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.

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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
  o Optional or additional to standard IVF
  o Claim to increase the chance of IVF ‘success’
  o An extra cost to the patient
• Sometimes used routinely (e.g. EmbryoGlue)
• Includes
  o Clinical and laboratory medicines, techniques, procedures (at IVF clinic)
  o Alternative or complementary therapies (e.g. acupuncture)
  o Nutritional supplements
What are IVF add-ons?

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

### Not add-ons

- ICSI for male-factor
- Genetic testing for inherited conditions
- Endometrial biopsy or laparoscopy undertaken for investigational purposes
- *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

Survey of 1590 Australian IVF patients

82% used one or more add-ons
- Median 2
- Range 0–18

72% cost extra

<table>
<thead>
<tr>
<th>Add-ons</th>
<th>Used add-on (n, %)</th>
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<tbody>
<tr>
<td>Acupuncture</td>
<td>692 (45.3)</td>
</tr>
<tr>
<td>PGT-A</td>
<td>422 (27.6)</td>
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<tr>
<td>Chinese herbal medicine</td>
<td>397 (26.0)</td>
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<tr>
<td>Heparin (clexane)</td>
<td>377 (24.7)</td>
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<tr>
<td>Aspirin</td>
<td>366 (24.0)</td>
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<tr>
<td>Timelapse imaging (Embryoscope)</td>
<td>358 (23.4)</td>
</tr>
<tr>
<td>EmbryoGlue</td>
<td>341 (22.3)</td>
</tr>
<tr>
<td>Melatonin</td>
<td>339 (22.2)</td>
</tr>
<tr>
<td>Prednisolone (corticosteroids)</td>
<td>334 (21.9)</td>
</tr>
<tr>
<td>Endometrial scratch</td>
<td>264 (17.3)</td>
</tr>
<tr>
<td>Androgens</td>
<td>204 (13.4)</td>
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<tr>
<td>Growth Hormone</td>
<td>180 (11.8)</td>
</tr>
<tr>
<td>Assisted hatching</td>
<td>120 (7.9)</td>
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<tr>
<td>Intralipid infusion</td>
<td>125 (8.2)</td>
</tr>
<tr>
<td>Physiological intracytoplasmic sperm injection (PICSI)</td>
<td>97 (6.4)</td>
</tr>
<tr>
<td>Intracytoplasmic morphologically selected sperm injection (IMSI)</td>
<td>88 (5.8)</td>
</tr>
<tr>
<td>Lipiodol flushing</td>
<td>86 (5.6)</td>
</tr>
<tr>
<td>Endometrial receptivity array (ERA)</td>
<td>53 (3.5)</td>
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</tbody>
</table>
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 has key roles in
  - Monitoring and reviewing emerging evidence relating to add-ons
  - Providing the public with easy-to-understand and independent information about add-ons
- VARTA cannot control which add-ons are made available to patients or prohibit their use.
Evidence-based medicine

Clinical Judgment

Relevant Scientific Evidence

Patients’ Values and Preferences

Evidence-based medicine

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?
Evidence-based medicine

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?
- Safety e.g. does this add-on carry any risk to me or to a pregnancy?
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 meta-analysis 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
  o Robust methodology
  o Most reliable results
  o 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
Acupuncture and assisted reproductive technology

Ying C Cheong, Sarah Dix, Ernest Hung Yu Ng, William L Ledger, Cindy Farquhar

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

Abstract

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 with other interventions to usual care, or comparing acupuncture with another treatment or placebo.
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.
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.
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/
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
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
EmbryoGlue
(Hyaluronic acid in embryo transfer media)

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
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
  o Regret it
  o 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
  o 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
Evidence-based medicine

Clinical Judgment

Relevant Scientific Evidence

Patients’ Values and Preferences

EBM

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.

1. **DO I REALLY NEED THIS TEST, TREATMENT OR PROCEDURE?** Tests may help you and your doctor or other health care provider determine the problem. Treatments, such as medicines, and procedures may help to treat it.

2. **WHAT ARE THE RISKS?** Will there be side effects to the test or treatment? What are the chances of getting results that aren’t accurate? Could that lead to more testing, additional treatments or another procedure?

3. **ARE THERE SIMPLER, SAFER OPTIONS?** Ask if there are alternative options to treatment that could work. Lifestyle changes, such as eating healthier foods or exercising more, can be safe and effective options.

4. **WHAT HAPPENS IF I DON’T DO ANYTHING?** Ask if your condition might get worse — or better — if you don’t have the test, treatment or procedure right away.

5. **WHAT ARE THE COSTS?** Costs can be financial, emotional or a cost of your time. Where there is a cost to the community, is the cost reasonable or is there a cheaper alternative?

https://www.choosingwisely.org.au/resources/consumers-and-carers/5questions
What are patients saying about IVF add-ons?

These quotes are from:
- 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 eating an orange or standing on my head!”
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
  o Randomised controlled trials
  o Cochrane reviews
  o HFEA website

• What is important to you?
  o Reliability of evidence
  o Cost
  o Risk
  o How will you feel afterwards?
Research Participation
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
Thank you