LISTER FERTILITY CLINIC
part of HCA Healthcare UK

Fertility Treatment Adjuvants

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.

Yellow: 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.

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ASSISTED HATCHING

HFEA Rating Red

HFEA Information

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.

ARTIFICIAL EGG ACTIVATION – CALCIUM IONOPHORE

HFEA Rating Amber

HFEA Information

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 fertilsation 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).

ELECTIVE FREEZE ALL CYCLES

HFEA Rating Amber

HFEA Information

What are elective freeze all cycles?

In a normal IVF cycle, one to two fresh embryos are transferred a few days after the egg collection and any remaining suitable embryos are frozen. Elective freeze all cycles involve creating embryos using IVF or ICSI and then freezing all of them so no embryos are transferred in the 'fresh' cycle. The embryos are thawed a few months later and transferred to the woman's womb as part of a frozen embryo transfer (FET) cycle.

There is some evidence that the body's hormonal response to fertility drugs can affect the lining of the womb, which makes it more difficult for the embryos to implant. Freezing the embryos means they can be transferred back into the woman when the womb lining is well developed.

It's also thought by having all their embryos frozen, women are at lower risk of suffering from ovarian hyperstimulation syndrome (OHSS), an overreaction to fertility drugs. This is because OHSS is more common and more severe when it occurs during a pregnancy.

There is also evidence that while the birthweight of babies born from normal fresh IVF cycles is lower, from FET cycles it is higher, closer to naturally conceived babies. Since birthweight is associated with risk of disease in later life, freeze all cycles may be safer for the baby.

Are there any risks of elective freeze all?

The freezing process is generally thought to be safe for the embryo, although there's always a risk that one or more embryos may not survive.

What's the evidence for freeze all cycles?

Research into freeze all cycles is progressing quickly. Some research suggests that pregnancy rates are increased by using frozen embryo transfers (FETs) rather than fresh transfers, and that the risks to mother and baby are lower. These include the risk of OHSS (above) and of low birthweight. However, at the moment, doctors don't know with enough confidence whether freeze all cycles are safer and more effective than conventional IVF or ICSI. There's currently a large clinical trial of freeze all cycles called E-Freeze, which you may be invited to join by your clinic.

Lister opinion:

Several large randomized trials (Shi et al, Vuong et al, NEJM 2018) and a systematic review (Maheshwari et al, 2018) have recently been published and the consensus is that frozen embryos work as well as fresh but not significantly better. So patients can be reassured that if they need to freeze for any reason (minimize OHSS) outcomes will not be compromised but we do not recommend routine elective freezing.

A further large review has looked at outcomes for mum and baby (Roque et al, HRU 2018) and showed no difference in birth defects but other pros and cons for both fresh and frozen transfer that do not give enough of a consensus to electively freeze.

A further information sheet on freeze-all cycles is available.

EMBRYO GLUE

HFEA Rating Amber

HFEA Information

What is embryo glue?

Embryo glue contains a natural substance called hyaluronan, which may improve the chance of the embryo implanting in the womb. It is added to the solution in the dish in which the embryos are kept before being transferred to the woman.

Are there any risks?

There are no known risks from using embryo glue.

What's the evidence for embryo glue?

Research from the Cochrane review shows that embryo glue containing hyaluronan increases pregnancy and live birth rates by around 10%. There is one high quality study in this review which shows that the use of embryo glue improves pregnancy and live birth rates. Other studies in the review were of moderate quality. Further high quality studies are needed before doctors can be confident of the benefits of embryo glue.

Lister opinion:
We are very confident in our current embryo culture techniques that provide excellent success rates. All embryo glue is a variation of culture medium. We are continually looking at ways to improve, and trialled embryo glue within our clinic and found no benefit over our standard techniques. Therefore, we do not recommend or offer embryo glue in view of this lack of benefit especially when there are costs involved to patients.

ENDOMETRIAL RECEPTIVITY TESTING (ERA AND ENDOMETRIO)

HFEA Rating Not categorised

HFEA Information Not available

Lister opinion:

In any cycle, there is a window of opportunity where the endometrium (lining of the womb) is receptive and ready to receive an embryo. It is essential in treatment that embryos be transferred in treatment during this endometrial "window of implantation".

The ERA test has been developed to evaluate the endometrial "receptivity" status of a woman. A small sample from the womb lining on the day an embryo would normally be transferred and is analysed to assess the expression of 236 genes that are key to implantation and is abnormal in approximately 25% of couples with recurrent implantation failure. In these couples, a personalised embryo transfer is then planned to coincide with their individual "window of implantation" improving chances of success.

Initial studies (Ruis Alonso, 2013 Fertil Steril) and our Lister data does demonstrate an improved outcome in these couples and although no randomised top quality studies have yet been published to support this data, a randomized trial is currently in press whose preliminary data demonstrated a significant improvement in outcomes.

Further studies have also suggested that assessing for an imbalance in the natural endometrial biome (natural bacteria lining in the reproductive tract) or for chromic endometritis (inflammation or infection of lining of the womb) and treating may improve outcome. Again these lack randomised studies at present and are only performed in conjunction with ERA testing (as the ENDOMETRIO test) in those with recurrent failures of top quality embryos after discussion

A further information sheet on the ERA and ENDOMTRIO (ERA test is available.

ENDOMETRIAL SCRATCHING

HFEA Rating Amber

HFEA Information

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.

IMSI (INTRACYTOPLASMIC MORPHOLOGY SELECTED SPERM INJECTION)

HFEA Rating Red

HFEA Information

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?

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.

INTRAUTERINE CULTURE

HFEA Rating Red

HFEA Information

What is intrauterine culture?

During a conventional IVF cycle, eggs are fertilised and allowed to develop in a special culture fluid inside an incubator. Intrauterine culture differs in that it allows the early stages of embryo development to take place within the patient's womb. As with conventional IVF, eggs and sperm are

collected and prepared. The eggs are fertilised and placed in an intrauterine culture device, which is inserted into the woman's womb.

The device stays in place for several hours during the initial stages of embryo development. When the device is removed, the embryos are put in an incubator until they are ready to be transferred back to the womb or frozen for use in future treatment.

Are there any risks?

There is currently very little evidence exploring the potential risks in using this device. It's worth noting that the womb is not the right place in the body for the embryo to develop at this stage. Normally it would be living in the 'fallopian' tube which connects the ovary to the womb.

What's the evidence for intrauterine culture?

There's currently no evidence to show that intrauterine culture improves birth rates and is safe. This is something you may wish to consider if you are offered this technique at an additional cost.

Lister opinion:

We do not offer this at the Lister.

PICSI (PHYSIOLOGICAL INTRACYTOPLASMIC MORPHOLOGY SELECTED SPERM INJECTION)

HFEA Rating Red

HFEA Information

What is PICSI?

Physiological intracytoplasmic sperm injection (PICSI) is a technique used to select sperm to use in ICSI treatment. It involves placing sperm with hyaluronic acid (HA), a natural compound in the body. PICSI identifies sperm that can bind to HA and these sperm are selected for use in treatment.

Are there any risks?

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

What's the evidence for IMSI?

There have been a number of studies comparing PICSI with standard ICSI, however there is very little evidence to suggest any benefit of using it. A large randomized study

was recently carried out which showed that using PICSI did not increase the chances of having a baby.

Lister opinion:

We do not offer this at the Lister as offer IMSI as sperm selection method choice in very select cases as discussed above.

PRE-IMPLANTATION GENETIC SCREENING (PGS)

HFEA Rating Amber (Day 5) / Red (Day 3)

HFEA Information

What is PGS?

PGS (also known as aneuploidy screening) involves checking embryos for abnormalities in the number of chromosomes. Embryos with an abnormal number of chromosomes may stop developing very early on, end in a miscarriage or a still birth, or the child may be born with a disorder such as Down's Syndrome.
To do PGS, embryologists remove a cell, or if at a later stage, several cells, from the embryo, which is then tested for any chromosomal abnormalities. The embryo can still develop with fewer cells, as long as this is done carefully.

Are there any risks?

- Although current PGS techniques are mostly very accurate, the test may give the wrong result (it may miss an abnormality or detect one that isn't there).
- Removing a cell from the embryo may damage it and prevent it from successfully developing once it's been transferred to the womb.
- Removing part of the embryo may cause changes in later growth in the womb, which may cause problems in later life.
- In some cases, cells within the same embryo are not chromosomally identical (known as 'mosaic'), which means that PGS may show that the embryo has chromosome abnormalities when in fact it's capable of producing a normal pregnancy or vice versa. In some clinics, mosaic embryos are considered for transfer, even though they show some abnormality.

What's the evidence for PGS?

In the past PGS was traditionally offered to women over 37, couples who had had several miscarriages or failed IVF cycles, people with a family history of chromosome problems, and men whose sperm may carry abnormal chromosomes. The cells were removed from the embryo at the 8-cell stage on day 3.

There is no evidence to show that this type of PGS is beneficial for these groups. In fact studies have shown that this type of PGS can actually reduce success rates, probably because of damage to the embryo.

Three small studies have now shown that PGS carried out at a later stage, the blastocyst embryo on day 5 or 6, might be helpful in selecting a viable embryo to transfer in younger patients who are typically under 37 with no history of miscarriage or failed IVF cycles. However, more evidence is needed to confirm these findings.

Lister opinion:

We do offer PGS at the Lister and as described above only on Day 5 to selected patients where it may be of benefit. Genetically testing an embryo does not change it so in itself will not change chances of a livebirth unless there are several to choose from. In this scenario screening can ensure we choose the most appropriate embryo and avoid freezing abnormal ones and subsequent failed cycles.

Also, in those with recurrent miscarriage testing maybe indicated to provide information to avoid transfer of an abnormal embryo and the potential for further emotional and physical trauma.

Further information on genetic screening is available.

REPRODUCTIVE IMMUNOLOGY TESTS AND TREATMENT

HFEA Rating Red

HFEA Information

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.

SPERM DNA TESTING

HFEA Rating Not categorised

HFEA Information

What is sperm DNA damage?

Half of the genetic information to make us is delivered by the sperm to the egg. It takes around two months for a mature sperm to be made and during this time the DNA of the sperm may become damaged.

A number of different tests might be used by your clinic to assess the level of DNA damage in your sperm. There is some evidence for a relationship between sperm DNA damage and the outcome of fertility treatment. However, the evidence is conflicting and depends on the type of test used by the clinic. The results of a sperm DNA damage test are unlikely to impact on the management of your treatment.

There is currently no traffic light rating for treatments relating to sperm DNA damage.

Are there any risks?

Sperm DNA damage testing is a non-invasive procedure performed on a semen sample, usually before treatment as an additional diagnostic test. There are no significant additional risks to the patient.

Lister opinion:

There are a number of tests for sperm integrity that have been used to assess levels of DNA damage. The one most widely researched that we have chosen to use is the Sperm COMET test.

Studies have demonstrated a longer time to natural conception and lower IUI/IVF success rate in those with higher sperm DNA damage levels even with normal sperm numbers (Bungum et al, AJA 2013). We therefore consider sperm DNA testing in those with otherwise unexplained cause of subfertility as this may play a factor to help guide need for treatment and also treatment choice (i.e. recommend ICSI if damage levels high). Our data confirms an inferior IVF success rate in these couples which is corrected by ICSI unless the levels are particularly high at which point we recommend a urological opinion to assess for any underlying cause (Nicopoullos et al, BFS 2018).

Evidence of a link to recurrent miscarriage has also led to a recommendation to consider testing also in these scenarios (ESHRE guideline, Recurrent Miscarriage 2016).

TIME-LAPSE IMAGING

HFEA Rating Amber

HFEA Information

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.