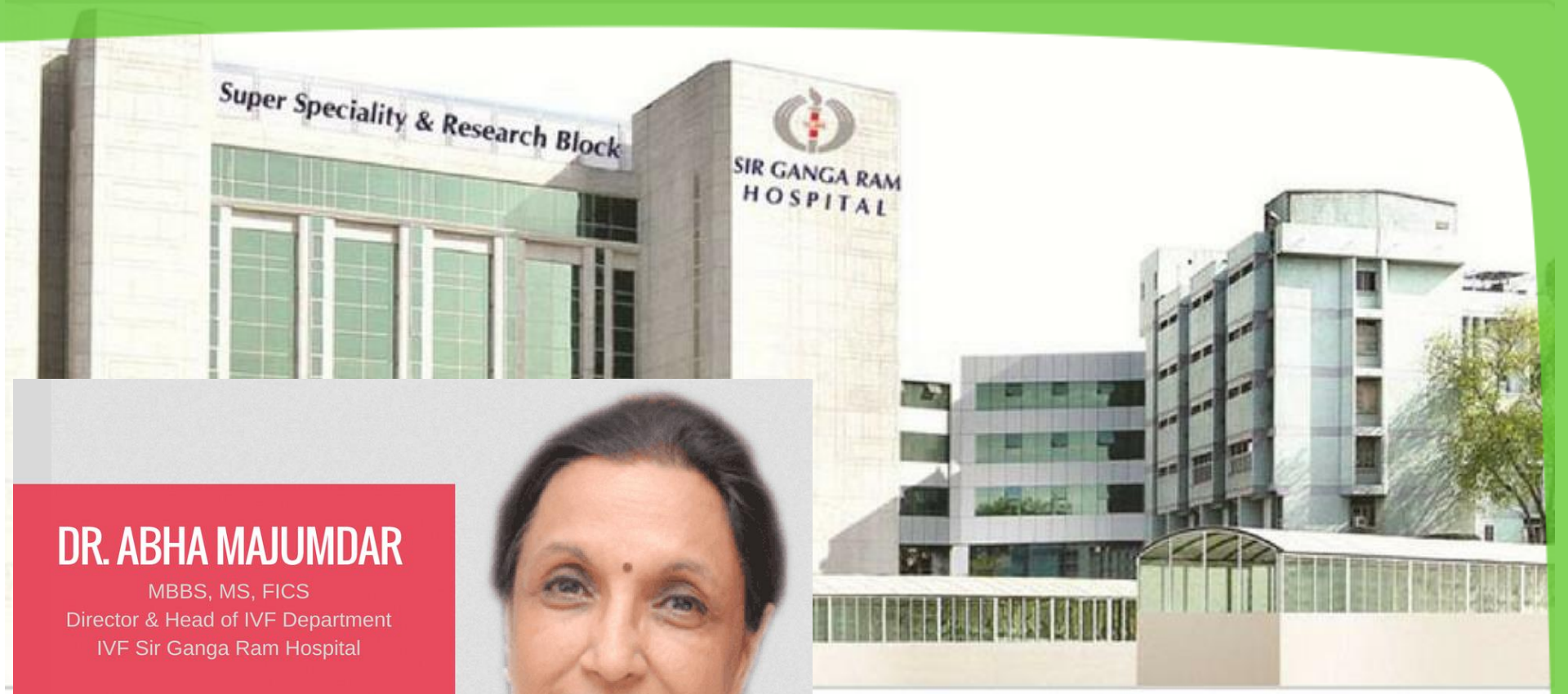
Prof. Abha Majumdar

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

‘**President’s Medal**’ for best medical graduate 1970-75
Awareded 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.



DR. ABHA MAJUMDAR

MBBS, MS, FICS
Director & Head of IVF Department
IVF Sir Ganga Ram Hospital

Expertise

Infertility, assisted reproductive techniques, reproductive endocrinology, endoscopic surgery for pelvic resurrection.

Director
Centre of IVF and Human Reproduction

Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi, 110060
Ph: 011 4225 4000/ 011 4225 1800/ 011 4225 1777/ 8375990881
Website: www.ivfgangaram.com

SGRH
IVF SIR GANGARAM HOSPITAL

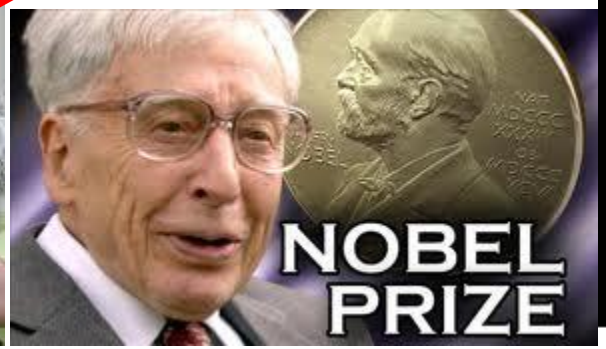
Endometrial scratch

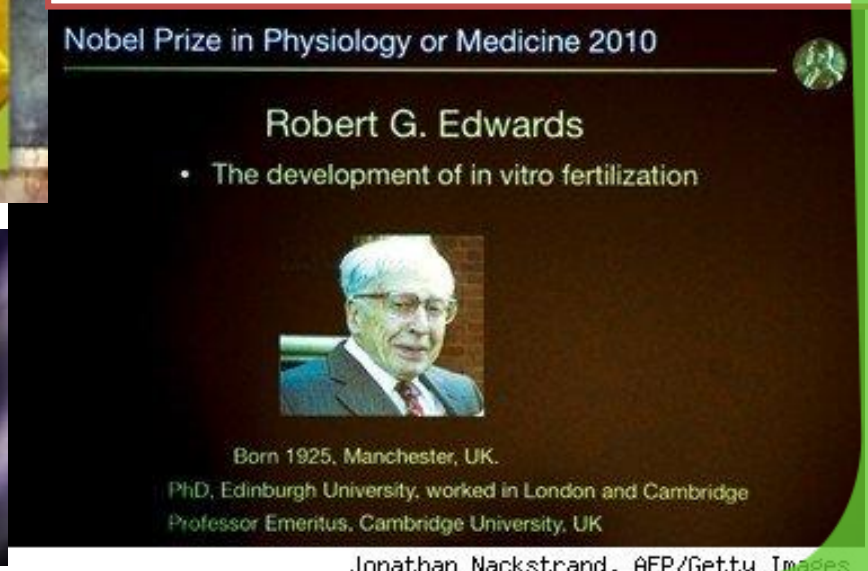
What is the

Single oocyte
Single embry
Single h

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

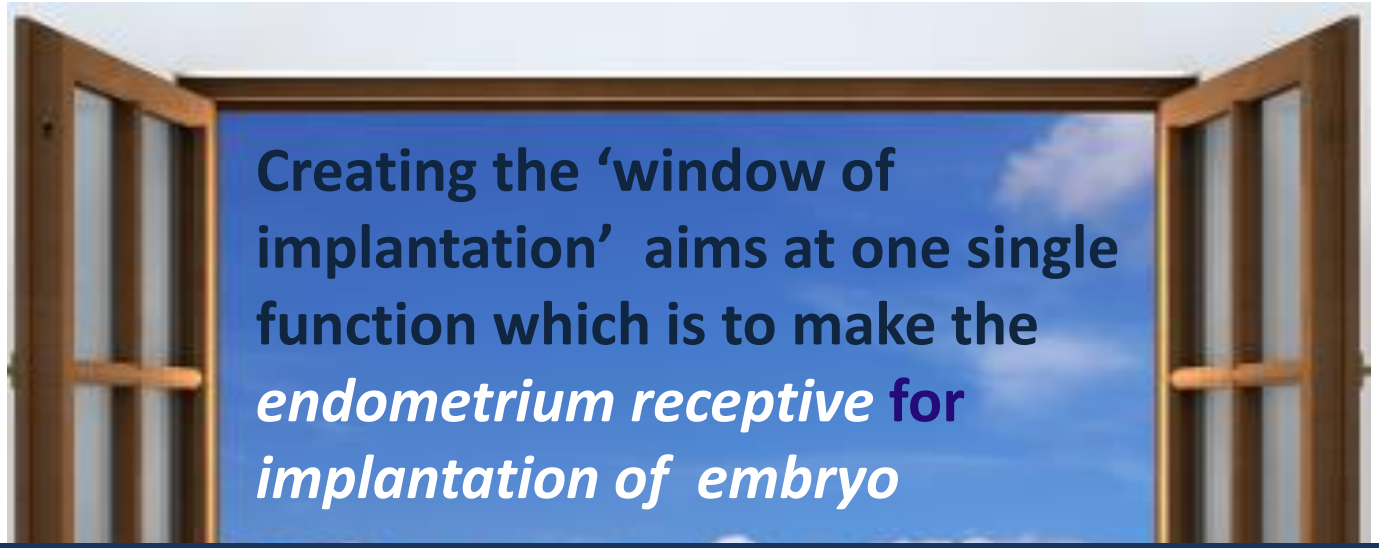
EMBRYO IMPLANTATION





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.

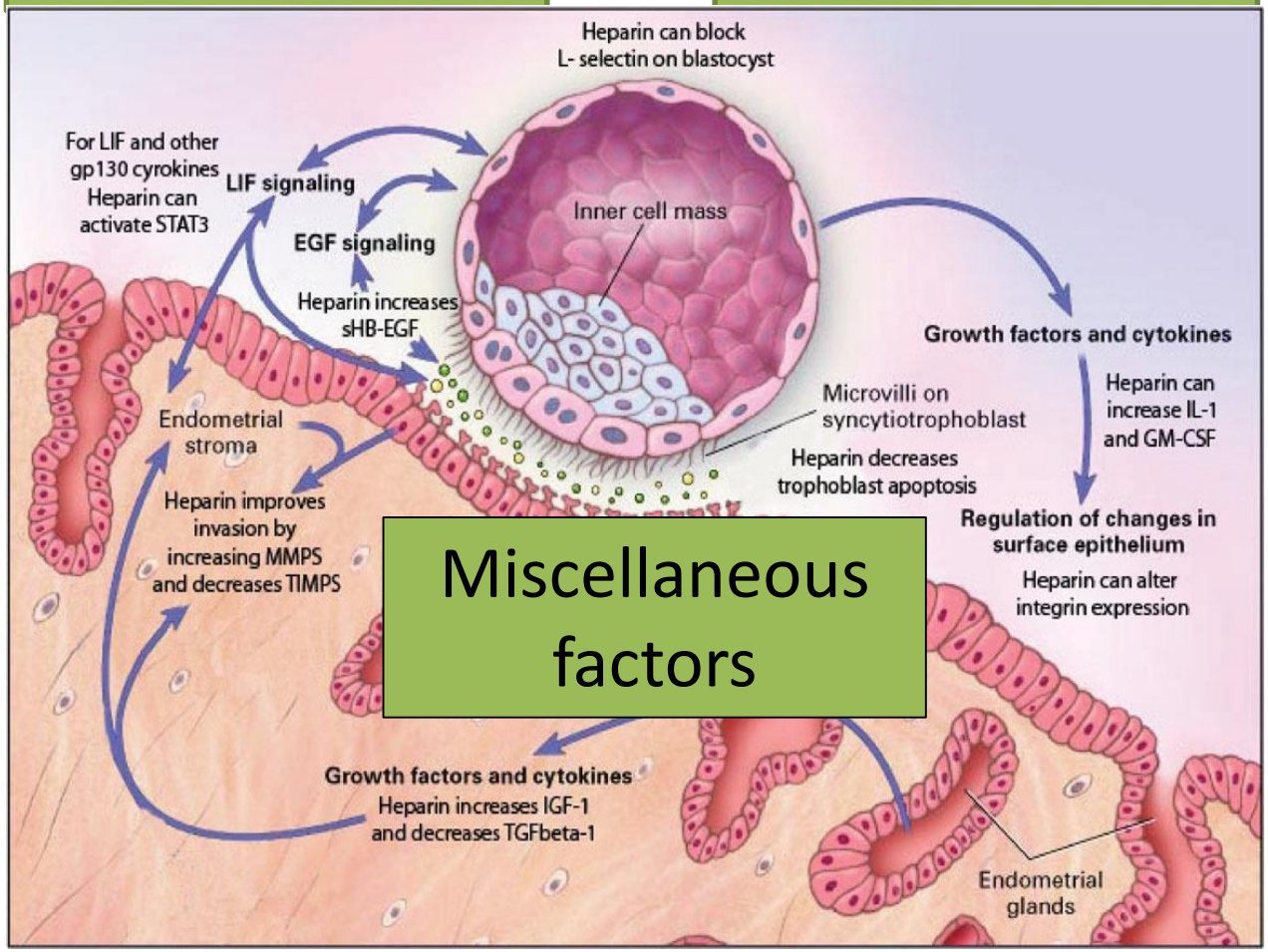


Only after development of IVF it was understood that Implantation failure is a major rate limiting step in happening of a successful pregnancy

Implantation failure

Defective Seed

Defective Soil



Miscellaneous factors

Embryo implantation

- The probability of an embryo successfully implanting is approximately 30%.
- Implantation failure can be multifactorial
- Recurrent implantation failures (RIF) may occur in 5–10% of women undergoing IVF cycles
- Significant proportion of RIF is related to endometrial receptivity.

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	Miscellaneous factors
Uterine cavity abnormalities/ thin/ thick endometrium	Embryo morpho… g…	…iosis and …ro-salpinges
Sub-endom… cause… adeno… intram… …ibroid	…e 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

Unexplained RIF

Endometrial scratch (ES)

ES is one of several strategies proposed to improve endometrial receptivity where no other cause is apparent in a normal looking endometrium

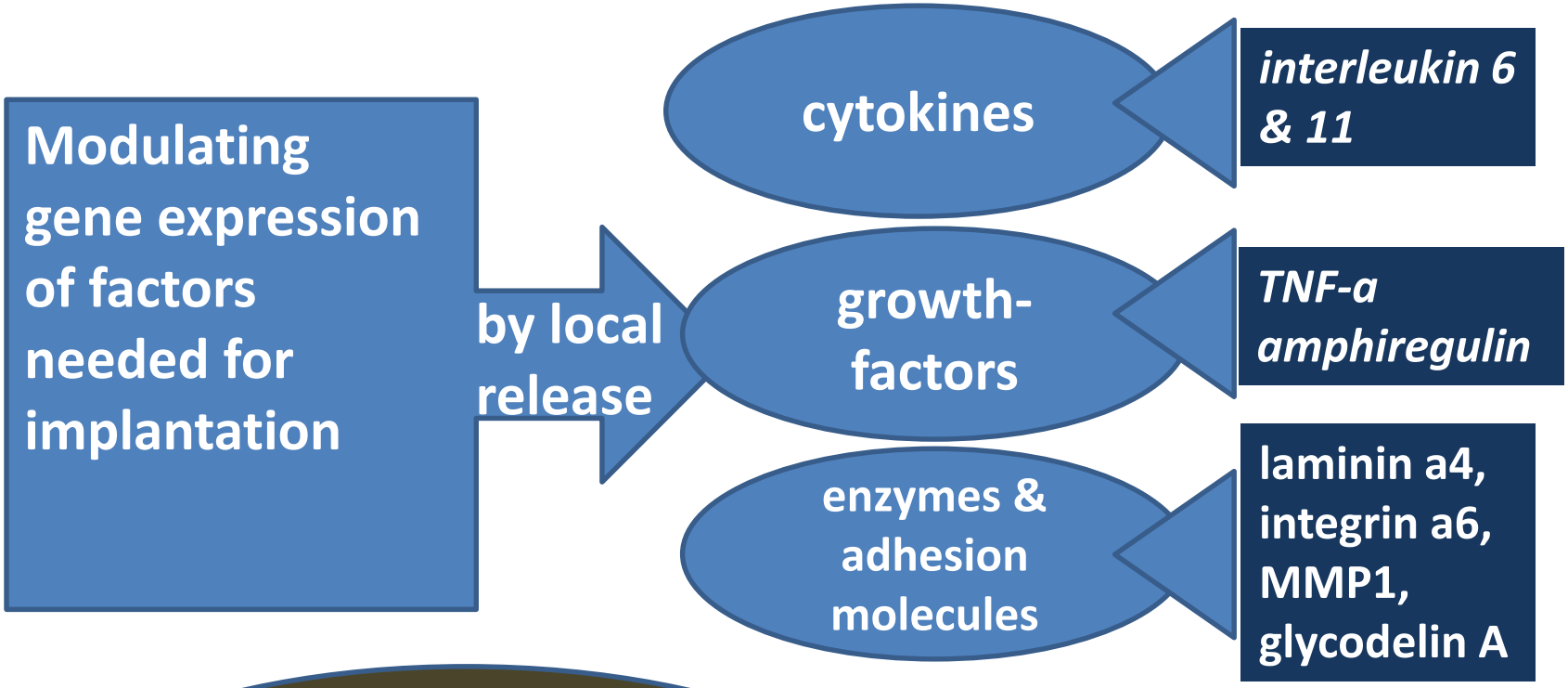
ES injury is mechanical manipulation of the endometrium by voluntary endometrial trauma aimed to improve its receptivity.

Barash was the first to introduce the concept of endometrial scratch where he observed that local injury to the endometrium doubles the incidence of successful pregnancies in patients undergoing IVF. ***Fertil. Steril. 2003, 79, 1317–1322.***

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.



The acute inflammatory process creates an angiogenic environment, which may promote embryo-uterine crosstalk and result in successful implantation.

ESI may possibly also mitigate the detrimental effects of OS on endometrium

Goel et al,.J Assist Reprod Genet 2017;34:1051–8.
Kalma et al.,Fertil Steril 2009;91:1042–9.e9..

Endometrial scratch (ES)

- *Endometrial regeneration*
- *Slowing down of disproportionate endometrial development often associated with OS cycle to restore embryonic-endometrial synchrony.*

The trauma can be achieved simply by a pipelle, biopsy curette, or hysteroscope at low cost and with no need of analgesia or anaesthesia

Hysteroscopy as an intervention for ES

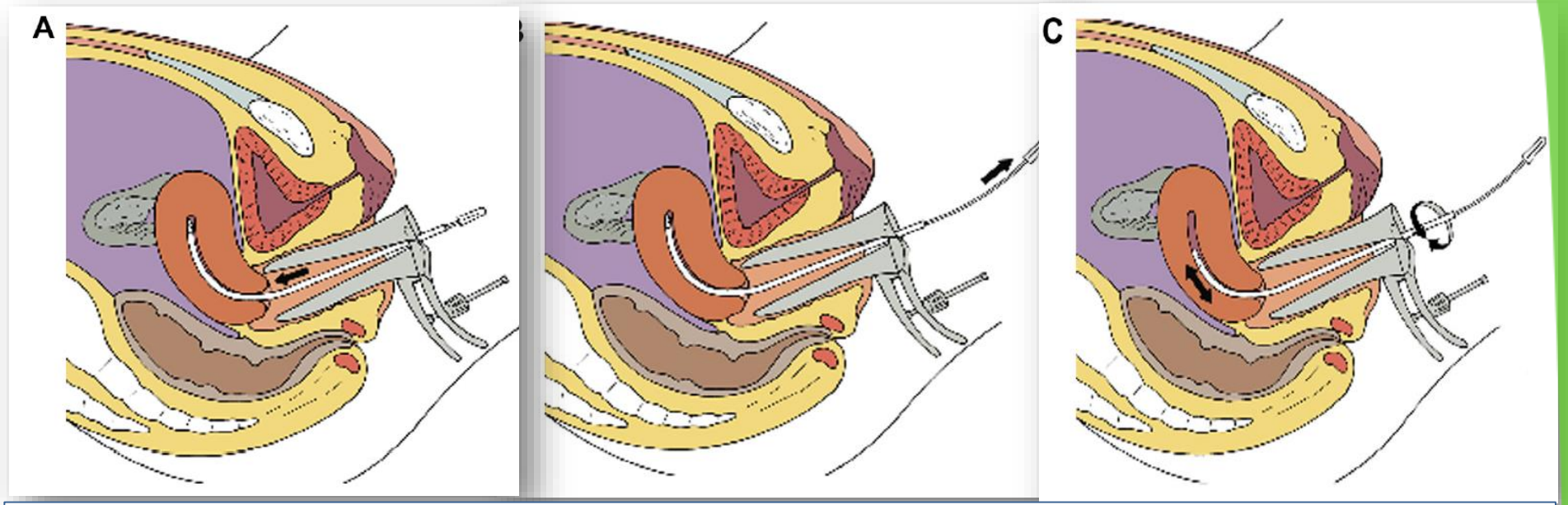
Hysteroscopy is used to treat endometrial pathologies that can interfere with embryo implantation. Benefits of hysteroscopy are beyond the possible 'injury' effect only:

- ❑ Correction of unsuspected intrauterine abnormalities in asymptomatic previously failed IVF patients.
- ❑ Assessment of cervical conditions to achieve an easier ET.

Therefore, studies based on hysteroscopy should not be combined with those exclusively based on endometrial biopsy to analyse the scratching effect.

Carlos and Bellver Hum Rep.2014, Pundir *et al.*, 2014

Endometrial scratch



Endometrial scratch

(A) Pipelle is inserted until it reaches the fundus.

(B) The inner plunger is withdrawn to apply a suction force to the endometrial cavity.

(C) Endometrial scratch of the superficial layer of endometrium is performed with the use of a ‘hoovering’ movement, combining a rotational and in-and-out movement of the pipelle sampler several times

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 (ES)

ES has been used in IVF cycles with variability:

- ❑ First or previous IVF failures (1 or more)
- ❑ Timing of scratch
  - luteal or follicular
  - Once or twice
  - previous cycle or same cycle
- ❑ Type of embryo transfer cycles
  - Fresh embryo transfer in stimulated cycle
  - FET in artificial cycle using HRT
  - FET in natural cycle

Fresh embryo transfer cycles (Barash et al., 2003; Baum et al., 2012; Gibreel et al., 2015; Guven et al., 2014; Inal et al., 2012; Karimzadeh et al., 2009; Mahran et al., 2016; Narvekar et al., 2010; Nastri et al., 2013; Raziel et al., 2007; Shohayeb and El-Khayat, 2012; Singh et al., 2015; Yeung et al., 2014) ***FET in HRT cycles (Aflatoonian et al., 2016; Dunne and Taylor, 2014) natural FET cycles (Jennifer Sze Man Mak et al.,2017)***

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

Meta-analysis and systematic reviews

ELSEVIER

Reproductive BioMedicine Online

Volume 25, Issue 4, October 2012, Pages 345-354

Article

Local endometrial injury and IVF outcome: a systematic review and meta-analysis

Tarek El-Toukhy, SeshKamal Sunkara, Yakoub Khalaf

In total, 901 participants included in 2 randomized (*n* = 193) and six non-randomized controlled studies (*n* = 708). The quality of studies was variable. Meta-analysis showed that clinical pregnancy rate was significantly improved after LEI in both randomized & non-randomized studies.

ELSEVIER

Reproductive BioMedicine Online

Volume 25, Issue 6, December 2012, Pages 561-571

Review

Endometrial injury to overcome recurrent embryo implantation failure: a systematic review and meta-analysis

Neelam Potdar [a], Tarek Gelbaya [b], Luciano G. Nardo [c]

Pooling of 7 controlled studies (four randomized and three non-randomized), with 2062 participants, showed that local endometrial injury induced in the cycle preceding ovarian stimulation is 70% more likely to result in a clinical pregnancy as opposed to no intervention

Endometrial injury in women undergoing assisted reproductive techniques (Review)

Nastri CO, Gibreel A, Raine-Fenning N, Maheshwari A, Ferriani RA, Bhattacharya S, Martins WP

2012

THE COCHRANE COLLABORATION®

Authors' conclusions Endometrial injury performed prior to the embryo transfer cycle improves clinical pregnancy and live birth rates in women undergoing ART.

OXFORD ACADEMIC

human reproduction

Volume 29, Issue 8
August 2014

Scratching beneath 'The Scratching Case': systematic reviews and meta-analyses, the back door for evidence-based medicine FREE

Carlos Simón ✉, José Bellver

Human Reproduction, Volume 29, Issue 8, 1 August 2014, Pages 1618–1621,
https://doi.org/10.1093/humrep/deu126
Published: 04 June 2014 **Article history** ▾

Hum Reprod. 2014 Aug;29(8):1618-21. doi: 10.1093/humrep/deu126. Epub 2014 Jun 4.

Scratching beneath 'The Scratching Case': systematic reviews and meta-analyses, the back door for evidence-based medicine.

Simón C[1], Bellver J[2].

This opinion paper, analysed the methodological and plausibility problem beneath 'the Scratching Case'.

It has been suggested not to dilute evidence-based medicine by a vicious circle created by the over-exploitation of inadequate or insufficient data to compute incorrect or incomplete conclusions through systematic reviews and meta-analysis.

To summarize > 300 publications can be found on this topic, but only four RCTs with poor quality were analysed in 3 meta-analyses published in the same year with the same conclusion.

Hum Reprod. 2014 Aug;29(8):1618-21. doi: 10.1093/humrep/deu126. Epub 2014 Jun 4.

Scratching beneath 'The Scratching Case': systematic reviews and meta-analyses, the back door for evidence-based medicine.

Simón C[1], Bellver J[2].

ES was first suggested a decade ago by Barash as a simple intervention to improve endometrial receptivity in patients undergoing ART. A decade later, this intervention is being widely advertised by some of our colleagues on their web pages, and patients are paying to undergo the 'scratching cycle' before their ART treatment cycle.

This intervention must not be advertised as an established practice to improve implantation until real good data demonstrates that it does. We, doctors, have to remind ourselves of the Hippocratic Oath of *Primum non nocere* which means first, do not harm.

Though more studies are still needed one should consider this evidence is probably better than that existing for all other interventions aiming to improve the reproductive outcomes of women with RIF with fortunately several new studies on the horizon.

Volume 29, Issue 12

Endometrial scratching for women with repeated implantation failure FREE

Carolina O. Nastri, Lukasz T. Polanski, Nick Raine-Fenning, Wellington P. Martins

Human Reproduction, Volume 29, Issue 12, 1 December 2014, Pages 2855–2856,
https://doi.org/10.1093/humrep/deu257
Published: 14 October 2014

Why are the authors compelled to convince readers against endometrial scratching?
Is endometrial scratching expensive and/or risky?
Endometrial biopsy using a Pipelle is an affordable procedure, and millions have been performed per year for diagnostic indications for decades as a safe and well-tolerated procedure.

Cochrane

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Endometrial injury in women undergoing assisted reproductive techniques

Study characteristics

The evidence is current to January 2015.

Cochrane authors included 14 clinical trials (2128 women) Effects of ES on outcomes of ART.

History of previous ET varied among studies.

13 trials ES in cycle prior to ET cycle.

1 trial ES on the day of oocyte retrieval.

Nastri CO, Lensen SF, Gibreel A, Raine-Fenning N, Ferriani RA, Bhattacharya S, Martins WP

Although current evidence suggests some benefit of ES, we need evidence from well-designed trials that avoid instrumentation of the uterus in the preceding three months, do not cause endometrial damage, stratify the results for women with and without recurrent implantation failure (RIF) and report live birth.

Key results

ES performed sometime during the month before the start of OS improves chances that a woman will achieve live birth and clinical pregnancy.

Moderate-quality evidence suggests that if 26% of women achieve live birth without endometrial injury, between 28% and 48% will achieve live birth with this intervention.

Contrary to this, endometrial injury performed on the day the eggs are picked up reduces the chances of pregnancy.

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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.

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

Result(s):10 studies included (1,468 participants).

Intervention group **higher LBR** (RR 1.38, 95% CI 1.05–1.80) and **clinical PR** (RR 1.34, 95% CI 1.07–1.67)
No difference in multiple PR, miscarriage rate, and EPR.

Double luteal ESI with flexible pipelle had greatest effect on LBR (RR 1.54, 95% CI 1.10–2.16) and clinical PR (RR 1.30, 95% CI 1.03–1.65).

ESI was **beneficial** for patients with **two or more previous ET failure,** but not for women with single previous failed ET.

No effect seen in women with **frozen-thawed ET** cycles.

Endometrial scratch in IUI cycles and in unexplained infertility

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CONFERENCE COVERAGE

Cochrane review: Endometrial scratching may promote implantation

Publish date: July 6, 2016

By Sharon Worcester

Ob.Gyn. News

This Cochrane review included 9 RCT's (1512 women) who underwent endometrial scratching and were trying to get pregnant from intercourse or IUI with unexplained subfertility.

Overall the results suggest a benefit from ES. However, all the studies have significant limitations and so the results may be biased. Thus not possible to say with any confidence whether ES can increase the probability of pregnancy in this group of women.

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.

Poor evidence quality (GRADE of evidence: low) that ESI improves CPR (OR 2.27, P<00001) and OPR (OR 2.04, P=.004) in patients undergoing IUI without increasing the risk of multiple pregnancy, miscarriage, or ectopic pregnancy (GRADE score: low/very low).

Results support clinicians by providing an updated summary on ESI use in IUI and advising about the uncertainties in the real chances of ESI improving CPR and OPR.

Despite the novel evidence provided by our analysis, there is still a **need for further robust, high-quality RCTs to confirm the effectiveness and safety ESI** before routinely recommending its use in patients undergoing IUI cycles.

Trials

Trial status Ongoing (recruitment commenced June 2014).

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]

Table 4 Recruiting centres

Recruiting centre	Country
Fertility Plus, Auckland	New Zealand
Repromed, Auckland	New Zealand
Fertility Associates, Wellington	New Zealand
Fertility Associates, Christchurch	New Zealand
Fertility Associates, Auckland	New Zealand
Sahlgrenska University Hospital, Gothenburg	Sweden
Leuven Fertility Centre, Leuven	Belgium
Royal Women's Hospital, Melbourne	Australia
Medical School of Ribeirao Preto, Sao Paulo	Brazil
El-Khayat Clinic, Cairo	Egypt

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) and
3) With subfertility related to polycystic ovarian syndrome (PCOS) who are on ovulation induction medication and attempting to conceive (PIP-PCOS).

The PIP study: design

Design

- Pragmatic, multi-centre, randomized controlled trial
- Endometrial scratch vs. no procedure (open - label)

Eligibility

- Autologous embryo transfer (fresh or frozen)
- No disruptive instrumentation in three preceding months (e.g. hysterosalpingogram, hysteroscopy)
- No contraindication to pipelle biopsy

Sample size

Anticipated effect of endometrial scratching considered separately in two sub groups (80% power, α=0.05)

Recurrent implantation failure (≥1 prior unsuccessful embryo transfers)

- 15 percentage point difference in live birth (31% vs 16%)
- 280 women required

Non-recurrent implantation failure (no prior unsuccessful embryo transfers)

- 8 percentage point difference in live birth (33% vs 25%)
- 1002 women required

Overall target: 1300

Primary analyses performed on the whole trial population

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

Conclusion

- Luteal ES in previous cycle improves CPR in RIF in IVF cycles (better in 2 failed ET compared to 1 failed ET)
- Better effectivity seen in fresh IVF cycles vs cryo ET
- ES in IUI cycles or in women with unexplained infertility in the same cycle also offers some benefit towards CPR
- This procedure is very simple and inexpensive hence its abuse more likely & introduction of iatrogenic chronic endometritis is a real possibility with substantial procedural pain .
- More robust data with adequately powered studies are still desirable to establish the real benefit and the PIP study with adequately powered RCTs appears to throw some more light on the scratch.
- Solid evidence is needed to draw any conclusions about the benefits before adopting it as a routine procedure

Thank you