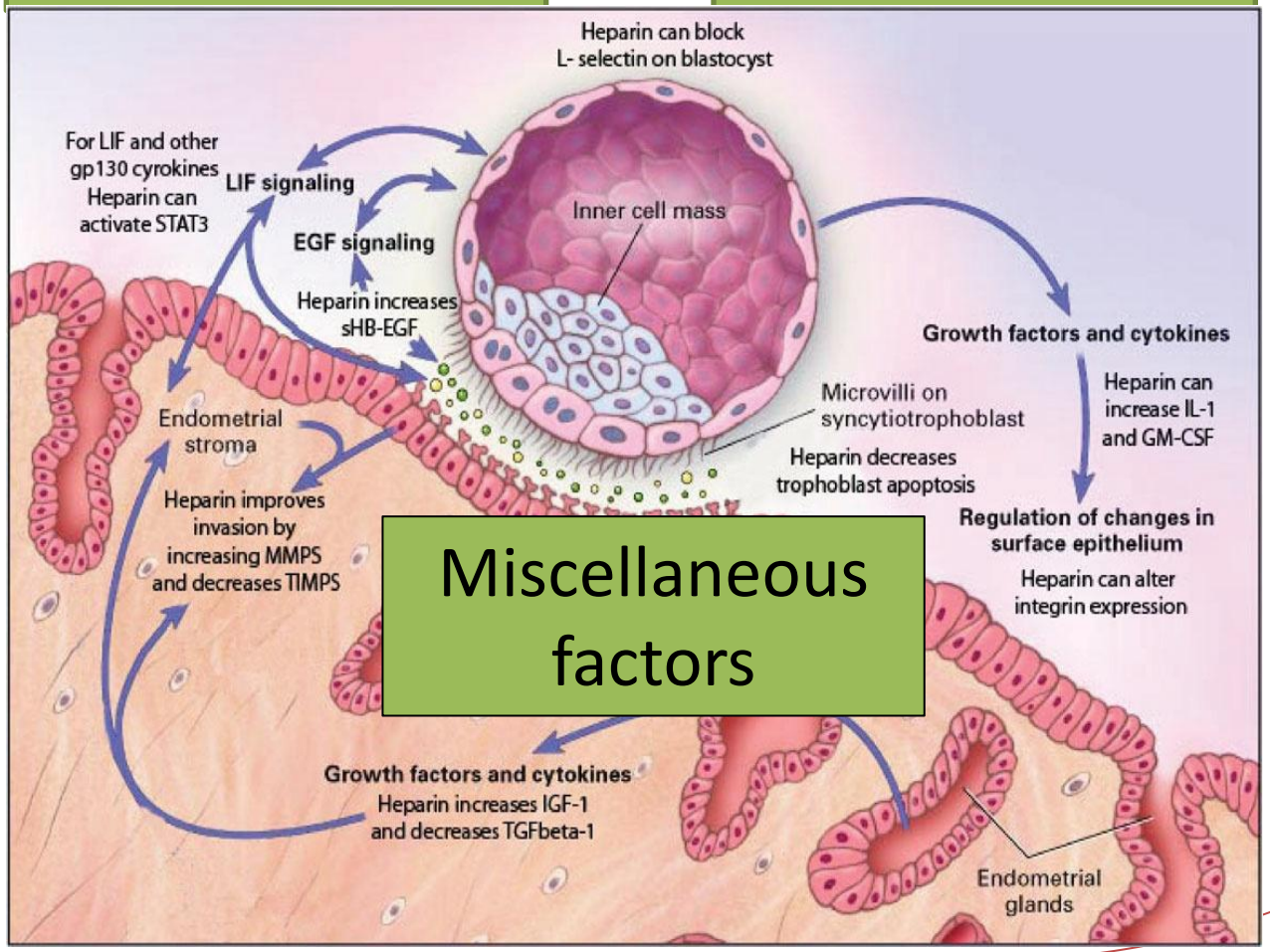


Only after development of IVF it was understood that Implantation failure is a major rate limiting step in happening of a successful pregnancy

Implantation failure

Defective Seed

Defective Soil



Miscellaneous factors

What does recurrent implantation failure mean?

- ≥8 of 8cell or = >5 blastocyst transferred *Rinehart J 2004*
- Failure of 3 cycles with reasonably good embryos transferred. *Margolioth et al; 2006*
- Failure to achieve a clinical pregnancy after transfer of at least 4 good-quality embryos in a minimum of 3 fresh or frozen cycles in a woman under the age of 40 years *C Coughlan et al., 2014 -*
- Recently if 2 good morphology euploid embryos fail to implant it is considered as recurrent implantation failure

Causes of RIF?

Defects in endometrial receptivity	Defects in the embryo transferred	Multifactorial factors
Uterine cavity abnormalities/ thin/ thick endometrium	Embryo morpholog… grow…	…sis and Hydro- …ges
Sub-endometrial … causes: ade… & intr…	…natch, …optimal culture conditions	Immunological factors/ thrombophlia affecting cross talk
Genetic …auses: Endometrial receptivity array	Aneuploidy	Hyper stimulated cycles, drug effect used for COS

Unexplained RIF

What can we treat?

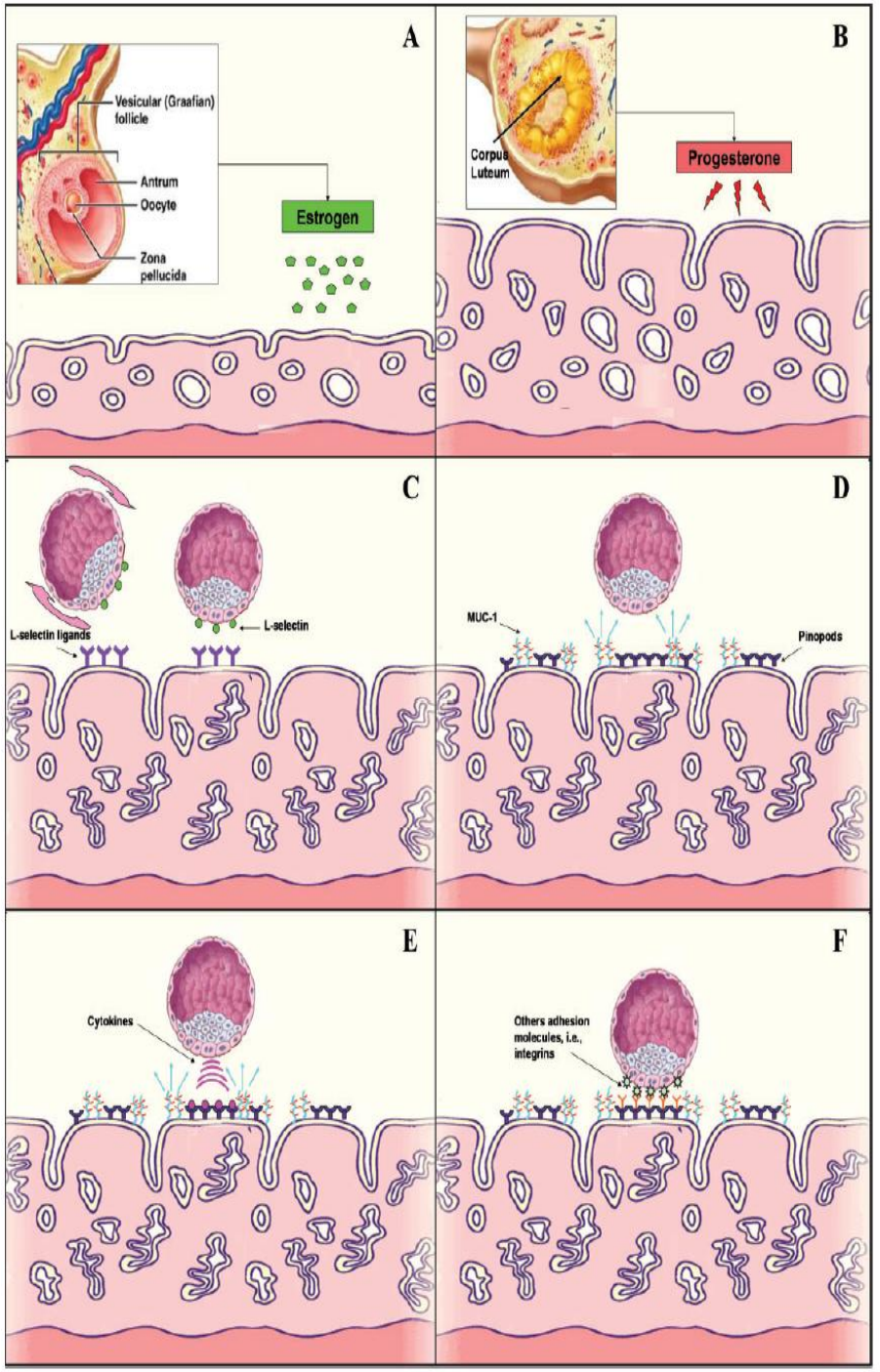
Endometrial defects

- Surgical
- Medical
- Genetic

Select a good embryo

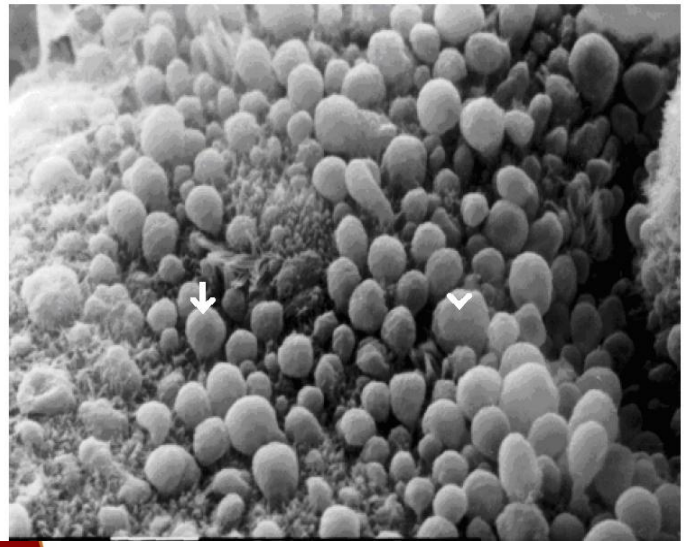
- Morphology/growth dynamics
- Assisted hatching
- PGS

Miscellaneous factors

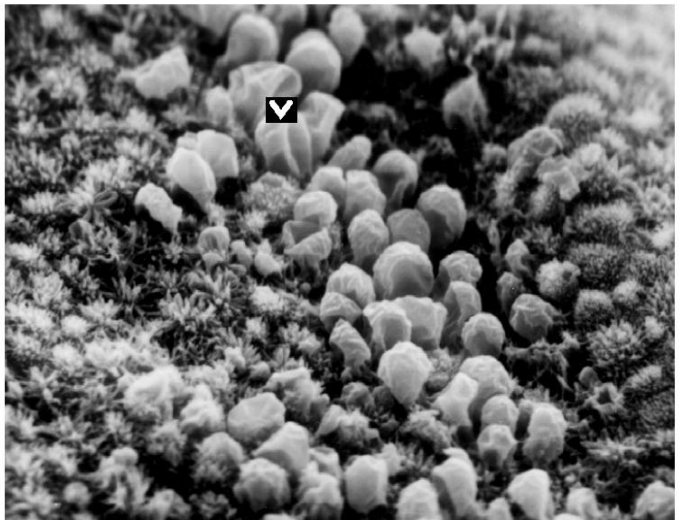


- Surgical
- Medical
- Genetic

treatment of Endometrial defects



Developed pinopodes on luteal Day 5



Regressing pinaodes on luteal day 7

Treating endometrial defects

Surgical

- Hysteroscopically
- Laparoscopically

Medical

Thin ET

All Treatment directed to

- Increase blood flow
- Stromal proliferation

Thick ET

- Treat with progestogens

Genetic testing ERA for personalized embryo transfer as per WOI

Vaginal sildenafil
Low dose aspirin
Pentoxiphyillin
High dose vit E
GCSF, GM CSF
PRP

Implantation failure

A normal looking endometrium may fail to implant embryo

Thin endometrium

A thin endometrium can also implant an embryo comfortably

Causes of RIF?

Defects in endometrial receptivity	Defects in the embryo transferred	Multifactorial factors
Uterine cavity abnormalities/ thin/ thick endometrium	**Embryo morphology and growth dynamics & blastocyst transfer**	Endometriosis and Hydro-salpinges
Sub-endometrial causes: adenomyosis & intramural fibroid	**failure to hatch, suboptimal culture conditions**	Immunological factors/ thrombophlia affecting cross talk
Genetic causes: Endometrial receptivity array	**Aneuploidy**	Hyper stimulated cycles, drug effect used for COS

Multi-factorial reasons

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Endometriosis
GnRH agonists 3–6 months pre IVF significantly increases ongoing PR.
GnRHa increases endometrial receptivity by upgrading αVβ3 integrin. *Surrey et al., 2002*

Drugs for OS: Endometrial and embryo qualities may be harmed by certain drugs. Frozen ET Mild stimulation/ Natural cycle IVF: less endometrial advancement

Hydrosalpinges
Bilateral hydrosalpinges: lower implantation rates by 35-50% & PR. Salpingectomy, clipping of tubes brings it back to normal *Zeyneloglu et al., 1998*

Increasing the possibility of cross talk by **immune acceptance……..**

Increasing cross talk

Immune-therapy

Auto/allo immunity (immune rejection)

- IVIG
- Intra-lipid
- Steroids
- LIT (*paternal or third party leucocyte immune therapy)*
- *Adalimumab*

Anti-coagulation

Thrombophilia (pro-thrombotic)

- Hereditary
- Acquired (APLA)

What is the aim of immune therapy?

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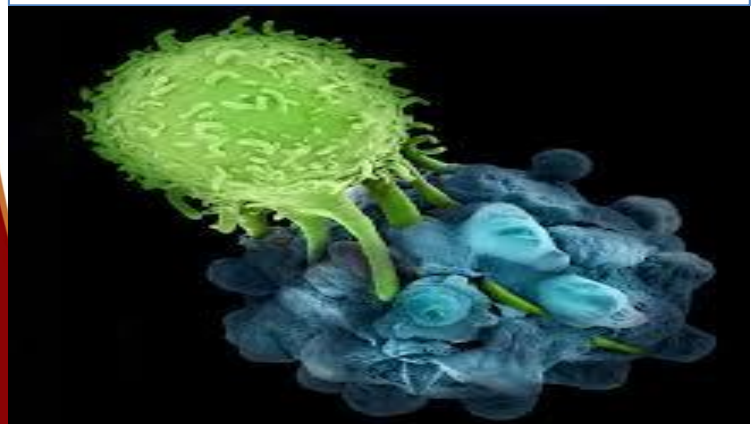
To create pro-implantation environment

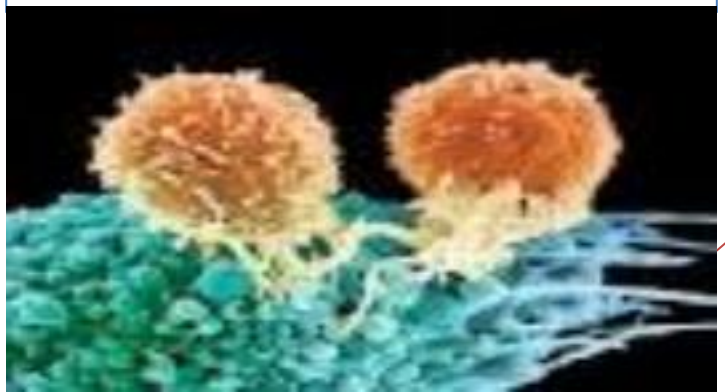
IVIG and steroids

Modulates T & B cells, NK cells, CD 56, monocytes & macrophages,
Down regulates antibody function



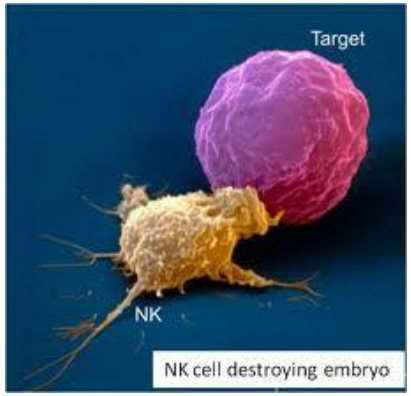
LIT and intra-lipid

Coats trophoblast, to render it undetectable by maternal immune system ***(APCA, anti idiotypic antibody, mixed lymphocyte reaction antibody)***



Auto-immunity- NK cells

- **Both** –peripheral and uterine- are part of the immune system
- **Both** express surface antigen CD56



Phenotypically and functionally they are different

Peripheral NK
<10% resemble uNK
90% are $CD56^{dim}$ and CD16+
Significant cytotoxic activity

Uterine NK
Appear in mid-secretory phase
80% are $CD56^{bright}$ and CD16-
Little cytotoxic activity

2 separate entities!

Peripheral NK

Association between pNK number or activity & RM/infertility

Kwak 1995
Aoki 1995
Ntrivalas 2001
Yamada 2003
Shakar 2003
Beer 1996
Matsubayashi 2001
Ntrivalas 2001

Emmer 2000
Souza 2002
Wang 2008
Vujisic 2004

Uterine NK

Association between uNK number or activity and RM/infertility

Clifford 1999
Quenby 1999
Quenby 2005
Tucerman 2007

Ledee-Bataille 2005

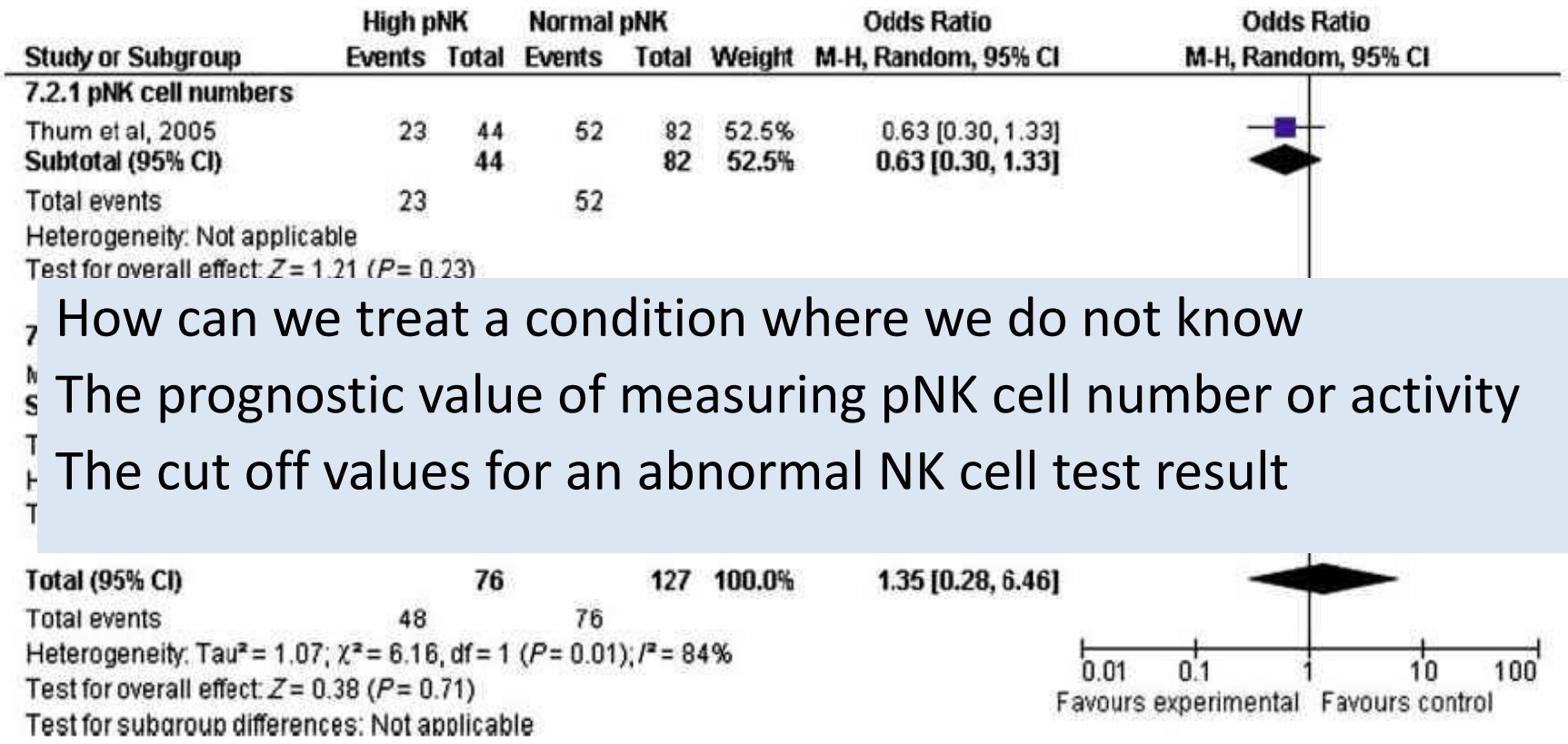
Michimata 2002
Shimada 2004

Matteo 2007

NK cells and infertility

Relevant citations on pNK (n=783)

Tang et al Hum Reprod 2011



- How can we treat a condition where we do not know
- The prognostic value of measuring pNK cell number or activity
- The cut off values for an abnormal NK cell test result

Odds of implantation failure after ART with high levels of pre-pregnancy peripheral NK cell parameters in women with infertility.

The role of immunotherapy in in Vitro Fertilization : A guideline

Practice committee of ASRM 2018 (Fertil Steril 2018)

- Good evidence to recommend ***against routine use of low-dose aspirin*** and ***corticosteroids*** during stimulation or luteal phase to improve live birth in ART cycles in the general population (Grade A).
- Insufficient evidence to recommend for or against ***local G-CSF or systematic G-CSF or GM-CSF or I/V fat emulsions or IVIG*** administration to improve endometrial thickness or CPR with IVF. (Grade C).
- ***Routine immunological testing not recommended*** in general ART population till clear cut association is established between the two.

ASRM guidelines 2013 for treatment of APLA in IVF cycles

- Although association between APLA & IVF failure has been suggested in some retrospective studies, no association is present in prospective studies summarized.
- Assessment of APLA not recommended in couples undergoing IVF
- Therapy is not justified on the basis of existing data.

Treatment risks

Heparin

- thrombocytopenia
- bleeding

Corticoids

- fluid retention
- mood swings
- weight gain
- risk of infections
- high BP & sugar
- cleft palate

IVIGs

- fever, hypertension
- headache
- dermatitis
- thrombo-embolism
- pulmonary edema
- anaphylaxis
- hepatitis & renal failure
- aseptic meningitis
- risk diabetes newborn

Low dose aspirin

- higher dose of FSH requirement in COS
- more immature oocytes

Gizzo S 2014

Adalimumab

Long term serious

- infections
- malignancy

IV fat emulsions

jaundice
hyperthermia

Causes of RIF?

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Unexplained RIF

Endometrial scratch

What is the

What is the biological process that may lead to an increased probability of pregnancy?

One theory is that endometrial scratching causes some sort of inflammatory response within the endometrium, similar to a scratch on any other part of the body.

It is likely that wound healing response following scratch improves the environment of the endometrium and makes it more likely for an embryo to implant and create a pregnancy.

Endometrial scratch How safe is it?

- Pain, vasovagal attack, demand of anaesthesia, difficult entry into uterine cavity, intermittent bleeding are procedural side-effects.
- Possibility of chronic endometrial inflammation, may be detrimental for embryo implantation and development, potentially leading to infertility and recurrent pregnancy loss.
- Pelvic abscess especially in women with adnexal masses
- Solid evidence is needed to draw any conclusions about the benefits of such iatrogenic inflammation on implantation before using it routinely as treatment for RIF.

Cicinelli E, Matteo M, Tinelli R, Lepera A, Alfonso R, Indraccolo U, et al. Prevalence of chronic endometritis in repeated unexplained implantation failure and the IVF success rate after antibiotic therapy. Hum Reprod 2015; 30:323–30. (49–51).

Endometrial scratch in IVF

Endometrial scratch in IUI cycles and in unexplained infertility

Endometrial scratch (ES)

Studies with beneficial effect of ES in women undergoing embryo transfer

Barash et al., 2003
Guven et al., 2014
Inal et al., 2012
Karimzadeh et al., 2009
Narvekar et al., 2010
Nastri et al., 2013
Raziel et al., 2007
Shohayeb et al, 2012
Singh et al., 2015

Studies which could not confirm the benefit of scratch in women undergoing embryo transfer

Baum et al., 2012
Yeung et al., 2014
Jennifer et al., 2017

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Endometrial scratch injury for women with one or more previous failed embryo transfers: a systematic review and meta-analysis of randomized controlled trials

Amerigo Vitagliano, M.D., Attilio Di Spiezio Sardo, M.D., Gabriele Saccone, M.D., Gaetano Valenti, M.D., Fabrizio Sapia, M.D., Mohan S. Kamath, M.S., Mija Blaganje, M.D., Ph.D., Alessandra Andrisani, M.D., Guido Ambrosini, M.D.

Conclusion(s)

The ESI may improve IVF success in patients with *two or more previous ET failures undergoing fresh ET.* The ESI timing and technique seem to play a crucial role in determining its effect on embryo implantation.

Fertility and Sterility® Vol. 109, No. 1, January 2018

Endometrial scratch injury before intrauterine insemination: is it time to re-evaluate its value? Evidence from a systematic review and meta-analysis of randomized controlled trials (8 trials = 1,871 IUI cycles)

ESI is expected to be safe, although clear evidence about its short-term and long-term complications is warranted.

ESI lead to **higher CPR** (OR 2.27) & **OPR** (OR 2.04) vs controls. Not higher risk of multiple pregnancy (OR 1.09), MR (OR 0.80), or EPR (OR 0.82).

Subgroup analysis based on **ESI timing** showed **higher clinical pregnancy rate** (OR 2.57) and ongoing pregnancy rate (OR 2.27) in **patients receiving ES in same cycle** of before hCG but not in patients in previous cycle.

Trial status Ongoing (recruitment commenced June 2014).

Trials

PIP STUDIES

— PIPELLE FOR PREGNANCY —

Lensen *et al. Trials* (2016) 17:216
DOI 10.1186/s13063-016-1301-9

Trials

STUDY PROTOCOL Open Access

Pipelle for Pregnancy (PIP): study protocols for three randomised controlled trials

Sarah Lensen[1*], Wellington Martins[2], Carolina Nastri[2], Lynn Sadler[1] and Cindy Farquhar[1]

Methods/design: The PIP trials are 3 multi-centre, RCTs designed to test 3 separate hypotheses:
Whether endometrial injury increases the probability of live birth in women or couples

1) Who are undergoing autologous embryo transfer as part of an IVF cycle (PIP-IVF)
2) With unexplained infertility who are attempting to conceive naturally (PIP-UE)
3) With subfertility related to polycystic ovarian syndrome (PCOS) who are on ovulation induction medication and attempting to conceive (PIP-PCOS)

Primary Outcome

	Scratch N=690	Control N=674	OR (95% CI)
Live Birth	**180 (26.1)**	**176 (26.1)**	**1.00 (0.78 to 1.27)**
Single	168 (24.3)	167 (24.8)	
Twin	11 (1.6)	9 (1.3)	
Triplet	1 (0.1)	0	

Interim results of PIP study presented in Barcelona ESHRE 2018

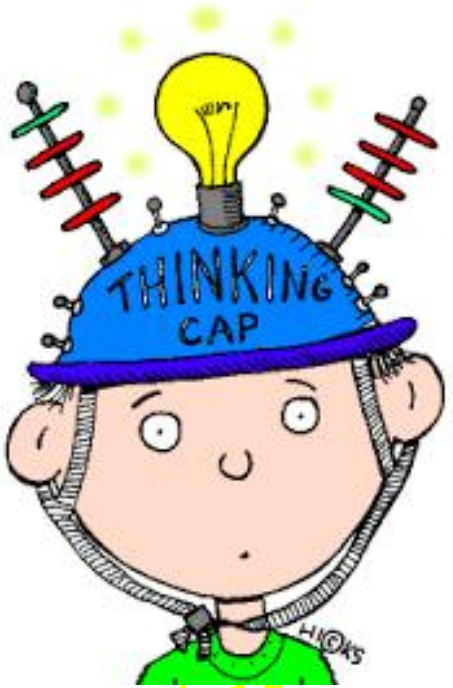
Proposed treatment for RIF

Endometrial receptivity	Embryonic defects	
Hysteroscopy: correction of cavity pathology Thin/thick endometrium by drugs or surgery	Morphol… bla…	…Ha … 6 months …pinges: Clipping … salpingectomy
Adenomyo… sub-… remo…	…ng	Immunotherapy : IVIG, LIT steroids or intralipid. aspirin and heparin not recommended presently
Endomet… Erray (ERA)… …on gene expression i… WOI	Pre-implantation genetic screening	Tailoring the stimulation to milder protocols and frozen ET

Unexplained RIF: scratch??? still finding our way out

Thank you

for giving me
a reason to scratch my brains



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