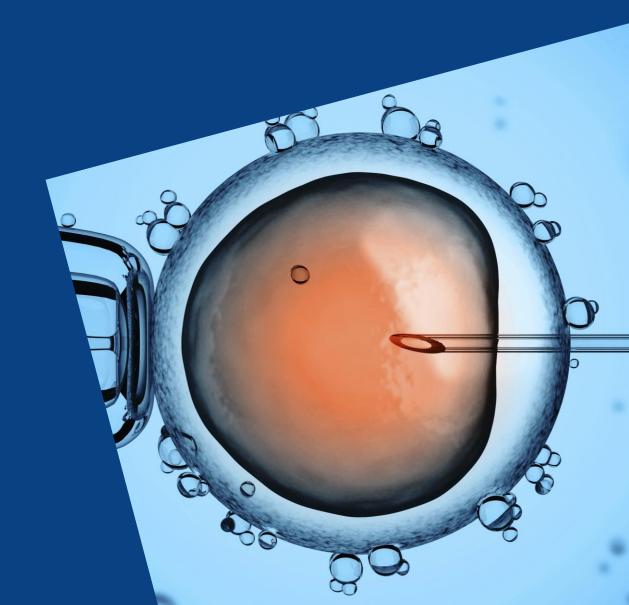


IVF add-ons

How to make choices that are right for you

VARTA webinar – July 2021 Dr Sarah Lensen and Prof Cindy Farquhar





Declarations of interest



Dr Sarah Lensen is an IVF and infertility researcher. She is an editor for the Cochrane Gynaecology and Fertility group. She has published scientific papers on IVF add-ons, with a particular focus on endometrial scratching and evidence from randomised trials.

In the last 5 years has received research/salary funding from

- NHMRC (National Health and Medical Research Council)
- University of Melbourne
- Auckland District Health Board
- Cochrane

She does not have any financial relationship with IVF clinics or any commercial companies.

Professor Cindy Farquhar is a fertility specialist and researcher at the University of Auckland. She is the Medical Director at Fertility plus, Auckland, New Zealand

In the last 5 years has received research funding from

- Health Research Council of New Zealand
- Auckland District Health Board
- Auckland Medical Research Foundation

She does not have any financial relationship with IVF clinics or any commercial companies.



Declarations of interest

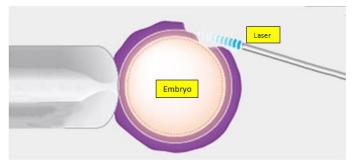
This VARTA seminar will cover IVF add-ons, including the scientific evidence supporting their use and aspects that people having IVF may like to consider

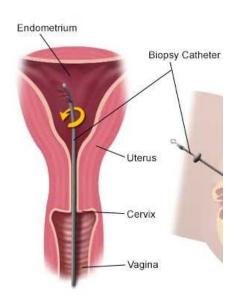
This information does not replace clinical advice from your doctor or fertility specialist.



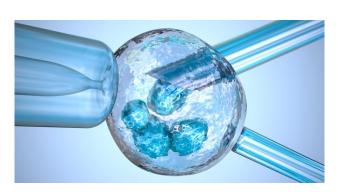
What are IVF 'add-ons'?

- AKA 'adjuvants' or 'optional extras'
- No established definition
- Usually
 - Optional or additional to standard IVF
 - Claim to increase the chance of IVF 'success'
 - An extra cost to the patient
- Sometimes used routinely (e.g. EmbryoGlue)
- Includes
 - Clinical and laboratory medicines, techniques, procedures (at IVF clinic)
 - Alternative or complementary therapies (e.g. acupuncture)
 - Nutritional supplements











What are IVF add-ons?

IVF add-ons are **not necessary or required** parts of an IVF cycle

Not add-ons

- Y ICSI for male-factor
- Genetic testing for inherited conditions
- Endometrial biopsy or laparoscopy undertaken for investigational purposes
- X Timelapse embryo incubation if used to improve workflow for embryologists

Add-ons

- ✓ ICSI for non-male infertility
- PGT-A (testing for aneuploidy wrong number of chromosomes)
- ✓ Endometrial scratching
- ✓ Timelapse imaging when claiming to increase IVF success/charging patients extra

How common is add-on use and how do patients decide whether to use them? A national survey of IVF patients

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S. Lensen (1) 1,*, K. Hammarberg (1) 2,3, A. Polyakov 1,4,5, J. Wilkinson (1) 6, S. Whyte 7,8,9,10, M. Peate 1, and M. Hickey (1) 1
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Survey of 1590 Australian IVF patients

82% used one or more add-ons

- Median 2
- Range 0–18

72% cost extra

Add-ons	Used add-on
	(n, %)
Acupuncture	692 (45.3)
PGT-A	422 (27.6)
Chinese herbal medicine	397 (26.0)
Heparin (clexane)	377 (24.7)
Aspirin	366 (24.0)
Timelapse imaging (Embryoscope)	358 (23.4)
EmbryoGlue	341 (22.3)
Melatonin	339 (22.2)
Prednisolone (corticosteroids)	334 (21.9)
Endometrial scratch	264 (17.3)
Androgens	204 (13.4)
Growth Hormone	180 (11.8)
Assisted hatching	120 (7.9)
Intralipid infusion	125 (8.2)
Physiological intracytoplasmic sperm	97 (6.4)
injection (PICSI)	
Intracytoplasmic morphologically	88 (5.8)
selected sperm injection (IMSI)	
Lipiodol flushing	86 (5.6)
Endometrial receptivity array (ERA)	53 (3.5)

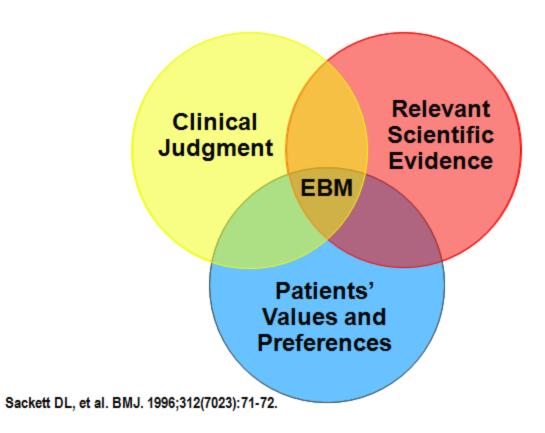


IVF add-ons in Victoria

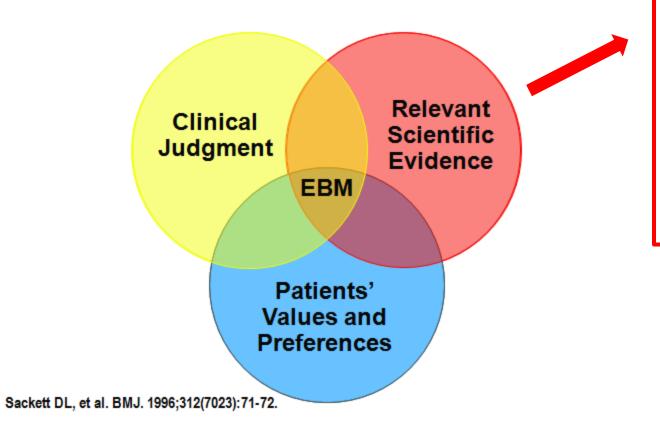
- VARTA is the state regulator for IVF in Victoria
- VARTA requires IVF clinics to
 - Provide patients with information about evidence, benefits and risks of add-ons
 - Notify VARTA of any new treatments or procedures offered to patients
 - VARTA
 Victorian Assisted Reproductive
 Treatment Authority

- VARTA has key roles in
 - Monitoring and reviewing emerging evidence relating to add-ons
 - Providing the public with easy-tounderstand and independent information about add-ons
- VARTA cannot control which add-ons are made available to patients or prohibit their use.





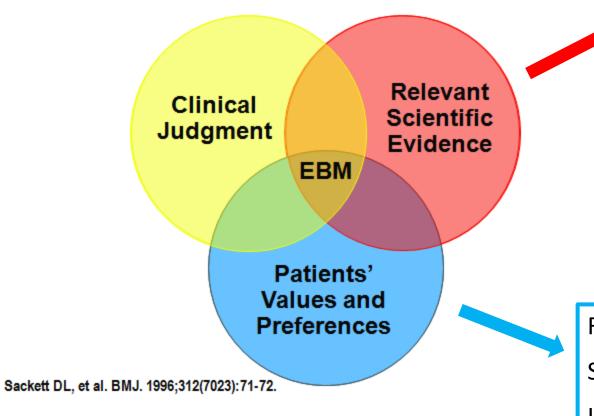




Randomised controlled trials and systematic reviews

- Effectiveness (efficacy) e.g. does this add-on increase live birth rates?
- Safety e.g. does this add-on carry any risk to me or to a pregnancy?





Randomised controlled trials and systematic reviews

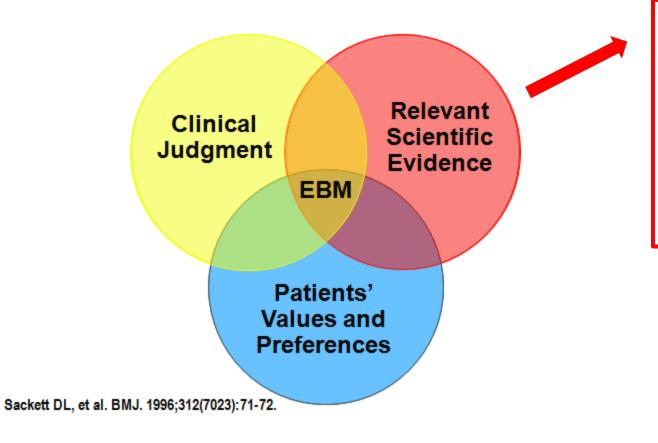
- Effectiveness (efficacy) e.g. does this add-on increase live birth rates?
- Safety e.g. does this add-on carry any risk to me or to a pregnancy?

Rights, values and preferences

Shared decision making

Informed consent



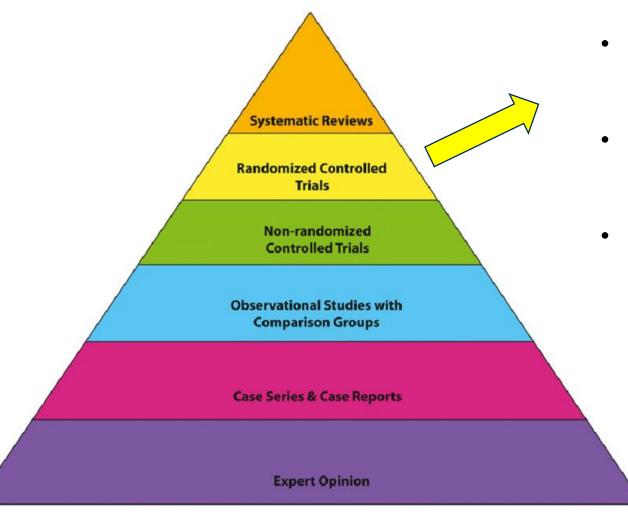


Randomised controlled trials and systematic reviews

- Effectiveness (efficacy) e.g. does this add-on increase live birth rates?
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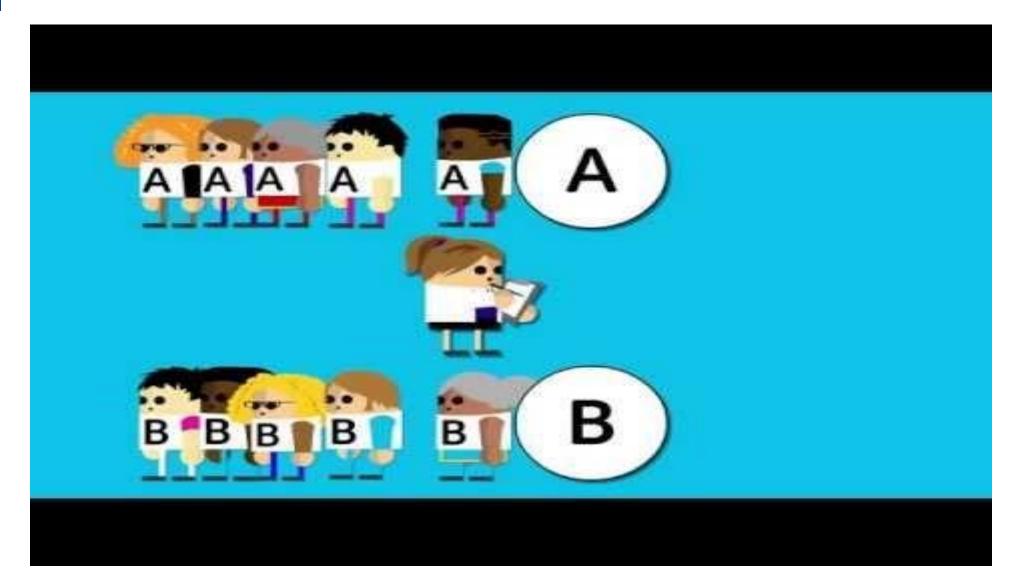


Randomised controlled trials



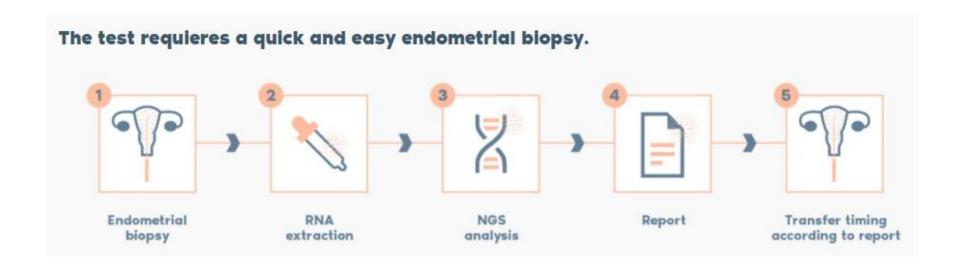
- People are allocated to groups at random (e.g. flipping a coin)
- 'Gold standard' robust research design for evaluating healthcare interventions
- Not always possible or ethical (but usually is for IVF add-ons)



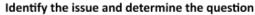




Cautionary tale: Endometrial Receptivity Array (ERA)



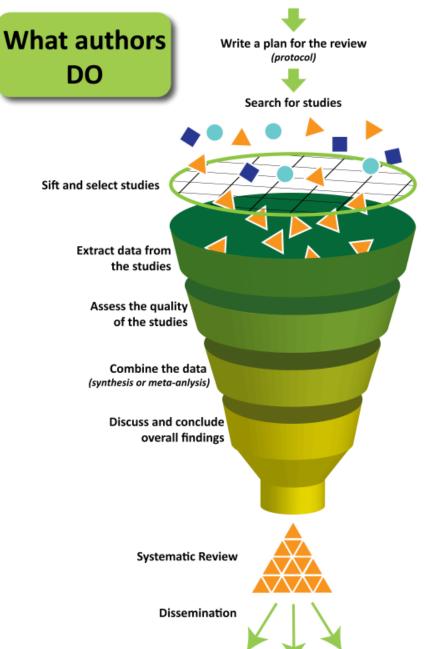
- Complicated and sophisticated test that claims to determine optimal timing of embryo transfer for each individual women
- Based on the concept and observational studies, used by thousands of women across the world
- First RCT published in 2020 found no improvement in live birth rates using ERA





Systematic reviews

- Systematic reviews are summaries of all available studies
 - Restricted to RCTs
- Individual RCTs combined in a metaanalysis to give an overall result
- Include a critical appraisal of the quality of the included RCTs
- Require training and skills





Cochrane

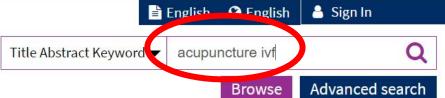
- International group of trained researchers
- Produce the highest quality systematic reviews
 - Robust methodology
 - Most reliable results
 - Critical appraisal of included studies
- Independent no funding from commercial companies
- Free access to Cochrane Library in Australia
- Plain language summaries
- IVF add-ons special collection



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Signs and symptoms to determine if a patient has COVID-19

Read the Review



COVID-19: working together Read the Editorial and Supplement





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Trials ▼

Acupuncture and assisted reproductive technology

Ying C Cheong, Sarah Dix, Ernest Hung Yu Ng, William L Ledger, Cindy Farquhar Authors' declarations of interest

Clinical Answers

Version published: 26 July 2013 Version history https://doi.org/10.1002/14651858.CD006920.pub3 ♂

Collapse all Expand all

New search

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Abstract

Available in English | Español | 日本語 | 한국어 | 简体中文

Background

Acupuncture is commonly undertaken during an assisted reproductive technology (ART) cycle although its role in improving live birth and pregnancy rates is unclear.

Objectives

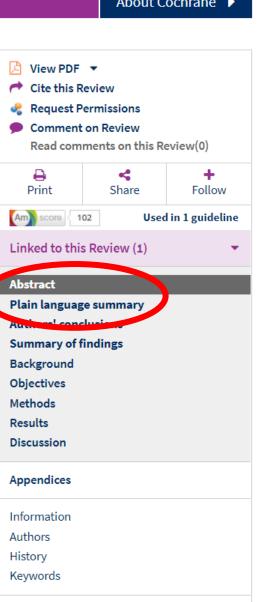
To determine the effectiveness and safety of acupuncture as an adjunct to ART cycles for male and female subfertility.

Search methods

All reports which described randomised controlled trials of acupuncture in assisted conception were obtained through searches of the Menstrual Disorders and Subfertility Group Specialised Register, CENTRAL, Ovid MEDLINE, EMBASE, CINAHL (Cumulative Index to Nursing & Allied Health Literature), AMED, www.clinicaltrials.gov (all from inception to July 2013), National Research Register, and the Chinese clinical trial database (all to November 2012).

Selection criteria

Randomised controlled trials of acupuncture for couples who were undergoing ART, comparing acupuncture treatment alone or



Available in English | Español | Hrvatski | 日本語 | 한국어 | 简体中文

Acupuncture and assisted conception

Review question: does acupuncture improve the outcomes of assisted reproduction?

Background: one in seven couples suffer from subfertility and many will seek help in the form of assisted reproductive technology (ART). Although the use of acupuncture has gained popularity, the use of this traditional Chinese medical treatment in conjunction with ART treatments is still controversial. This review summarised the evidence from well designed studies and evaluated the effectiveness and safety of acupuncture in assisted conception.

Search date: the evidence is current to July 2013.

Study characteristics: there were 20 randomised controlled studies identified. Six studies compared acupuncture at the time of egg collection (912 women) and 14 studies compared acupuncture in assisted conception (3632 women). The studies were further divided into those which used placebo needles in their control groups versus those that had controls who did not undergo any treatment. All the studies identified involved participants undertaking in vitro fertilization (IVF); there were no studies reporting the effect of acupuncture in ovulation induction or intrauterine insemination.

Funding of included studies: no included studies had external funding.

Key results: there is no evidence of benefit for the use of acupuncture in participants undergoing assisted conception treatment around the time of embryo transfer or at egg collection in terms of improving the live birth rate, ongoing or clinical pregnancy rate. There is also no evidence that acupuncture has any effect on miscarriage rate or had significant side effects.

Quality of the evidence: overall, the results are not similar across the studies. This was due to different study designs including the use of different types of control groups that could have introduced bias. More research is needed before recommendations can be made, including studies in which some controls receive placebo needling and others receive no intervention.



Cochrane special collection: IVF add-ons



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Title Abstract Ke

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In vitro fertilisation – effectiveness of add-ons

16 October 2020



As many as one in seven couples experience difficulty becoming pregnant [1], and many of them turn to fertility treatments for help. *In vitro* fertilisation (IVF) is generally considered the most advanced treatment option, and is recommended in many cases, regardless of the cause of subfertility. IVF is now widely available as a treatment option, with over 1 million IVF cycles taking place across the globe each year. However, despite numerous advances in IVF technology over the years, the success rate remains modest, at approximately 30% per IVF cycle [2]; although success rates vary depending on many patient and treatment factors, such as female age and cause of infertility. Even though the

probability of getting pregnant and having a baby increases with additional IVF cycles, unfortunately many people finish their IVF treatment without success.

Laboratory add-ons

Hyaluronic acid in embryo transfer media for assisted reproductive technologies

In an IVF cycle, the embryo is transferred into the womb in a solution containing compounds to help the embryo adhere successfully to the inside of the womb (implantation). Hyaluronic acid is a natural compound found in the body that acts as a binding and protective agent, and is often added to embryo transfer media to help implant the embryo. This review aims to determine whether adding adherence compounds to embryo transfer media improves pregnancy outcomes, including improving live birth and decreasing miscarriage, in women undergoing assisted reproduction.

Clinical add-ons

Granulocyte-colony stimulating factor administration for subfertile women undergoing assisted reproduction

Granulocyte-colony stimulating factor (G-CSF) is a naturally occurring growth factor, and has been suggested to play an important role in the process of embryo implantation. It is proposed that giving women G-CSF near the time of embryo transfer may increase the probability of the embryo implanting. This review summarises the available evidence on the effectiveness and safety of G-CSF in women undergoing IVF. Associated Cochrane Clinical Answer. How does granulocyte-colony stimulating factor administration compare with placebo/no treatment for subfertile women undergoing assisted reproduction?

Add-ons for the endometrium

Intrauterine administration of human chorionic gonadotropin (hCG) for subfertile women undergoing assisted reproduction

Free access

Human chorionic gonadotropin (hCG) has an important role in embryo implantation and the early stages of pregnancy. It has been suggested that injection of hCG into the womb near the time of embryo transfer, might increase the chance of pregnancy. This review investigates whether intrauterine administration of hCG around the time of embryo transfer improves clinical outcomes in subfertile women undergoing IVF. Associated Cochrane Clinical Answer. What are the benefits and harms of intrauterine administration of human chorionic gonadotropin (hCG) around the time of embryo transfer for subfertile women undergoing assisted reproduction?



HFEA traffic light system





More than one high quality RCT shows procedure increases live birth rates.



Conflicting evidence from RCTs



No evidence from RCTs

https://www.hfea.gov.uk/treatments/treatment-add-ons/

Endometrial scratching



Endometrial scratching is rated amber

What is endometrial scratching?

In order to have a successful pregnancy, an embryo needs to 'implant' in the womb; if it doesn't, the patient will need to start their cycle again.

Most embryos don't implant because they've been unable to develop fully to the implantation stage or because of a developmental mismatch between the stage of the embryo and the lining of the womb.

However, in a small number of cases an embryo won't implant because the lining of the womb isn't providing them with the right environment.

Endometrial scratching is carried out before IVF. During the procedure the lining of the womb (the endometrium) is 'scratched' using a small sterile plastic tube.

The theory is that this procedure triggers the body to repair the site of the scratch, releasing chemicals and hormones that make the womb lining more receptive to an embryo implanting. Some also suggest the treatment may activate genes that make the womb lining more receptive to an embryo implanting.

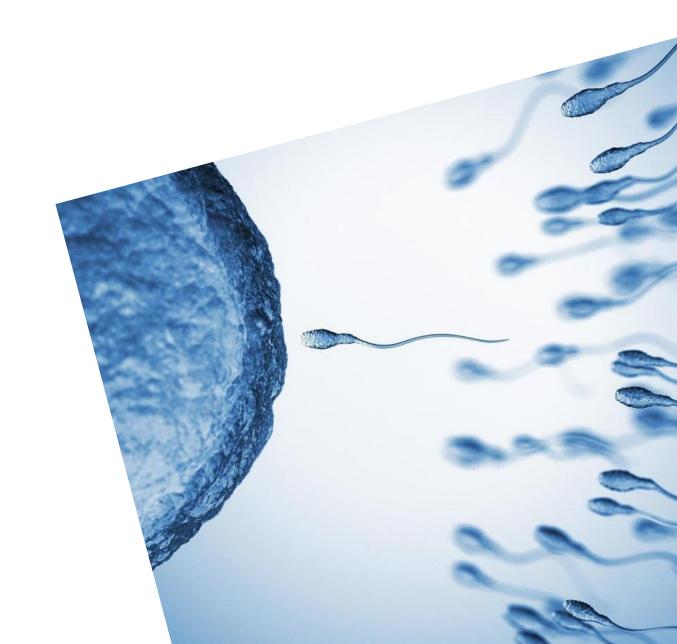
What's the evidence for endometrial scratching?

Earlier studies were of poor quality and showed conflicting results. The latest four RCTs have been high quality studies and have shown that there could be **up to** 5% improvement in live birth rate. Further high-quality studies are needed before doctors can be confident of the benefits of endometrial scratching.

At the October 2020 Scientific and Clinical Advances Advisory Committee (SCAAC) meeting the Committee evaluated the evidence base for endometrial scratch. Minutes of this discussion and the evidence used to inform this discussion are available on the SCAAC webpage.



Evidence for common IVF add-ons





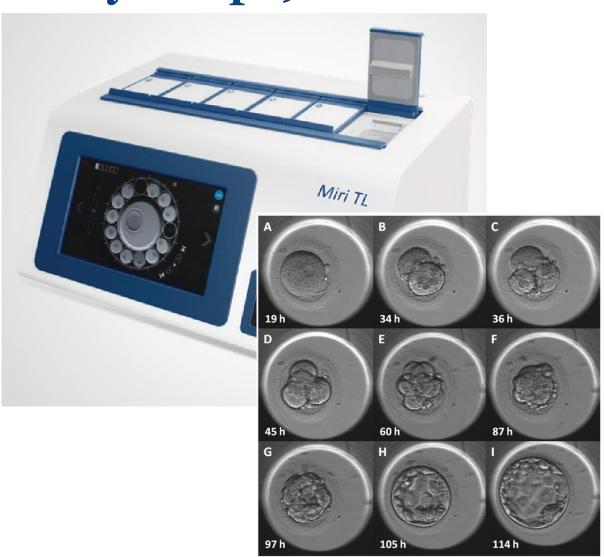
Time-lapse imaging (Embryoscope)

Continuous uninterrupted incubation of embryos, suggested to

- Improve environment as not disturbing embryos for assessment
- Algorithms help pick the best embryo

Offered by 33% of IVF clinics in Australia
Used by 22% of IVF patients

- Cost extra 27% of the time





Time-lapse imaging (Embryoscope)

Evidence updated January 2019
Included 9 RCTs

No evidence of any difference in

- Live birth rates
- Pregnancy rates
- Miscarriage rates



Cochrane Database of Systematic Reviews

Time-lapse systems for embryo incubation and assessment in assisted reproduction (Review)

Armstrong S, Bhide P, Jordan V, Pacey A, Marjoribanks J, Farquhar C





Amber



Ultra-high magnification (IMSI) sperm selection

During ICSI, sperm are normally viewed under a microscope and selected based on their morphology

IMSI provides higher magnification (over 6000x)

Offered by 23% of IVF clinics in Australia
Used by 6% of IVF patients

- Cost extra 50% of the time





Ultra-high magnification (IMSI) sperm selection

Evidence updated November 2019

Included 13 RCTs

No evidence of any difference in

- Live birth rates
- Pregnancy rates
- Miscarriage rates



Cochrane Database of Systematic Reviews

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

Teixeira DM, Miyague AH, Barbosa MAP, Navarro PA, Raine-Fenning N, Nastri CO, Martins WP





Red



Hyaluronic acid is a natural compound found in the body that acts as a binding and protective agent in tissues. It is often added to embryo transfer media with the aim of helping to implant the embryo

Offered by 23% of IVF clinics in Australia
Used by 22% of IVF patients

- Cost extra 60% of the time



EmbryoGlue (Hyaluronic acid in embryo transfer media)

Evidence updated January 2020

Included 26 RCTs

EmbryoGlue probably increases

- Live birth rates
- Pregnancy rates



Cochrane Database of Systematic Reviews

Hyaluronic acid in embryo transfer media for assisted reproductive technologies (Review)

Heymann D, Vidal L, Or Y, Shoham Z





Amber



Conflicting evidence or no evidence?

"There is no evidence, yet"

"Anything is worth a try"

"There is a chance it will help"

Remember that, without good evidence we don't know what effect the add-on has

It might

- Reduce your chances of conceiving
- Be unsafe or have an unintended consequence
- Cost you so much
 - Regret it
 - Can't afford more IVF





Anecdotal evidence

Information from family, friends, or through online forums

"It worked for them"

People are more likely to share experiences that were positive or negative (and not neutral)

People overlook coincidence and attribute success or failure to specific circumstances

Anecdotal accounts may be biased (not trustworthy)

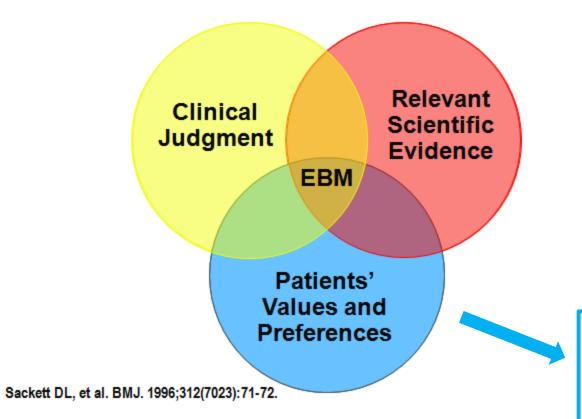
Useful for

- Understanding patient experience (e.g. availability, cost, waiting lists, pain etc.)
- Raising possible treatment options
 - Then look at the evidence and discuss with your doctor

Not useful for

 Whether an add-on is effective (will help you have a baby) or safe





Rights, values and preferences

Shared decision making

Informed consent



Choosing wisely

5 QUESTIONS TO ASK YOUR DOCTOR OR OTHER HEALTH CARE PROVIDER BEFORE YOU GET ANY TEST, TREATMENT OR PROCEDURE

Some tests, treatments and procedures provide little benefit. And in some cases, they may even cause harm.

Use the 5 questions to make sure you end up with the right amount of care — not too much and not too little.

https://www.choosingwisely.org.au/resources/consumers-and-carers/5questions

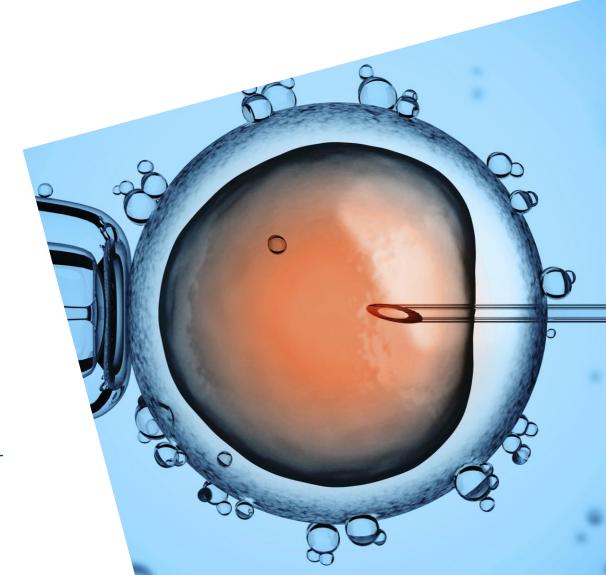
DO I REALLY Tests may help you and your doctor or other health **NEED THIS TEST,** care provider determine the problem. Treatments, TREATMENT OR such as medicines, and procedures may help to treat it. 2 PROCEDURE? WHAT ARE Will there be side effects to the test or treatment? THE RISKS? What are the chances of getting results that aren't accurate? Could that lead to more testing, additional treatments or another procedure? **ARE THERE** Ask if there are alternative options to treatment SIMPLER, SAFER that could work. Lifestyle changes, such as eating **OPTIONS?** healthier foods or exercising more, can be safe and effective options. WHAT HAPPENS Ask if your condition might get worse — or better — IF I DON'T DO if you don't have the test, treatment or procedure ANYTHING? right away. WHAT ARE Costs can be financial, emotional or a cost of your THE COSTS? time. Where there is a cost to the community, is the cost reasonable or is there a cheaper alternative?



What are patients saying about IVF add-ons?

These quotes are from

- UK Competition and Markets Authority Report: https://www.gov.uk/cma-cases/self-funded-ivf-consumer-law-guidance
- Survey conducted by UniMelb





Regret vs satisfaction

"There's no proof of success, but it's a peace-of-mind thing"

"I feel we were unfairly made to purchase add ons that did not give us any extra chance, just left us out of pocket"

"Many years and finally a baby... best choices I ever made was not to give up and try all extras"

"For me personally it has made zero difference so far. My very 1st cycle, my husband and I used no vitamins, no add ons... we have a son from that cycle.

Every subsequent cycle we have used add ons and we have so far had no success sadly."

"They just told me what it [scratch] was and how it could be beneficial, so at that point it's like, it's only an extra £250, we might as well. If it doesn't work, then you're going to think, well, if only I had spent that £250 extra and it could have worked"

"When a doctor mentions an "experimental" drug like testosterone, you immediately think it might give you an edge and be the thing that does the trick. But I now think my rational mind was compromised during that time and that the testosterone was no more likely to help than 34 eating an orange or standing on my head!"



An informed decision

Informed consent is an important part of all healthcare decision making.

Informed consent relies upon

- Accurate and relevant information about the proposed intervention
- Alternative options
- Understanding of the benefits and material risks
- An opportunity to ask questions





Take-home messages

- Many different IVF add-ons are available, but very few are supported by scientific evidence of safety and effectiveness
- Trusted information
 - Randomised controlled trials
 - Cochrane reviews
 - HFEA website
- What is important to you?
 - Reliability of evidence
 - Cost
 - o Risk
 - O How will you feel afterwards?





Research Participation



University of Melbourne Research Panel

This Panel consists of people with experience of infertility or fertility treatments, who are available to contribute to research projects. This includes having input into the design or development of a research project, or being involved in a research project as a participant.

fertility-researchpanel@unimelb.edu.au





IVF add-on information in Australia

Government grant to UniMelb

- Develop and disseminate resources about IVF add-ons
- Help shared decision-making

IVF patients to provide input

Ideas, suggestions, or to volunteer to help: sarah.lensen@unimelb.edu.au



Australian Government

National Health and Medical Research Council







Thank you