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Revisiting add-ons for assisted reproductive technology

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Outline

- What are add-ons
- Clinical IVF add-on
- Add-on in the laboratory
- Why add-ons
- When is it appropriate to use an add-on?
- Recommendations

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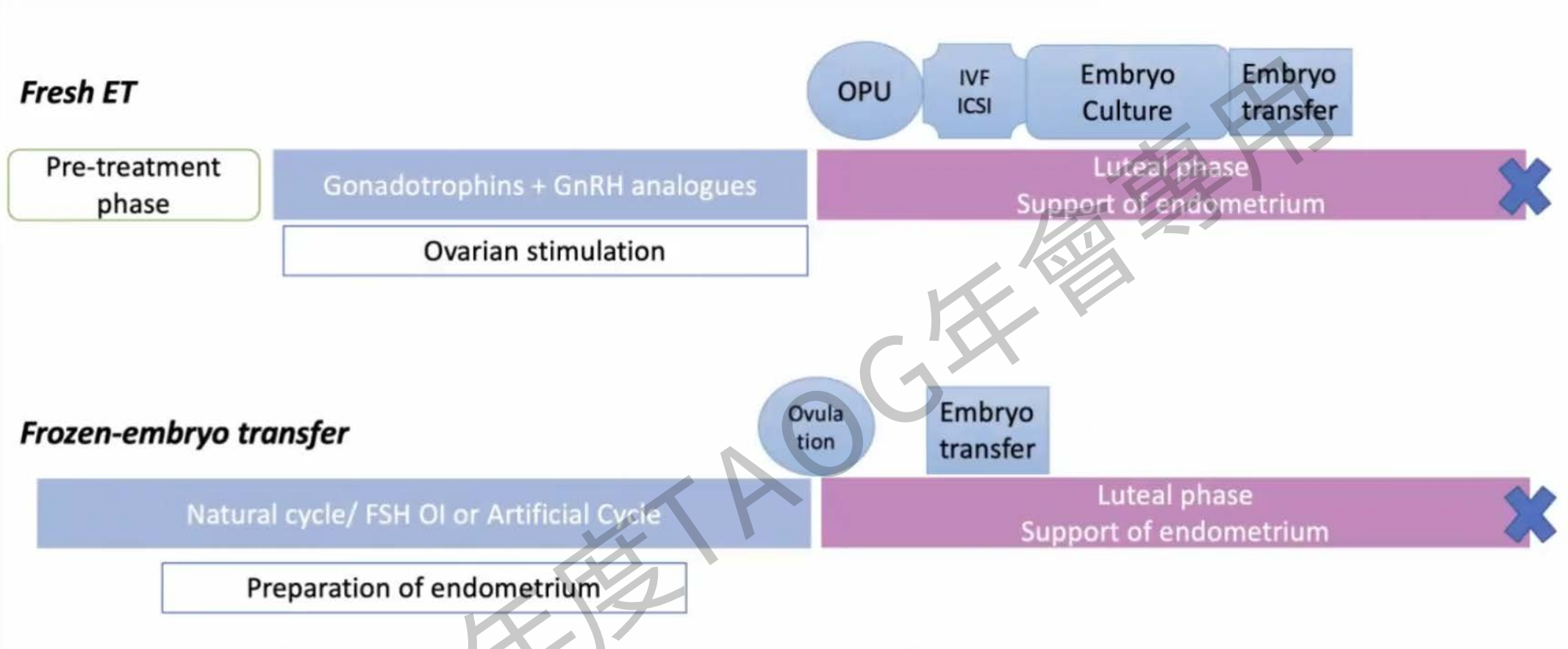
What are treatment add-ons?

- optional additional treatments, also referred to as ‘supplementary’, ‘adjuvants’ or ‘embryology treatments’
- often claim to be effective at improving the chances of having a baby (live birth rate) but the evidence to support this for most fertility patients is usually missing or not very reliable
- likely to involve an additional cost on top of the cost of a routine cycle of proven fertility treatment. Some treatment add-ons can cost hundreds or thousands of pounds each

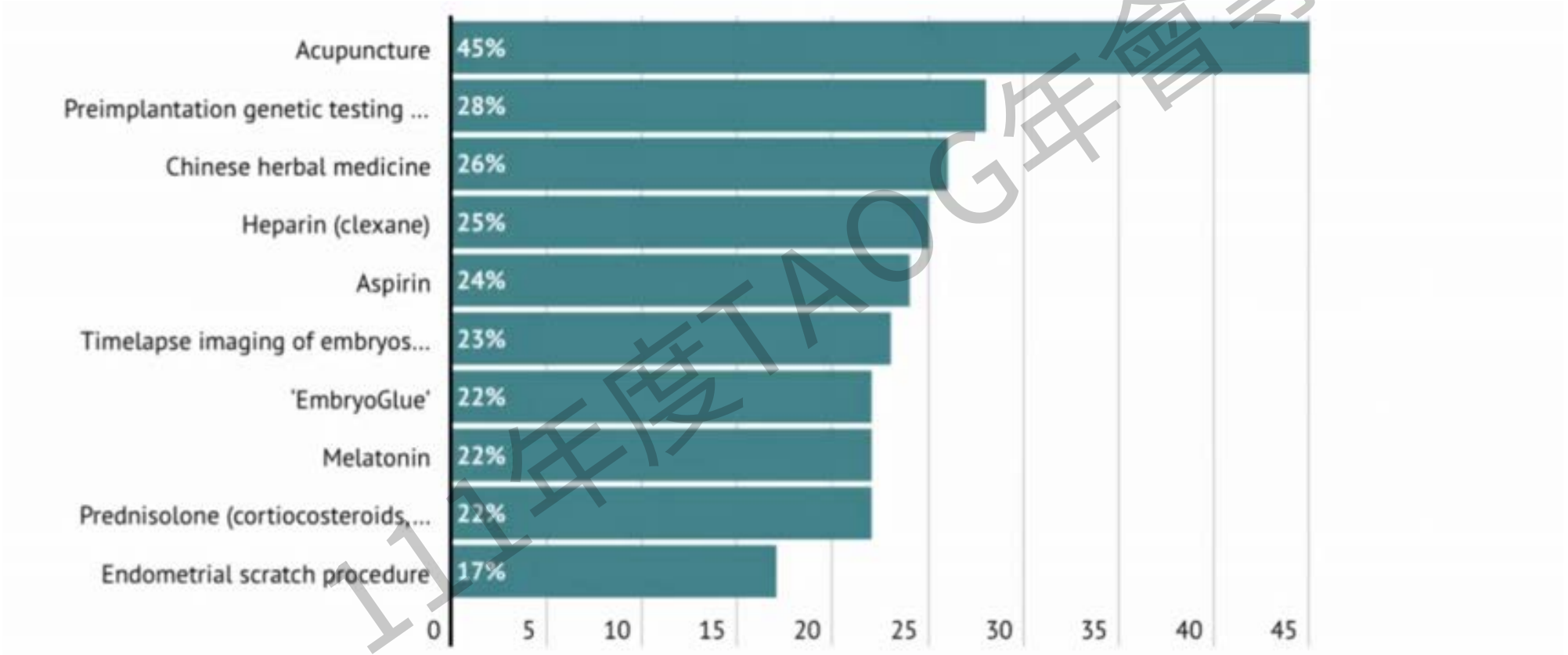


For most patients, **having routine cycles of proven fertility treatment are effective without using any treatment add-ons**

It might be more effective and/or affordable to pay for multiple routine proven treatment cycles

How common is add-on used- a national survey in Australia

Human Reproduction, Vol.36, No.7, pp. 1854–1861, 2021
Advance Access Publication on May 4, 2021 doi:10.1093/humrep/deab098



Among women having IVF in the last 3 years, 82% had used one or more IVF add-on, most commonly acupuncture, preimplantation genetic testing for aneuploidy and Chinese herbal medicine

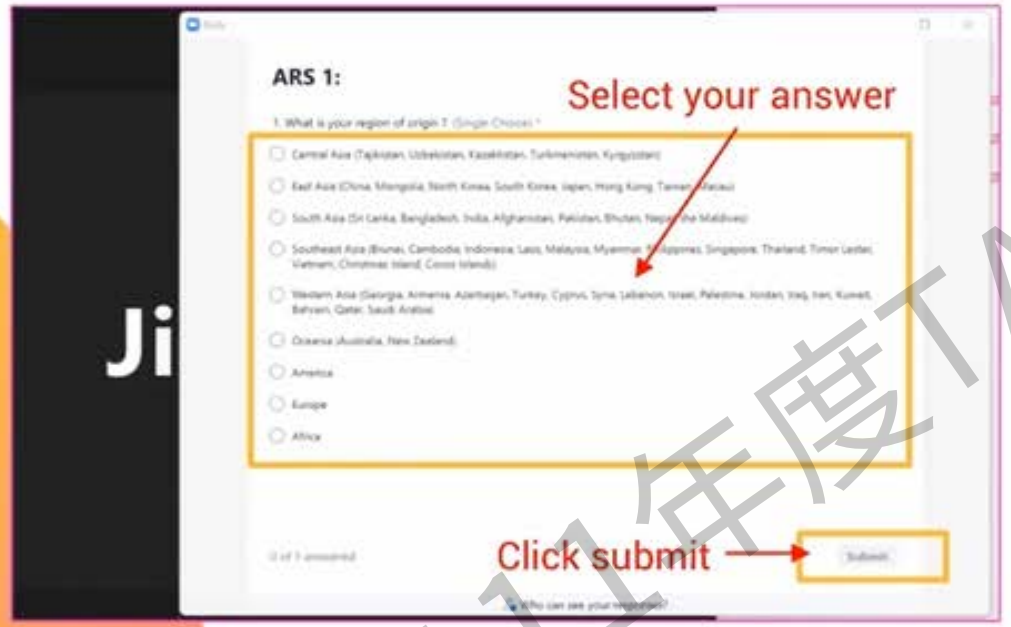
Aspire 2022

The 11th Virtual Congress of the Asia Pacific Initiative on Reproduction

Addressing the Challenges of Human Reproduction | Thursday, 28 April - Sunday, 1 May, 2022

Tell us which side are you on?

73% --> 71%



Before our expert speakers start their presentations, we would like to know which side are you on!

A poll window will appear on your screen, please vote your side and click submit.

Adding Adjuvant in Poor Responder

YES / NO

Traffic light system for add-ons

Human Fertilisation & Embryology Authority

Green - A green rated add-on has **more than one high quality RCT** which shows that the procedure is effective at improving the chances of having a baby for most fertility patients. These treatment add-ons may be routinely used in fertility treatments and information on these can be found elsewhere on our website, for example the use of **intracytoplasmic sperm injection (ICSI)** if the cause of infertility is sperm related. Therefore, green rated add-ons will not be included in this review list.

Amber - We give an amber symbol for an add-on where there is **conflicting evidence from RCTs** to show that an add-on is effective at improving the chances of having a baby for most fertility patients. This means that the evidence is not conclusive and further research is required, and the add-on should not be recommended for routine use.

Red - We give a red symbol for an add-on where there is **no evidence from RCTs** to show that it is effective at improving the chances of having a baby for most fertility patients.

HFEA has been concerned about add-ons being mis-sold "for a number of years“

HFEA created a “traffic light” system rating different treatments based on expert reviews of the scientific evidence to make it easier to understand the scientific evidence for each treatment add-on.

Clinical adjuncts in in vitro fertilization: a growing list

Mohan S. Kamath, M.S.,[a] Mariano Mascarenhas, M.S.,[b] Sebastian Franik, M.D.,[c] Emily Liu, F.R.A.N.Z.C.O.G.,[d] and Sesh Kamal Sunkara, M.D.[e]

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Clinical IVF add-ons (1)

- **SCREENING HYSTEROSCOPY**: it may benefit a select group of women who have had one or more unsuccessful IVF attempts and a history of difficult embryo transfers.
- **STIMULATION REGIMENS**

1. **DHEA**: possible beneficial effect in poor responders (75 mg, 3M),current evidence is too inconsistent to draw any firm conclusions on the beneficial effect of DHEA for poor responders undergoing IVF.

2.**Testosterone**: possible beneficial effect in poor responders, testosterone pretreatment has not been proven to be beneficial for poor responders, and evidence from larger ongoing RCTs is awaited

3.**Growth Hormone**: lack of strong evidence to support the use of adjuvant GH in ART. Furthermore, there is no agreement on the dosage and length of GH administration, which have varied among the studies.

4.**Aspirin**: low-dose aspirin is widely used in contemporary clinical practice, even though there is no proven efficacy for routine use of aspirin as an adjuvant in IVF treatment. The safety data remain limited in this field, and current evidence does not exclude the possibility of adverse effects.

Clinical IVF add-ons (2)

- **Heparin**: heparin may have a benefit in women with RIF in whom thrombophilia is identified, but this needs to be carefully considered and balanced against the potential side effects and cost.
- **Antioxidants for the Female Partner:** the cost of antioxidants varies greatly due to different proprietary formulations. No published studies have investigated the cost-effectiveness of antioxidant use for female subfertility before IVF.
- **Antioxidants for the male Partner:** the current evidence is of low quality due to small study sizes and the high risk of bias due to poor reporting of methods.
- **PLATELET-RICH PLASMA:** option for improving endometrium thickness (RCT, CPR increase in RIF) and ovarian reserve (no RCTs), Currently, the use of PRP in reproductive medicine should be considered experimental**.**

Summary of evidence for use of add-ons in clinical practice for in vitro fertilization (1)

Intervention	Description	Evidence	Quality of evidence	Summary of evidence
Screening hysteroscopy	Absence of identifiable pathology on transvaginal ultrasound	Significantly higher LBR (RR 1.26; 6 RCTs, n =2,745). only high-quality trials were included, no significant difference in LBR (RR 0.99; 2 RCTs, n =1452)	Low	AMBER 
DHEA	Androgen prehormone Given orally as pretreatment before IVF	Statistically significant higher composite outcome of LBR/OPR (OR 1.81; 8 RCTs, n =878); difference no longer statistically significant after excluding studies at high risk of bias (OR 1.50;; 5 RCTs, n = 306)	Moderate	AMBER 
Testosterone	Androgen administered as patches or gel before IVF	Statistically significantly higher LBR (OR 2.60; 4 RCTs, n =345); difference was no longer statistically significant after excluding studies at high risk of bias (OR 2.00; 95% CI, 0.17–23.49; 1 RCT, n = 53)	Moderate	AMBER 

(Fertil Steril 2019;112:978–86)

Summary of evidence for use of add-ons in clinical practice for in vitro fertilization (2)

Intervention	Description	Evidence	Quality of evidence	Summary of evidence
Growth hormone	Hormone used as adjunct in poor responder population	Statistically significantly higher LBR (RR 1.73; 95% CI, 1.25–2.40; 9 RCTs, n =562) Statistically significantly higher LBR (OR 5.39; 95% CI, 1.89–15.35; 4 RCTs, n =165)	Very low Not available	Amber 
Aspirin	Nonsteroidal Anti-inflammatory agent	No statistically significant difference in LBR (RR 0.91; 95% CI, 0.72–1.15; 3 RCTs, n = 1053)	Moderate	Red 
Heparin	Antithrombotic agent	No statistically significant difference in LBR (RR 1.13; 95% CI, 0.99–1.43; 4 trials, n =776) Statistically significantly higher LBR (OR 1.77; 95% CI, 1.07–2.90; 3 RCTs, n = 386)	Moderate Very low	Red 

(Fertil Steril 2019;112:978–86)

Summary of evidence for use of add-ons in clinical practice for in vitro fertilization (3)

Intervention	Description	Evidence	Quality of evidence	Summary of evidence
Antioxidants for female partner	Biochemical compounds given as single or combined therapy before IVF	No statistically significant difference in LBR (OR 1.21; 95% CI, 0.69–2.11; 4 RCTs, n =230)	Not available	Red 
Antioxidants for male partner	Biochemical compounds given as single or combined therapy before IVF	Statistically significantly higher LBR (Peto OR 3.61; 95% CI, 1.27–10.29; 2 RCTs, n=90)	Not available	Amber 
Platelet rich plasma	Intrauterine infusion in women with thin endometrium or RIF	No statistically significant difference in OPR (33.3% vs. 18.2%; P1⁄4.260; n =83) Statistically significantly higher CPR (53.3% vs. 24.4%; OR 3.63; 95% CI, 1.48–8.90)	Not applicable	Amber 

(Fertil Steril 2019;112:978–86)

From: The efficacy of add-ons: selected IVF "add-on" procedures and future directions

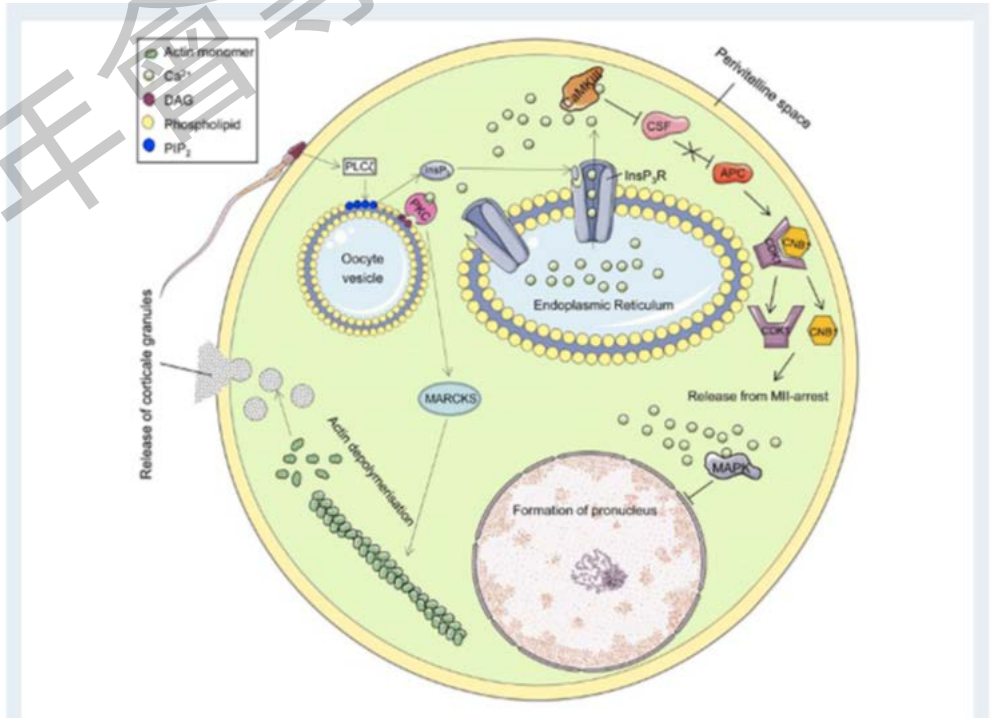
Add-on	HFEA Rating	Current Evidence (Cochrane Review or Best Available)	Quality of Evidence	Cost*
Time-lapse imaging (TLI)	Amber	No advantage or disadvantage in pregnancy rate (PR), live birth rate (LBR), or miscarriage rate	Low to very low	
Assisted hatching (AH)	Red	May slightly improve PR	Low to very low	$$
EmbryoGlue	Amber	Slightly improves PR and LBR	Moderate	$$
Sperm DNA fragmentation testing	None	Poorly predictive of pregnancy outcomes when administered to all patients	Unclear	$$
Artificial oocyte activation (AOA)	Amber	Improves PR and LBR	Low to moderate	$$
Endometrial receptivity assay (ERA)	Red	No advantage or disadvantage in PR	Low	$$
Physiological ICSI (PICSI)	Red	No advantage or disadvantage in LBR	Low	$
Preimplantation genetic testing for aneuploidies (PGT-A)	Red	No advantage or disadvantage in cumulative LBR, LBR after first embryo transfer, or miscarriage rate with polar body biopsy or with use of FISH for genetic analysis (*Cochrane review does not comment on outcomes after blastocyst biopsy or next-generation sequencing*)	Low to moderate	$$$
Intrauterine/Intravaginal culture	Red	No improvement in LBR	Low to very low	$$$
Intracytoplasmic morphologic sperm injection (IMSI)	Red	Uncertain if this intervention improves PR and LBR, or decreases miscarriage rates	Very low	$
Immunological tests and treatments (steroids, intralipids, IVIG, TNF-α blockers)	Red	No evidence supports the use of these agents in improving LBR; patients may experience significant adverse effects	Low to very low	$$
Endometrial Scratching	Amber	Unclear effect on PR or LBR, no impact on miscarriage rate	Moderate	$
Elective freeze all cycles	Amber	May increase PR and LBR; reduces risk of ovarian hyperstimulation syndrome	Moderate	$$

Journal of Assisted Reproduction and Genetics (2022) 39:581–589

Artificial oocyte activation

Artificial egg activation calcium ionophore is rated amber because there is conflicting evidence from randomised controlled trials (RCTs) to show that it is effective at improving the chances of having a baby for patients that are eligible to undergo this treatment.

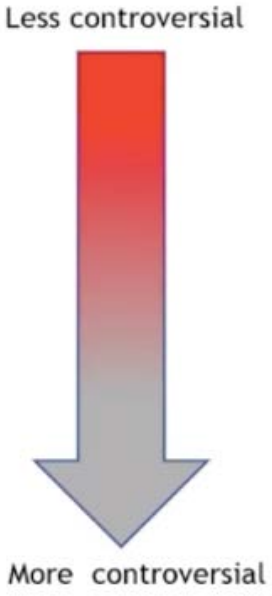
- The incidence of total fertilization failure after ICSI is 1–5% .
- ICSI using mature sperm, round spermatids and globozoospermia, artificial oocyte activation may provide a means of improving fertilization rates in such cases.
- AOA can rescue cycles showing severe male factor infertility, deficient oocyte maturation (Kim et al., 2015), developmental problems, or both.
- Systemic reviews of RCTs concluded that there is insufficient clinical evidence to recommend its use in practice
- The process of oocyte activation is thought to ultimately influence normal embryo development, epigenetic imprinting and pregnancy outcome
- The HFEA state that oocyte activation with calcium ionophores may improve fertilization rates in ICSI cycles where failed fertilization has previous been observed.
- No RCTs to demonstrate that it is effective or follow up studies on the safety of this technique



Clinical prospects for AOA and oocyte activation

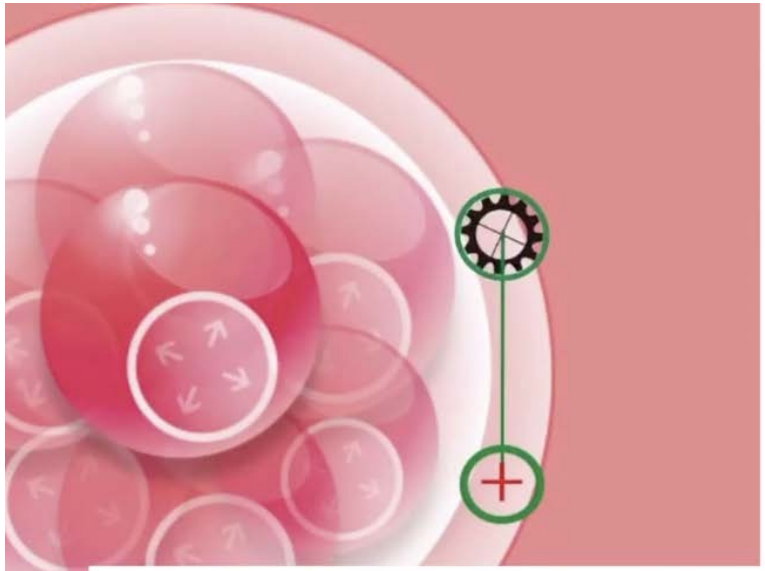
Indications for assisted oocyte activation (AOA)

- Repeated cycles with ICSI failure due to sperm defects
- Primary prevention (e.g. TESE, globozoospermia)
- Rescue AOA (6-20h post-ICSI)
- Repeated cycles with poor embryo development



ASSISTED HATCHING

Assisted hatching is rated red because there is no evidence from randomised controlled trials (RCTs) to show that it is effective at improving the chances of having a baby for most fertility patients.



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Cochrane Database of Systematic Reviews

Published:
12 December 2012

Authors:
Carney S-K, Das S, Blake D, Farquhar C, Seif MM, Nelson L

Primary Review Group:
Gynaecology and Fertility Group

Assisted hatching of fertilised eggs to improve the chances of pregnancy in assisted conception (IVF and ICSI)

- Potential clinical application
  - PGT-A/ PGT-M
  - Thick zona pellucida
  - Advanced maternal age
  - Elevated FSH levels
  - Embryo frozen-thaw cycles
  - Recurrent embryo implantation failure
- Risks
  - Damage to individual blastomeres
  - Increased risk of monozygotic twins

Elective freeze all cycles

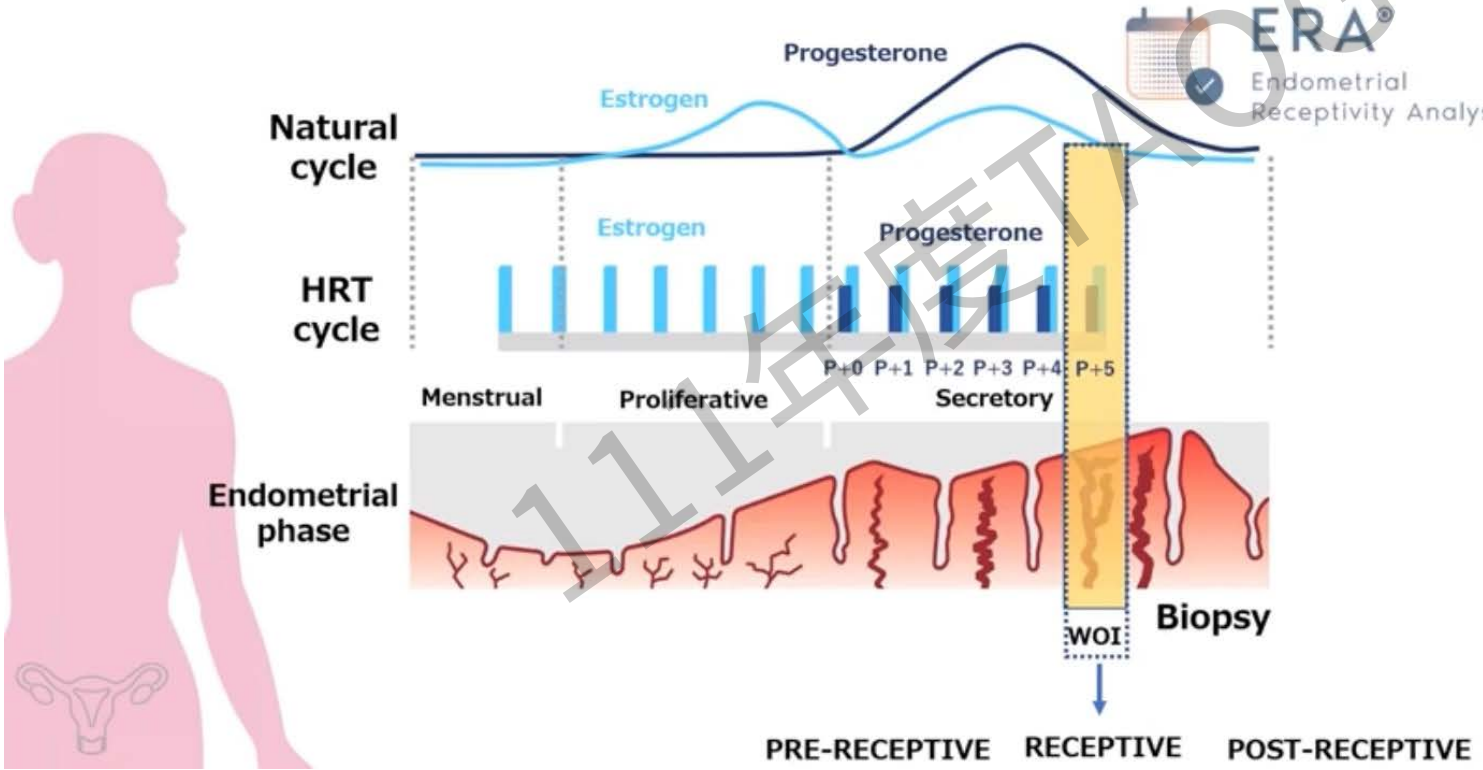
Elective freeze all cycles is rated amber because there is conflicting evidence from randomised controlled trials (RCTs) to show that it is effective at improving the chances of having a baby for most fertility patients.

- Elective freeze all cycles involve creating embryos using IVF or ICSI and then choosing to freeze them all
- Useful in some selected cases
  - Prevention of OHSS
  - Thin EM
  - Elevated progesterone level in follicular phase
  - PGT patients
- Disadvantages
  - Cost
  - Damage of the embryos
  - Obstetric and neonatal complications

Endometrial Receptivity Array (ERA)

The use of ERA as part of fertility treatment in healthy patients is rated red. This is because there is no evidence from randomised controlled trials (RCTs) to show that they are effective at improving the chances of having a baby for most fertility patients.

- A diagnostic tool to identify the window of implantation
- Based on the expression of 238 genes to determine when the endometrium is receptive



> Endometrial biopsy at progesterone +5 days

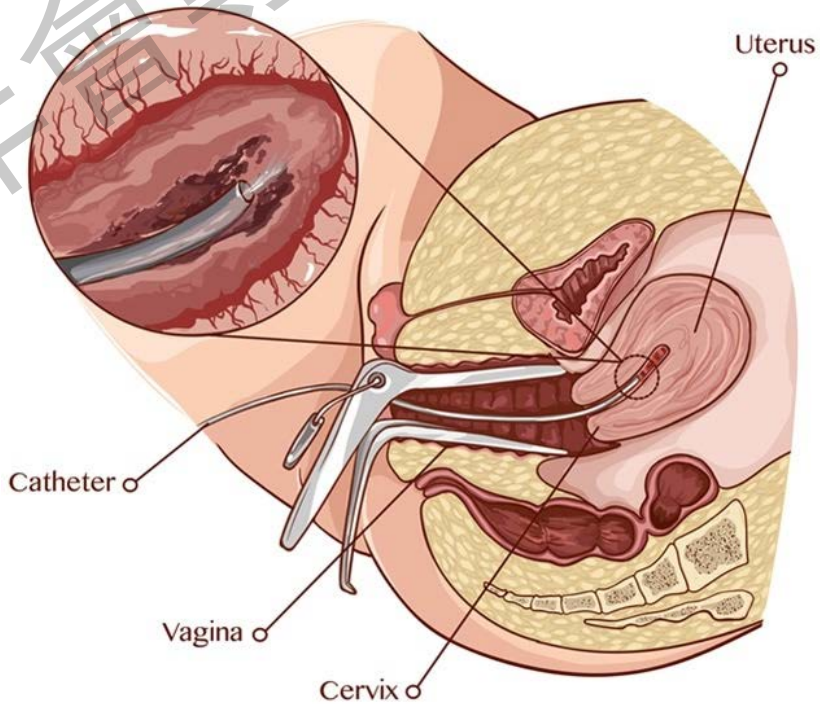
> RNA sequencing by NGS

> High reproducibility (~3 years)

Endometrial scratching

Endometrial scratching is rated amber because there is conflicting evidence from randomised controlled trials (RCTs) to show that it is effective at improving the chances of having a baby for most fertility patients.

- Endometrial scratching, also known as endometrial injury, is carried out before IVF
- The theory is that this procedure triggers the body to repair the site of the scratch, releasing chemicals and hormones that make the endometrium more receptive to an embryo implanting.
- Some also suggest the treatment may activate genes that make the endometrium more receptive to an embryo implanting.
- Conflicting results
- Pain, blood loss, infection

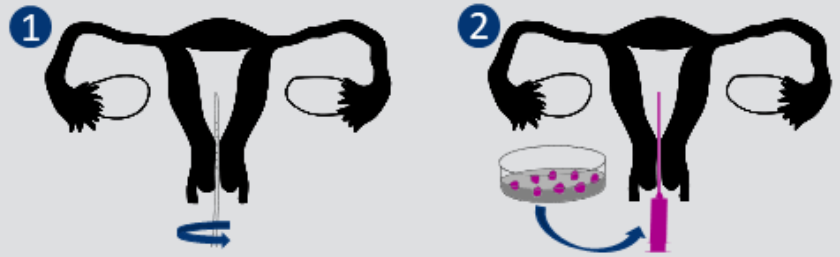


Endometrial injury in IVF

An Emory University collaboration with Cochrane

Is endometrial injury prior to embryo transfer safe and effective in women undergoing IVF?

Background



Some research suggests that scratching the endometrium (1) before embryo implantation (2) increases the chance of pregnancy in women undergoing IVF.

Outcomes

Effect unclear:

Live birth rate
IVF = 27%
with endometrial injury = 27-32%

Clinical pregnancy
IVF = 32%
with endometrial injury = 31-37%

Little to no difference in effect

Endometrial injury does not appear to affect the chance of having a **miscarriage** from IVF.

Associated with *mild to moderate pain* and some minimal bleeding

Methods

Literature search of randomized controlled trials (RCTs) comparing endometrial injury to no intervention or sham procedure.

38 RCTs → Bias analysis → 8 used for primary analysis ✓

Limitations

- Small sample sizes (median sample size = 157)
- Most studies excluded from primary analysis due to poor quality and high risk of bias
- Unable to assess bleeding and pain as these outcomes were collected only in the intervention arm for most studies

The effect of endometrial injury on live birth and clinical pregnancy among women undergoing IVF *is unclear*. Evidence *does not support* the routine use of endometrial injury for women undergoing IVF.

Lensen SF, Armstrong S, Gibreel A, Nastri CO, Raine-Fenning N, Martins WP. Endometrial injury in women undergoing in vitro fertilisation (IVF). Cochrane Database of Systematic Reviews 2021, Issue 6. Art. No.: CD009517. Visual reviewed by Cochrane Gynaecology and Fertility | @CochraneCGF

Aug 2021

Creators: Arielle Valdez-Sinon, PhD, MS4 | @ariellevaldez
Rachel Fried, MS4 | @RachelFried6
Editor: Caroline Coleman, MD | @cg_coleman

Hyaluronate enriched medium (e.g. EmbryoGlue)

Amber

Hyaluronate enriched medium is rated amber because there is conflicting evidence from randomised controlled trials (RCTs) to show that it is effective at improving the chances of having a baby for most fertility patients.

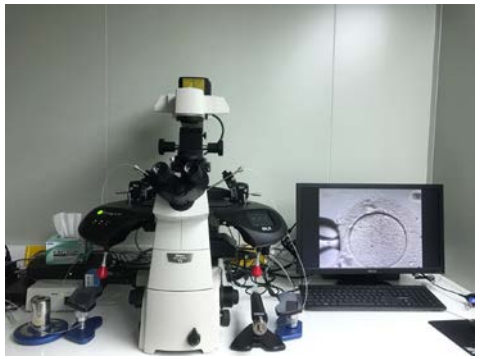
- Use of a specific embryo transfer (ET) medium enriched with the glycoprotein (HA)
- HA is naturally present in the female reproductive tract and endometrium and forms a viscous solution which could enhance the ET process and avoid embryo expulsion
- Cochrane (17 RCTS) moderate quality evidence for an improvement in CPR and LBA, with an associated increase multiple pregnancy rate (Bonlekoe et.al 2014)
- The published evidence may be suggestive of a beneficial effect of the use of HA supplemented ET media, but further high-quality studies are needed
- Further RCTs are needed to evaluate the efficacy of HA as an adherence compound during ET with respect to eSET and the possibility of reducing the multiple pregnancy rate

Immunological tests and treatment for fertility

The use of immunological tests and treatments as part of fertility treatment in healthy patients is rated red. This is because there is no evidence from randomised controlled trials (RCTs) to show that they are effective at improving the chances of having a baby for most fertility patients.

- Steroid
- Intralipids
- Intravenous immunoglobulin (IVIG)
- TNF-alpha blocking agents (TNF-alpha inhibitors) e.g. infliximab, adalimumab, etanercept

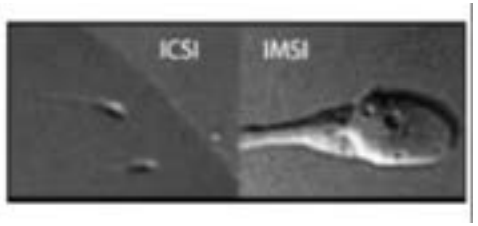
Advanced sperm selection techniques



- Methods to select healthy, mature, and genetically normal sperm for fertilization in the expectation that this will improve the outcomes of traditional IVF or ICSI treatments.

RIGIO introduces HBA and PICSI - YouTube
utube.com

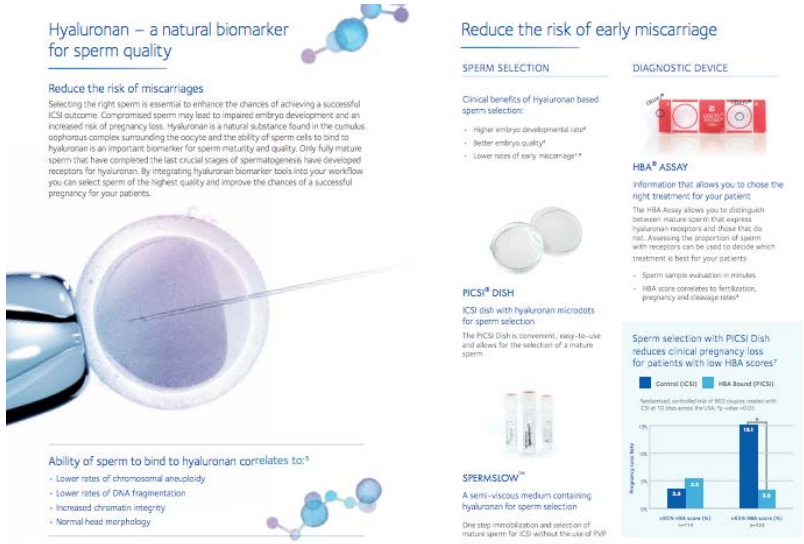
- **PICSI**: co-incubation of sperm with HA to better identify the sperm for ICSI. Sperm which express receptors to bind to HA have better morphology and motility as well as low rate of sperm DNA fragmentation and better chromatin structure. **Cochrane review**: little or no effect on LBR or CPR but may reduce miscarriage .



- **IMSI:** motile sperm organellar morphology examination under higher magnification **(6000 to 13000)** to define the quality. Disadvantage: length of time required to examine and select spermatozoa. **Cochrane review**: no improvement in CPR, LBR, or miscarriage rate with IMSI when compared with routine ICSI.

Physiological intracytoplasmic sperm injection (PICSI)

PICSI is rated red because there is no evidence from randomised controlled trials (RCTs) to show that it is effective at improving the chances of having a baby for most fertility patients.



CORRESPONDENCE | VOLUME 394, ISSUE 10206, P1319-1320, OCTOBER 12, 2019

Hyaluronan-selected sperm should not be considered an add-on

Lodovico Parmegiani

Published: October 12, 2019 • DOI: https://doi.org/10.1016/S0140-6736(19)31245-0

Physiological, hyaluronan-selected intracytoplasmic sperm injection for infertility treatment (HABSelect): a parallel, two-group, randomised trial

David Miller, Susan Pavitt, Vinay Sharma, Gordon Forbes, Richard Hooper, Siladitya Bhattacharya, Jackson Kirkman-Brown, Arri Coomarasamy, Sheena Lewis, Rachel Cutting, Daniel Brison, Allan Pacey, Robert West, Kate Brian, Darren Griffin, Yakoub Khalaf

	PICSI	ICSI	Absolute difference (95% CI)	Odds ratio (95% CI)	p value
Term livebirth					
Primary analysis*	27·4% (379/1381)	25·2% (346/1371)	2·2% (−1·1 to 5·5)	1·12 (0·95 to 1·34)	0·18
Sensitivity analysis†	27·5% (379/1379)	25·3% (346/1370)	2·2% (−1·1 to 5·5)	1·13 (0·95 to 1·34)	0·17
Secondary endpoints					
Clinical pregnancy	35·2% (487/1382)	35·7% (491/1375)	−0·5% (−4·0 to 3·1)	0·98 (0·84 to 1·15)	0·80
Miscarriage	4·3% (60/1381)	7·0% (96/1371)	−2·7% (−4·4 to −0·9)	0·61 (0·43 to 0·84)	0·003
Premature birth	3·3% (46/1381)	3·3% (45/1371)	0·0% (−1·3 to 1·4)	1·02 (0·67 to 1·55)	0·94
Exploratory endpoints					
Fertilisation rate (%)‡	66% (24·0)	69% (24·0)	3·0% (−0·47 to 6·5)	1·15 (0·98 to 1·34)	0·09
Biochemical pregnancy	39·5% (546/1383)	39·5% (544/1377)	0·0% (−4·0 to 4·0)	1·00 (0·86 to 1·17)	0·99

Data are % (n/N), unless otherwise stated. PICSI=physiological intracytoplasmic sperm injection. ICSI=intracytoplasmic sperm injection. *Adjusted for maternal age, previous miscarriage, and hormonal indicators of ovarian reserve. †Adjusted for hyaluronan-sperm binding score, maternal age, previous miscarriage, and hormonal indicators of ovarian reserve. Odds ratios are shown alongside absolute differences. ‡Data are mean (SD); denominators were 1386 for the PICSI group and 1380 for the ICSI group.

Table 3: **Trial outcomes**

***Lancet* 2019; 393: 416–22**

Intracytoplasmic morphologic sperm injection (IMSI)

IMSI is rated red because there is no evidence from randomised controlled trials (RCTs) to show that it is effective at improving the chances of having a baby for most fertility patients.

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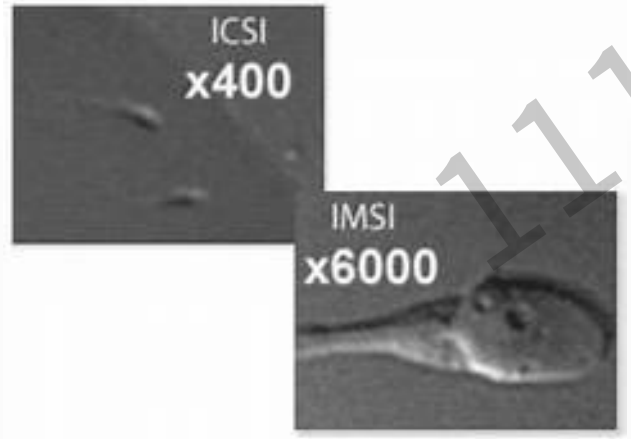
Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction

Danielle M Teixeira, Andre H Miyague, Mariana AP Barbosa, Paula A Navarro, Nick Raine-Fenning, Carolina O Nastri, Wellington P Martins Authors' declarations of interest

Version published: 21 February 2020 Version history
https://doi.org/10.1002/14651858.CD010167.pub3



Regular (ICSI) compared with ultra-high magnification (IMSI) for assisted reproduction

Patient or population: couples undergoing assisted reproduction treatment

Setting: fertility clinics

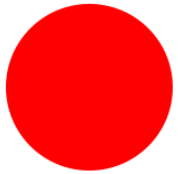
Intervention: sperm selection under ultra-high magnification (IMSI)

Comparison: sperm selection under regular magnification (ICSI)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk ICSI	Corresponding risk IMSI			
Live birth per allocated couple	243 per 1000	269 per 1000 (216 to 337)	RR 1.11 (0.89 to 1.39)	929 (5 studies)	⊕⊖⊖⊖ very low[a,b]
Miscarriage per allocated couple	70 per 1000	75 per 1000 (54 to 103)	RR 1.07 (0.78 to 1.48)	2297 (10 studies)	⊕⊖⊖⊖ very low[b,c]
Miscarriage per clinical pregnancy	230 per 1000	207 per 1000 (157 to 276)	RR 0.90 (0.68 to 1.20)	783 (10 studies)	⊕⊖⊖⊖ very low[b,c]
Clinical pregnancy per allocated couple	320 per 1000	394 per 1000 (355 to 438)	RR 1.23 (1.11 to 1.37)	2775 (13 studies)	⊕⊖⊖⊖ very low[c,d,e]
Congenital abnormalities per live birth	No studies reported on this outcome				

- **Pros and Cons of IMSI**
- **According to reports, the success rate of IMSI is 66% and that of normal sperm injection is 33%. There are some advantages to IMSI:**
- This technique doubles the pregnancy rate lowering the abortion rate by 60%.
- In this case, normal sperm is selected lowering the chances of miscarriage.
- It helps to determine fertility hence enhancing fertility and pregnancy rates.
- **IMSI has a lot of disadvantages, which includes:**
- It is a time taking and expensive process.
- Leads to multiple pregnancies when compared to ICSI.

Pre-implantation genetic testing for aneuploidy (PGT-A)



PGT-A for day five embryos is rated red because there is no evidence from randomised controlled trials (RCTs) to show that it is effective at improving the chances of having a baby for most fertility patients.

The value of the universal application of PGT-A to all patients is currently unclear and is often recommended in selected populations, such as:

- Couples with unexplained recurrent pregnancy loss or those with recurrent aneuploidy in their miscarriages
- Repeated implantation failure during IVF cycles
- Men with severe male factor infertility
- Couples already undergoing PGD testing
- Couples undergoing IVF who desire single embryo transfer

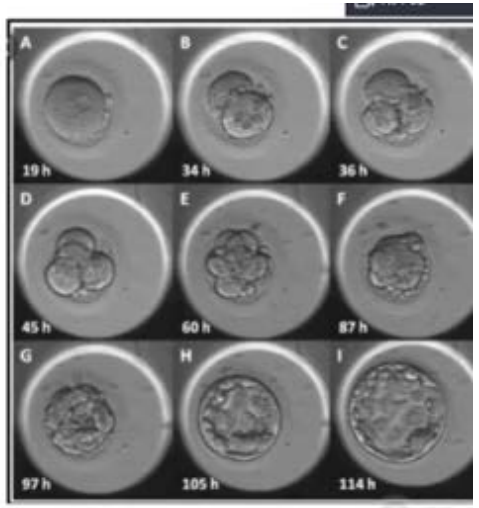
However, clear evidence for limiting PGS to these groups is lacking

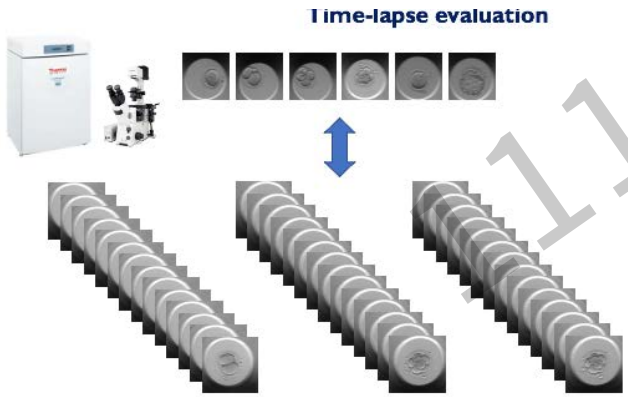
Risks associated with preimplantation genetic testing

- Physical damage to embryos from biopsy
  - No current evidence for resultant anatomic deformities
  - Cleavage stage biopsy is associated with deleterious effects on the embryo, including developmental lag and increased rates of embryonic death before uterine implantation
- Biological misdiagnosis
  - Mosaicism
- Methodological misdiagnosis
  - Allele drop-out
  - Amplification errors
  - Hybridization errors
- Technological misdiagnosis Human error
- Unknown risks
- Because preimplantation genetic testing is a relatively new and emerging technology, deleterious effects of embryo biopsy, especially those related to late onset disorders, may not be evident until children born as a result of this technology become older

Time-lapse imaging

Time-lapse incubation and imaging is rated amber because there is conflicting evidence from randomised controlled trials (RCTs) to show that it is effective at improving the chances of having a baby for most fertility patients.



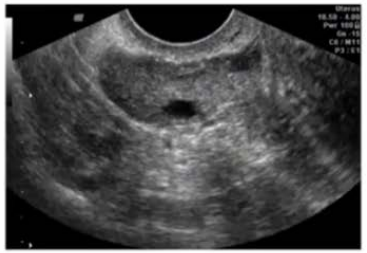


- Taking pictures over time and reviewing them as a film
- Prediction models using information from different embryo cleavage timing and patterns (Meseguer et.al 2011, Peterson et al.2016)
- Usefulness TL imaging in IVF: not missing important events during culture , Q.C, teaching applications , more information to the patients and an increase in LBR.
- Insufficient good quality evidence of differences in LBR or OPR, miscarriage and stillbirth, or CPR to choose between TLS, with or without selection software (AI), and convention incubator(Cochrane 2019)
- More RCT are needed to distinguish whether there are clinical benefit for embryo selection algorithms based on TL information leading to an increase LBR and whether there are benefits from uninterrupted embryo culture (Armstrong et.al 2014)

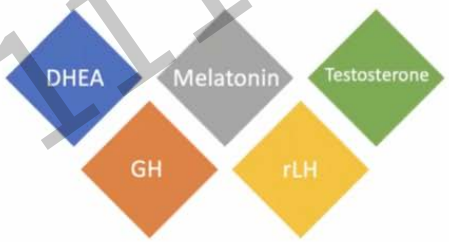
Traffic light rating	Definition	Add-ons currently under this rating
Red	No evidence to show that it is effective and safe	Assisted hatching PGS (day 3) IMSI PICSI Intrauterine culture Reproductive immunology tests and treatment
Amber	There is a conflicting body of evidence for this add-on, further research is required	Artificial egg activation calcium ionophore Elective freeze all cycles Embryo glue Endometrial scratching PGS (Day 5) Time-lapse imaging
Green	There is more than one good quality RCT which shows that the procedure is effective and safe	None

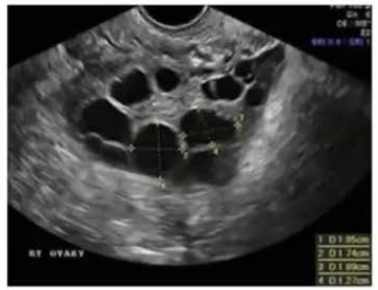
Reasons why so many add-ons in ART?

- Informations from internet, hearsay from others, ….
- It may help, worth a try
- There is some evidence for it
- The “nothing to lose” mentality, no real harm
- Doctors and patients want to try something different
  - It could give p’t hope to continue the journey
- A reason to try one more time, it can keep p’t in the clinic
- ……



Interventions proposed





To improve oocyte/embryo quality and quantity

(Modified from Dr. Venetis in Taiwan Life Conference 2022)

Reasons why not adding an adjuvant

- It doesn't work
  - Clinical perspective
    - Critical appraisal of clinical trials- quality, design, power, bias, analysis…
  - Scientific perspective
    - Adjuvant and main-stream treatment
  - Pathophysiological perspective
- It may cause harm
  - Financial, doctor-patient trust, reputation, practice…
- It is a slippery slope

Modified from Prof TC Li, Aspire 2002

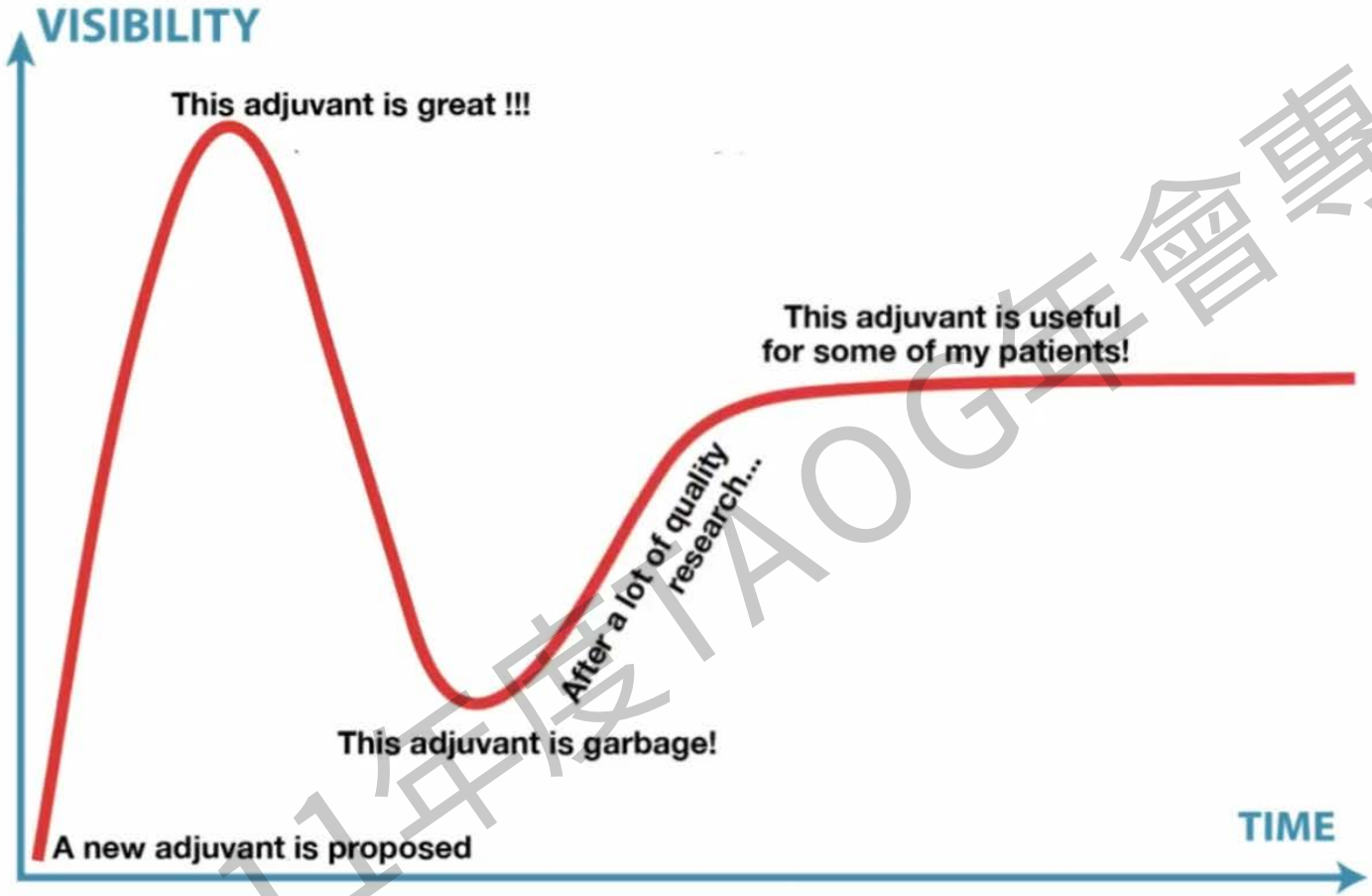
Recommendations for using an add-on

- Choose one with the least adverse effects
- Be a responsible practitioner
- Be honest with your patients
- Avoid an expensive adjuvant
- Take steps to minimize medico-legal liability
- Other options?

The practice of medicine is a mixture of science and art
It is dangerous without science yet boring without art

Modified from Prof TC Li, Aspire 2002

Relax and keep the research going

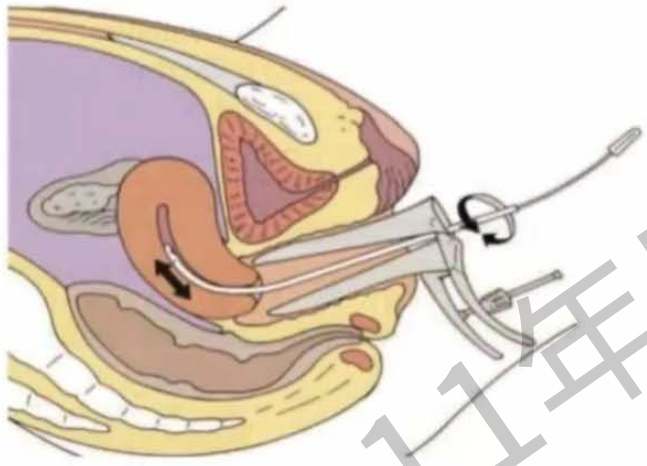


For example:
Endometrial scratching
ERA

(from Dr. Venetis in Taiwan Life Conference 2022)

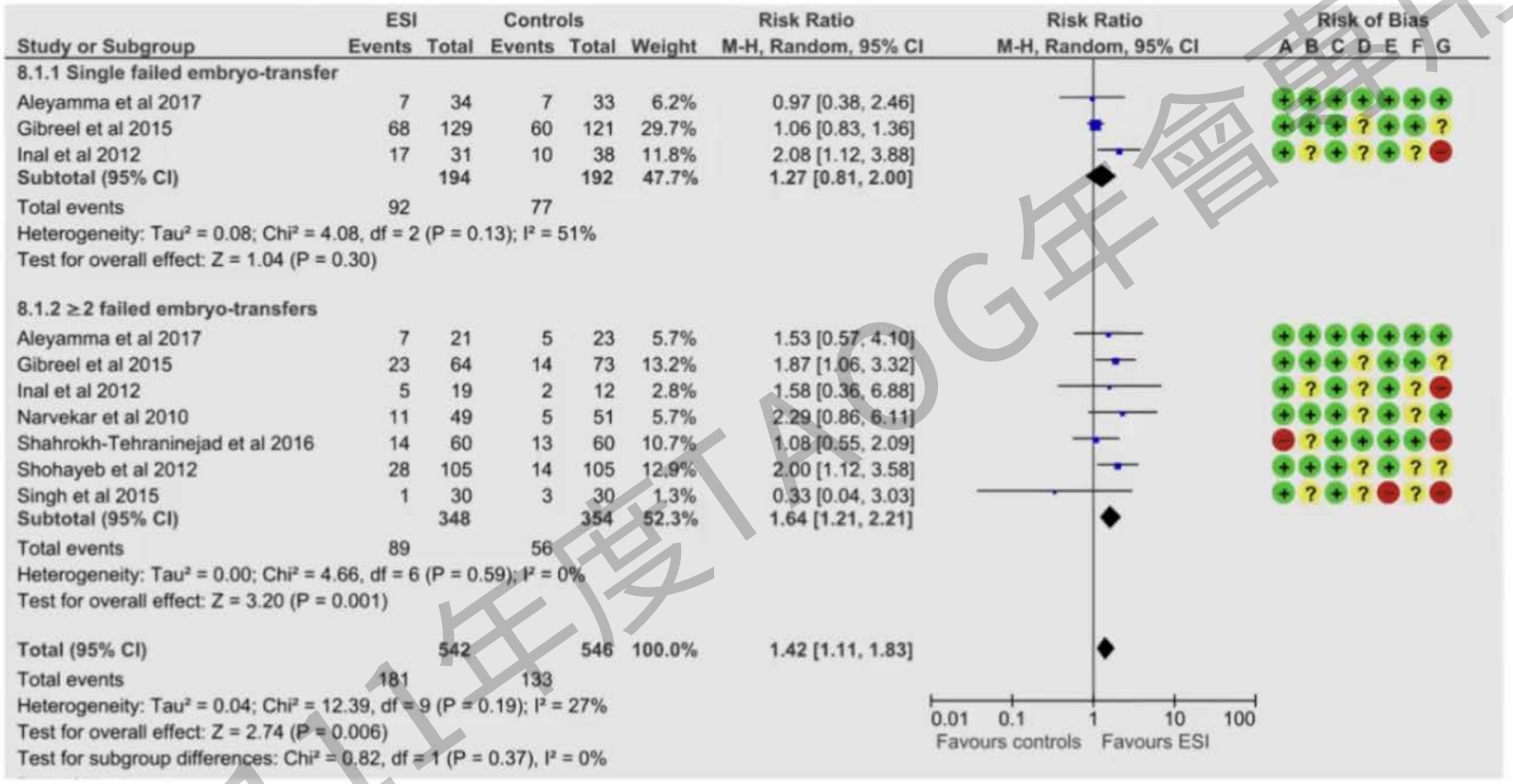
Endometrial scratch

ENDOMETRIAL SCRATCH



- Discovered by accident in RIF patients
- Multiple RCTs with conflicting results
- Different methods of the intervention
- Multiple meta-analyses
- For years, thousands of patients have been subjected to endometrial scratching

Endometrial Scratching in RIF

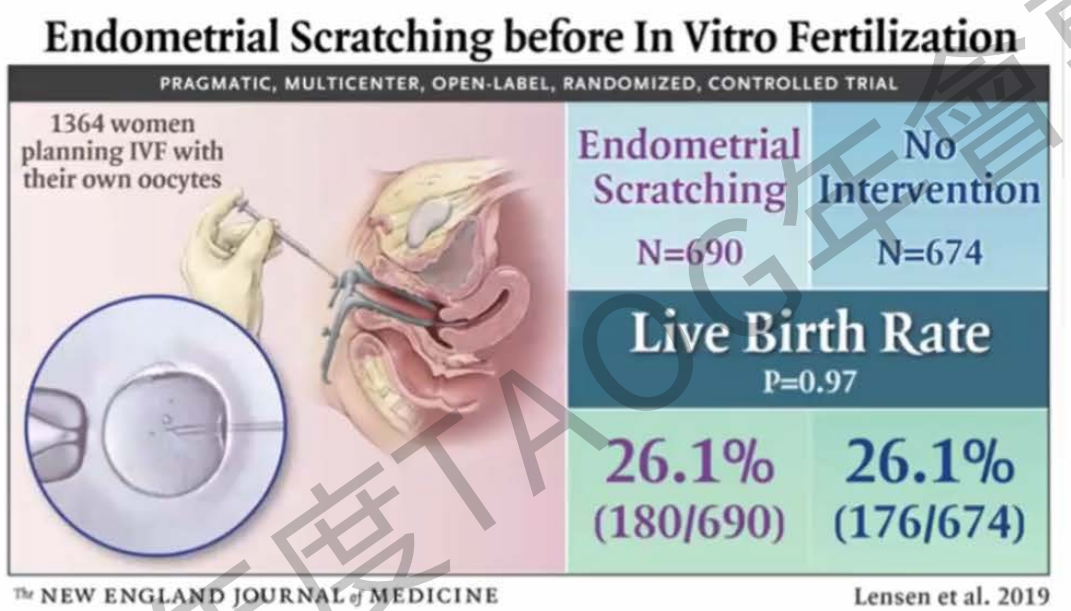


Study or Subgroup	ESI Events	ESI Total	Controls Events	Controls Total	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 Single failed embryo-transfer						
Aleyamma et al 2017	7	34	7	33	6.2%	0.97 [0.38, 2.46]
Gibreel et al 2015	68	129	60	121	29.7%	1.06 [0.83, 1.36]
Inal et al 2012	17	31	10	38	11.8%	2.08 [1.12, 3.88]
Subtotal (95% CI)		**194**		**192**	**47.7%**	**1.27 [0.81, 2.00]**
Total events	92		77			
Heterogeneity: Tau² = 0.08; Chi² = 4.08, df = 2 (P = 0.13); I² = 51%						
Test for overall effect: Z = 1.04 (P = 0.30)						
8.1.2 ≥2 failed embryo-transfers						
Aleyamma et al 2017	7	21	5	23	5.7%	1.53 [0.57, 4.10]
Gibreel et al 2015	23	64	14	73	13.2%	1.87 [1.06, 3.32]
Inal et al 2012	5	19	2	12	2.8%	1.58 [0.36, 6.88]
Narvekar et al 2010	11	49	5	51	5.7%	2.29 [0.86, 6.11]
Shahrokh-Tehraninejad et al 2016	14	60	13	60	10.7%	1.08 [0.55, 2.09]
Shohayeb et al 2012	28	105	14	105	12.9%	2.00 [1.12, 3.58]
Singh et al 2015	1	30	3	30	1.3%	0.33 [0.04, 3.03]
Subtotal (95% CI)		**348**		**354**	**52.3%**	**1.64 [1.21, 2.21]**
Total events	89		56			
Heterogeneity: Tau² = 0.00; Chi² = 4.66, df = 6 (P = 0.59); I² = 0%						
Test for overall effect: Z = 3.20 (P = 0.001)						
Total (95% CI)		**542**		**546**	**100.0%**	**1.42 [1.11, 1.83]**
Total events	181		133			
Heterogeneity: Tau² = 0.04; Chi² = 12.39, df = 9 (P = 0.19); I² = 27%						
Test for overall effect: Z = 2.74 (P = 0.006)						
Test for subgroup differences: Chi² = 0.82, df = 1 (P = 0.37), I² = 0%						

RR: 1.64
(1.21-2.21)

Vitagliano et al., 2018, F&S

Endometrial Scratching in RIF



No evidence of an effect in women with ≥2 previous implantation failures compared to those with ≤1 prior failures

Lensen et al., 2019, NEJM

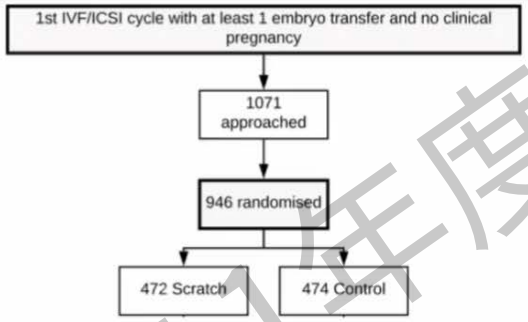
New Data…

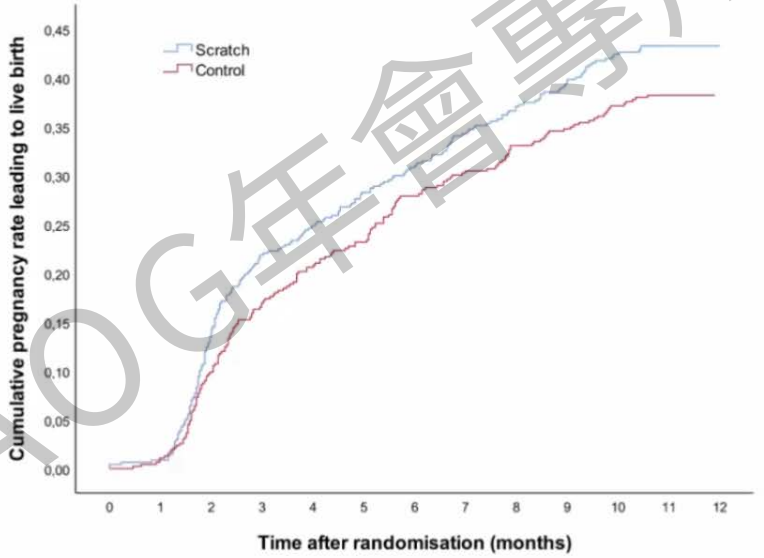

Human Reproduction, Vol.36, No.1, pp. 87–98, 2021
Advance Access Publication on December 8, 2020 doi:10.1093/humrep/deaa268

human reproduction ORIGINAL ARTICLE *Infertility*

Endometrial scratching in women with one failed IVF/ICSI cycle—outcomes of a randomised controlled trial (SCRaTCH)

N.E. van Hoogenhuijze[1,*], F. Mol[2], J.S.E. Laven[3], E.R. Groenewoud[4],

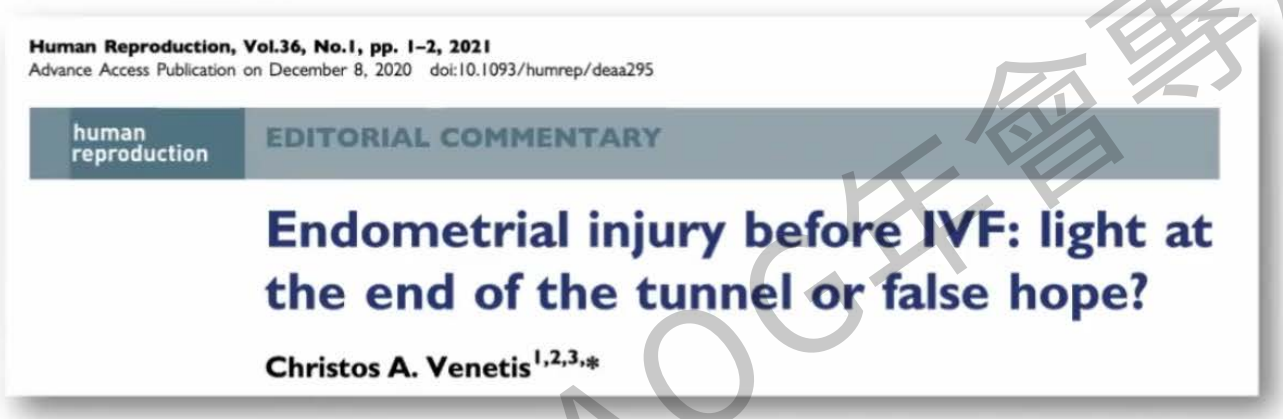




"After the fresh transfer, 4.6% more live births were observed in the scratch compared to control group (110/465 versus 88/461, respectively, risk ratio (RR) 1.24 [95% CI 0.96–1.59]). These data are consistent with a true difference of between -0.7% and +9.9% (95% CI)"

Van Hoogenhuijze et al., 2021, Hum Reprod

New data: Has something really changed?



Human Reproduction, Vol.36, No.1, pp. 1–2, 2021
Advance Access Publication on December 8, 2020 doi:10.1093/humrep/deaa295

human reproduction

EDITORIAL COMMENTARY

Endometrial injury before IVF: light at the end of the tunnel or false hope?

Christos A. Venetis[1,2,3,*]

If there is indeed a subgroup of patients that benefit or a specific technique of endometrial scratching that maximizes the benefit, our research efforts should focus on identifying these and conclusively proving their value.

Until this milestone has been achieved, offering endometrial scratching to patients in clinical practice would be based more on wishful thinking rather than on good quality evidence

The responsible use of treatment add-ons in fertility services: a consensus statement

Principles of responsible innovation

1. Clinics should only offer treatment add-ons under the following conditions:

   a) Where more than one high quality study demonstrates a treatment add-on to be safe and effective, clinics should continue to monitor their success rates and long-term follow-up data and report adverse incidents. Clinics should stop offering the treatment add-on to patients if concerns are raised regarding safety or effectiveness.

   b) Where evidence of safety and effectiveness is limited or conflicting, clinics offering treatment add-ons should be open with their data to add to the evidence-base for the add-on.

   c) Where there is no evidence to support safety and efficacy, treatment add-ons should only be offered to patients in a research setting with sound methodology and approval from a research ethics committee.

Take home messages- add ons

- Inconclusive effects in ART, but their use is still quite common
- Proposed in challenging cases of ART
- Driven by both doctors and patients wishing for a better outcome
- Evidence around their efficacy and safety is limited
- Some are quite experimental, some lacking a plausible physiological mechanism of action
- Some might be beneficial for certain patients
- Research is required to identify which is useful for which population

Thanks for listening