Fertility treatment adjuvants

About Patient One (check your name and DoB carefully)

First name

Surname

Date of birth:

Patient I.D.

About Patient Two (check your name and DoB carefully)

First name

Surname

Date of birth:

Patient I.D.

What are adjuvants?

The HFEA defines adjuvants (or "add-ons") as "optional extras that you may be offered on top of your normal fertility treatment, often at an additional cost. They're typically emerging techniques that may have shown some promising results in initial studies but haven't necessarily been proven to improve pregnancy or birth rates."

To make it easier to identify which add-ons have a lot of evidence supporting their effectiveness and safety and which have very little evidence, or should be considered experimental, the HFEA have produced information rating these add-ons.

What do the ratings mean?

The HFEA, in their information state that the "only way to be confident that a treatment is effective in humans is to carry out a randomised controlled trial (RCT). In an RCT, patients are assigned randomly to two groups: a treatment group, given the new treatment and a control group, given either a well-tried treatment or a placebo. The number of patients included is very important, with more patients giving more accurate results. Ideally, several different groups of researchers or scientists should have performed high quality RCTs and follow up studies to be sure a new procedure is effective and safe."

Randomised Trials are not always available for all potential tests / treatments due to difficulties in funding research in reproductive medicine as well as difficulties often found in recruiting people to such studies.

On occasion, a clinical decision or recommendation is based on the best alternative evidence available.

HFEA ratings:

Green: There is more than one good quality study which shows that the procedure is effective and safe.

Amber: There is a growing body of evidence which is showing promising results but where further research is still required.

Red: No evidence to show that it is effective and safe.

We outline below the tests rated by the HFEA, their recommendations along with a comment on the Lister Fertility Clinic approach or any update in evidence since the HFEA recommendation.

Assisted Hatching HFEA Rating: Red

What is assisted hatching?

The egg and early embryo are surrounded by a thick layer of special proteins called the zona pellucida. Before an embryo can implant in the womb it has to break out or 'hatch' from its zona pellucida. Some people think that assisted hatching - using acid, lasers or other tools to thin or make a hole in the zona pellucida - helps the embryo to hatch.

Are there any risks?

There is always some risk of damaging embryos with these types of procedures.

What's the evidence for assisted hatching?

The National Institute for Clinical Excellence (NICE) is the national body advising doctors on treatments. It says: "Assisted hatching is not recommended because it has not been shown to improve pregnancy rates." NICE also says that further research is needed to find out whether assisted hatching has an effect on birth rates and to examine the consequences for children born as a result of this procedure.

Some clinics believe assisted hatching can lead to higher birth rates in very select cases. For example, it has been noted that the zona pellucida may be thicker in some older women, so weakening or thinning it may help the embryos hatch, but this hasn't been proven.

Lister opinion:

This is not a procedure routinely offered even in those subgroups where there is some data from reviews of randomized trials of a benefit in pregnancy rate (advanced maternal age, frozen blastocysts) but not yet evidence of benefit in livebirth (Martins et al, HRU 2012).

On occasion, when the zona is visibly assessed to be thick in the lab prior to transfer, it may be recommended but this is very rare.

<u>Artificial Egg Activation – Calcium Ionophore</u> HFEA Rating: Amber

What is egg activation?

When a sperm meets an egg, it triggers a process called 'egg activation' which starts off the process of embryo development, while at the same time allowing only one sperm to fertilise the egg. If the egg doesn't activate, then it won't develop. Egg (or oocyte) activation may be stimulated by chemicals called calcium ionophores. These chemicals can be added to the embryo in the lab.

Are there any risks?

In theory, egg activation using calcium ionophores could cause embryos to have abnormal numbers of chromosomes, which would cause the pregnancy to miscarry. As yet there's not enough evidence to decide whether these risks are a serious concern. Given the possible risks, clinics offering this treatment are expected to do so only in selected patients who have had failed fertilisation and to justify their reasons for doing so.

What's the evidence for egg activation?

In the few studies done to date, egg activation using calcium ionophores may improve fertilisation rates in ICSI cycles where the egg and sperm have failed to activate in previous treatment cycles. However, there are no RCTs to show that it is effective or follow up studies on the safety of this technique.

Lister opinion:

Where there is recurrent fertilization failure with ICSI or repetitively low fertilisation rates, in the absence of suitable alternative treatment options, we do offer Calcium Ionophore treatment and have published successful case reports (Nicopoullos et al, JARG 2015).

<u>Endometrial Scratching</u> HFEA Rating: 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 woman will need to start her 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 and is intended to correct problems with the womb lining. 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.

Are there any risks?

There is a small risk that if you have an infection within your cervix before 'scratching', this may cause the infection to spread up into the uterus. Your clinic can treat this if necessary.

What's the evidence for endometrial scratching?

Early results suggest that endometrial scratching could increase pregnancy rates, although stronger evidence is needed to prove this. There's currently a large clinical trial underway in the UK called Endometrial Scratch Trial, which you may be invited to join by your clinic.

Lister opinion:

We await further trials with interest but based on current evidence (Vitagliano et al, Fertil Steril, 2018) we would consider offering those with 2 or more failed cycles where embryos were of top quality an endometrial scratch. The evidence of benefit after 1 failed cycle is more limited at present so is not routinely recommended although any potential physiological mechanism of benefit may still apply.

A further information sheet on endometrial scratch is available.

When is it done?

It should be done in the week prior to your period after which will be starting stimulation drugs. These is no evidence of any benefit once bleeding has started and beyond that it may do more harm then good by disturbing the womb lining in the run up to embryo transfer.

Could this affect the chances of getting pregnant naturally in that month?

In most women where a scratch is being performed, the chances of natural conception is very small and often couples will be on the contraceptive pill which will also make pregnancy unlikely. However, in the unlikely event of a fertilised egg naturally having implanted that could lead to a pregnancy the scratch may stop this occurring. We ideally recommend avoiding unprotected intercourse from your period to a scratch.

How is it done?

It is very similar to an embryo transfer procedure which you would have previously have had. However, in contrast to the transfer (where we do not want to disturb the lining) we will be gently moving the instrument within the uterus for a few seconds.

You should come with a **partially full bladder**. If no recent Chlamydia result you will need **prophylactic Antibiotics.**

How do I book?

Please call the nurses or liaise with your doctor who will book it for you at the appropriate time of your cycle. It is performed daily at either 09.15, 16.00, 16.15 or 16.30.

IMSI (Intracytoplasmic Morphology Selected Sperm Injection) HFEA Rating: Red

What is IMSI?

Intracytoplasmic morphologically selected sperm injection (IMSI) is a sperm selection method used in intracytoplasmic sperm injection (ICSI). The technique involves using a microscope to view sperm under very high magnification (over x6000). This allows clinics to view detailed images of sperm.

Are there any risks?

IMSI is a non-invasive test performed on a semen sample as an additional step in the ICSI process. The risks associated with the use of ICSI also apply to IMSI; there are no significant additional risks to the patient or embryo.

What's the evidence for IMSI?

There have been several RCTs within the last decade. Systematic reviews suggest that IMSI could be beneficial in specific situations such as previously failed ICSI attempts. The research that has been carried out does not support the use of IMSI over standard ICSI for infertile men. One small study found that IMSI had improved pregnancy outcomes in older women, however this study was carried out with a small number of women and the link, if any, between IMSI and older eggs is not fully understood.

Lister opinion:

This is a modification of the standard ICSI procedure and one of a number of sperm selection techniques that have been suggested to potentially improve outcome. The major difference between IMSI and ICSI is that a higher magnification is used to assess sperm morphology allowing the embryologist to identify tiny defects in the sperm head that would not otherwise be visible with standard ICSI.

Reviews of randomized trials have shown a benefit in pregnancy but not livebirth rates so it cannot be justified in routine practice (Cochrane,2013).

However, other trials of lower quality have suggested benefit over standard ICSI in certain groups such as those with previous failed ICSI cycles (Klement et al, 2013 Fertil Steril), significant male fertility (Balaban et al, 2011 RBMO), those undergoing PGS (Figeira et al, 2011) and in the selection of sperm with lower levels of sperm DNA damage (Hammoud et al, 2012 Andrologia).

We therefore use in selected cases such as those above. A further information sheet on IMSI is available.

Reproductive Immunology Tests and Treatment HFEA Rating: Red

What is reproductive immunology?

Reproductive immunology is a field of study that looks at how a woman's immune system reacts when she becomes pregnant. Usually, your immune system works by fighting off any invading cells that it doesn't recognise because they don't share your genetic code. In the case of an embryo, the immune system learns to tolerate it even though it has a different genetic code from the mother.

Some scientists believe that in some cases of miscarriage or infertility, the mother's immune system may fail to accept the embryo due to these differences in their genetic codes.

Are there any risks?

There are various different treatments associated with reproductive immunology, which are used to suppress the body's natural immunity, and all of which have risks:

- Steroids (e.g. prednisolone): Risks include high blood pressure, diabetes and premature birth.
- Intravenous immunoglobulin (IVIg): Side effects can include headache, muscle pain, fever, chills, low back pain, and rarely thrombosis (blood clots), kidney failure and anaphylaxis (a bad allergic reaction to the drug).
- TNF-a blocking agents (e.g. adalimumab, infliximab): Remicade is not recommended for use during pregnancy. Side effects can include infections including septicaemia, chronic infections such as tuberculosis, and severe allergic reactions to the drug.
- Intralipid infusions: Side effects include headache, dizziness, flushing, nausea and the possibility of clotting or infection.

What's the evidence for reproductive immunology?

There is no convincing evidence that a woman's immune system will fail to accept an embryo due to differences in their genetic codes. In fact, scientists now know that during pregnancy the mother's immune system works with the embryo to support its development.

Not only will reproductive immunology treatments not improve your chances of getting pregnant, there are risks attached to all these treatments, some of which are very serious.

Lister opinion:

We concur that there is no convincing evidence of randomised trial level to support immune testing and as such do not offer it as a first line treatment.

Following published research we performed in conjunction with an immunologist, we historically offered an immune screening test based on these research findings. This test is not offered as a first line test in any couple and is now only occasionally performed in those limited couples with multiple cycle failure of top quality blastocysts with no other cause of cycle failure found. The information provided is in keeping with the HFEA / RCOG recommendations and given to all patients prior to testing or treatment.

A further information sheet on reproductive immunology is available from: (https://ivf.org.uk/investigations/reproductive-immunology/).

Time-lapse Imaging HFEA Rating: Amber

What is time-lapse imaging?

In IVF, time-lapse imaging is used to help select the embryos most likely to successfully develop into a baby. In conventional IVF, the embryologist will check the developing embryos each day under a microscope, which involves removing them from the incubator for a brief period.

Time-lapse imaging allows the embryologist to take thousands of images of the embryos as they grow without disturbing them. Not only does this mean the embryos do not have to be removed from the incubator, it also allows the embryologist to get a continuous view of each embryo as it develops, rather than just viewing them once a day.

The embryologist can then choose a specific embryo for implantation based on criteria such as rate of development and the number and appearance of cells. Indeed, being undisturbed while they grow may improve the quality of the embryos.

Are there any risks?

No, there are no known risks to the woman or her embryos from time-lapse imaging.

What's the evidence for time-lapse imaging?

There have been various studies to try and see if time-lapse imaging can improve birth rates. Initial research has shown some promise, but it's still very early days.

There's certainly not enough evidence to show that time-lapse imaging improves birth rates, which is something you may want to consider if it's being offered to you at an extra cost.

Lister opinion:

We concur that evidence of any real benefit of routine use of time-lapse imaging is lacking. Since the HFEA information was published, a large review has reiterated that "there is no evidence time-lapse is more effective than conventional methods of embryo incubation" (Cochrane review, 2018). We are also very confident of the quality and therefore outcomes of our current incubation methods and therefore have not and will not be moving to routine time-lapse incubators.

We have 2 Embryoscopes (a type of time-lapse incubator) that are sometimes recommended (<1% of cycles) where a clinician or embryologist feels that the information on timing of embryo development may be useful for embryo selection above and beyond conventional methods or may aid understanding of causes of cycle failure.

1 Consent

It is very important that you and your partner, if you have one, discuss your choice of each additional techniques, failure to do so may cause delays when you come to your clinic appointment.

Please only consent to the treatments that have been agreed with you and your consultant as part of your treatment plan. If you are in any doubt this can be confirmed with your nurse at your pre-assessment appointment.

Patient 2.	Patient 1.	
☐	☐	**Assisted Hatching** - I/We do consent to use Assisted Hatching in my/our fresh treatment cycle.
☐	☐	**Artificial Egg Activation** - I/We do consent to use Artificial Egg Activation in my/our fresh treatment cycle.
☐	☐	**Endometrial Scratching** - I/We do consent to use Endometrial Scratching in my/our treatment cycle.
☐	☐	**IMSI** - I/We do consent to use IMSI in my/our treatment cycle.
☐	☐	**Reproductive Immunology Tests and Treatment** - I/We do consent to use Reproductive Immunology Tests and Treatment in my/our treatment cycle. I/We have read the additional information provided on the Lister Fertility Clinic's website (https://ivf.org.uk/investigations/reproductive-immunology/). and have the opportunity to discuss with the Lister clinical team.
☐	☐	**Embryoscope** - I/We do consent to use Embryoscope as an additional technique in my/our fresh treatment cycle

2 Declaration

I/ We confirm that: *

- I/We have read and understood the information provided by The Lister Fertility Clinic about adjuvants.
- I/We have had a discussion with my doctor and have had the opportunity to discuss this procedure.
- I/We understand what the adjuvant involves and are aware of any risks and limitations.
- I/We understand that the HFEA "traffic light rating" system and the rating for the adjuvant we are consenting to.
- I/We understand that there is no guarantee that the transfer of embryos following the use of any adjuvant will result in a successful pregnancy.
- I/We understand that the use of any adjuvant treatment will be at an additional cost (for prices see current price list).

Date

Date