Developing a traffic light system for treatment add ons

Strategic delivery:	☐ Setting standards	☒ Increasing and informing choice	☐ Demonstrating efficiency economy and value
Details:			
Meeting	Scientific and Clinical Advances Advisory Committee (SCAAC)		
Agenda item	3		
Paper number	HFEA (02/17)01		
Meeting date	06 February 2017		
Author	Anna Quinn, Scientific Policy Manager		
Output:			
For information or decision?	For decision		
Recommendation	Members are asked to: • note the findings from a review of the quality of evidence for treatment add ons; • agree the recommended 'traffic light' rating for each treatment add on.		
Resource implications	None		
Implementation date	Website launch Spring 2017		
Communication(s)	Decisions will be passed on to the communications team to incorporate into the new treatment add ons website content.		
Organisational risk	☐ Low	☒ Medium	☐ High
Annexes	Annex A: Treatment add ons traffic light ratings Annex B: Final treatment add ons website content		

1. Introduction

1.1. Fertility treatment add ons are additional therapies and techniques which are claimed to increase the chance of pregnancy and birth from IVF or other fertility treatments. These add ons can be costly and may involve additional risks to the patient, and often there is limited evidence that they increase pregnancy or birth rates Some add ons have been offered for a number of years while others are more recent developments.

1.2. Central to the HFEA's 2017-2020 strategy is publishing clear patient information about the efficacy of treatments and treatment add ons. We want to increase lay people's insights into the science behind treatments and the evidence base for different treatment types, so that they can make informed decisions about their treatment options. To this end, new patient information and a traffic light system for treatment add ons will be published on the HFEA website in Spring 2017. We also want to encourage more research – laboratory and clinical - which will add to the evidence base for treatment add ons and ultimately improve the quality of treatment.

1.3. The committee considered patient information on treatment add ons in February and June 2016 and members have worked between meetings. Members have agreed website text for the following nine add ons that they think patients most need information about:

- Artificial egg activation
- Assisted hatching
- Elective freeze-all
- Embryo glue
- Endometrial scratching
- Intrauterine culture
- Preimplantation genetic screening
- Reproductive immunology
- Time-lapse imaging

1.4. Clear and honest patient information about these nine add ons will be published when the new HFEA website launches in Spring 2017, along with an indication of the likely price range for add ons. To accompany the patient information, we have been working with the committee to develop a visual indication of whether the use of a particular add on is supported by good quality clinical evidence. This indicator will take the form of a traffic light system.

2. Traffic light system

2.1. As mentioned above, a traffic light system will be used alongside our patient information to give a quick, visual indication of whether any particular add on is

supported by good quality clinical evidence. The categories that treatment add ons will be sorted into are:


Red: add ons with little or no published evidence to support them, or where the evidence shows they do not improve clinical outcomes;


Amber: add ons with moderate evidence supporting their use; and,


Green: add ons that are supported by high quality clinical evidence.

Independent assessment of the quality of evidence

2.2. In order to categorise the nine treatment add ons under consideration, it was necessary not only to identify the published evidence around each add on, but also to assess the quality of that evidence. For this reason, we sought advice from an expert in systematic reviews and evidence assessment to carry out an independent assessment of the quality of evidence (using the GRADE methodology[1]) for each treatment add on.

2.3. For each treatment add on, the evidence published in the last 10 years was sent to an independent reviewer. Where there was a large body of published evidence, only randomised controlled trials were sent in order to limit the time taken for the review. The reviewer then carried out an assessment of the quality of evidence for each add on using the GRADE methodology.

2.4. A paragraph summarising the findings of this assessment for each add and the independent reviewer's recommended ratings can be found at Annex A, along with the current traffic light rating agreed in consultation with the committee. Where the independent reviewers recommended rating does not match the current rating, the committee will be asked to agree the final traffic light rating for the add on. Two add ons (reproductive immunology and time-lapse imaging were not assessed by the independent reviewer as the committee has reviewed them in detail recently. The patient information for treatment add ons can be found at Annex B.

3. Next steps for treatment add ons

Process for review

3.1. As new research is published it will be necessary to review our assessment of the quality of evidence to ensure that our patient information and traffic light system remain up to date.

3.2. As part of SCAAC's annual horizon scanning process, the Executive will collate published research relating to treatment add ons and ask the committee to assess whether the current patient information or traffic light rating for any treatment add ons needs to be reviewed. The Executive will then seek an

[1] GRADE is an approach for grading the quality of evidence and the strength of recommendations. It was developed by the Grading of Recommendations, Assessment, Development and Evaluation Working Group.

independent assessment of the quality of evidence for the treatment add on and consider whether any amendments are required.

3.3. Based on the research collated through the horizon scanning process, the committee will also be asked if any new treatment add ons need to be added to the HFEA patient information. If a need for new patient information is identified, the Executive will seek an independent assessment of the quality of evidence for the particular add on and assign a traffic light rating to it.

3.4. We propose that for 2017 we consider developing patient information and a traffic light rating for:

- DNA fragmentation
- Intracytoplasmic morphological sperm injection (IMSI)
- Physiological intracytoplasmic sperm injection (PICSI)

Delivering the HFEA 2017-2020 strategy

3.5. The new patient information and traffic light system will be published on the HFEA website in Spring 2017. This will be accompanied by an awareness campaign.

3.6. We will work closely with stakeholders and professional societies to consider what responsible innovation looks like and will hold a discussion on this topic at the HFEA conference in March 2017

3.7. We will explore how we could encourage and perhaps facilitate research which adds to the evidence base for each treatment add on (and future ones)

4. Recommendations

4.1. The committee is now asked to:

- consider the quality of evidence for each treatment add on based on the findings from an independent assessor at annex A;
- agree traffic light categories for each treatment add on; and
- agree proposals for patient information and traffic light rating at 3.4. for 2017

Annex A: Treatment add ons traffic light ratings

1. Artificial egg activation

Background

Artificial egg activation is currently rated as amber. There is some evidence that egg activation using calcium ionophore may improve fertilisation rates in ICSI cycles where activation has failed in previous treatment cycles. The patient information will highlight that only a few studies have been carried out to date. The independent reviewer has assessed the quality of evidence around artificial egg activation and recommends a traffic light category of red due to the limited evidence available. The committee is therefore asked to agree a final traffic light category for artificial egg activation.

Current traffic light category:

Traffic light category recommended by independent reviewer:

Independent reviewer comments:

"Two studies were reviewed. The first, Meerschaut 2012, was a within-patient design on sibling oocytes that did not specify allocation method. The design does not allow interpretation of the clinical outcomes but more embryos were fertilised in the 'activation' arm. The second, Aytac 2015, randomised couples with diminished ovarian reserve but normal sperm parameters and no previous fertilisation failure. They identified both more transfers in the activation group and more pregnancies per transfer, leading to statistically non-significant, higher ongoing pregnancy rate. Results overall therefore show early promise but there is very little clinical evidence to make a recommendation for practice."

2. Assisted hatching

Background

Assisted hatching is currently rates as red. The National Institute for Health and Care Excellence says that "assisted hatching is not recommended because it has not been shown to improve pregnancy rates"[2]. The independent reviewer was in agreement with the committee's traffic light rating as there was no clear evidence of effectiveness. The committee is asked to confirm that assisted hatching will be categorised as red.

Current traffic light category (also recommended by independent reviewer):

Independent reviewer comments:

"a) Fresh embryos: Nine studies, comprising eight RCT and one retrospective cohort, were reviewed. Studied populations included younger and older women (e.g. Kutlu 2010) with a range of prognoses. Intervention was applied to all embryos except in Hagemann 2010, where only those with thick zona pellucida (ZP) were treated. All described intervention with embryos at Day 2 or 3 performed on the day of transfer except Balakier 2009, in which timing was unreported. Most used a laser to thin the ZP. Alternative approaches assessed by RCT were creation of a hole by laser (Sagoskin 2007, Razi 2013) and chemically (Hagemann 2010). In the retrospective study, Chang 2016, any form of assisted hatching was included. No RCT reported a secure method of allocation concealment but three reported blinding of clinician and patient. The estimated OR for clinical outcome ranged from 0.58 to 1.3, with the largest studies centred around 1.0.

b) Frozen embryos: Six studies, comprising four RCT, one matched experimental design and one retrospective cohort, were reviewed. The four RCT, all published by 2010, allowed broad eligibility criteria for women whose embryos had been frozen at cleavage stage and survived thawing. Three RCT compared laser thinning with no intervention. The other, Fang 2010, used an ICSI needle to pierce the ZP and expanded for up to 30 seconds to thin using hydrostatic pressure. This was compared with piercing alone. The experimental design, Wang 2016, non-randomly assigned different extents of laser thinning to sets of four sibling embryos. No study reported a secure method of allocation concealment. Only Ge 2008 and Valojerdi 2010 reported blinding of the clinician, and only the former also reported blinding of the patient. It is not possible from the published data to reconstruct clinical results from the 'per embryo' presentation of Fang 2010 and therefore to assess their claim of benefit. Balaban 2006 and Ge 2008 reported promising but non-significant effects. Results of Valojerdi 2010 are irreconcilable with these,

[2] National Institute of Health a Care Excellence. Fertility problems: assessment and treatment. Point 1.12.5.5. https://www.nice.org.uk/guidance/cg156/chapter/Recommendations. Accessed January 2017

reporting statistically significant harm with non-overlapping confidence intervals. One proposed explanation is the use of vitrified embryos. Vitrification was also used in the experimental design of Wang 2016, which observed improved hatching but decreased blastocyst formation with increased intervention. Unfortunately these data were presented and analysed as if from an unmatched design."

3. Elective freeze-all

Background

Elective freeze-all is currently rated as amber. The freezing process is generally thought to be safe for the embryo, although there's always a risk that some embryos may not survive. One possible benefit of elective freeze-all is reducing the risk of ovarian hyperstimulation syndrome (OHSS). It is currently unclear whether freeze-all cycles are safer or more effective than conventional IVF or ICSI. The independent reviewer assessed the quality of evidence around elective freeze-all and recommended a red traffic light rating due to lack of evidence is this area. However, the independent reviewer did not assess the safety or efficacy of frozen embryo transfer more generally. The committee is therefore asked to agree a final traffic light category for elective freeze-all.

Current traffic light category:

Traffic light category recommended by independent reviewer:

Independent reviewer comments:

"Three RCT were reviewed. Despite description of good trial methods, Aflatoonian 2010 has been retracted following "results of an investigation" due to "serious methodological flaws". Clearly results cannot be relied upon. The two remaining studies, Shapiro 2011a and 2011b, were from the same team. They compared freezing of all oocytes followed by blastocyst transfer with fresh blastocyst transfer, selecting the best one or two for transfer in each case. The difference was in eligibility criteria, reporting 'normal responders' (8 to 15 antral follicles) in 2011a and 'high responders' (>15 antral follicles) in 2011b. Each used an insecure method of allocation concealment and blinding would not have been possible. Both stopped early on planned interim analyses: the first for efficacy and the second due to unacceptably high multiple conception rate. Despite this, both found statistically non-significant higher rates of 10-week pregnancy with the freeze-all policy."

4. Embryo glue

Background

Embryo glue is currently rated as green. This rating was agreed based on a Cochrane review which shows that embryo glue containing hyaluronan increases pregnancy and live birth rates by around 10%. The independent reviewer assessed the quality of evidence around embryo glue and recommended an amber traffic light rating. Whilst almost all studies reported an increase in clinical outcomes with embryo glue, most studies were of moderate quality and some were at high risk of bias. The committee is therefore asked to agree a final traffic light rating for embryo glue.

Current traffic light category:

Traffic light category recommended by independent reviewer:

Independent reviewer comments:

Nine studies, comprising eight RCT and one prospective, matched design, were reviewed. There was substantial variation in eligibility criteria with frozen and fresh transfers on day 2 to day 5 of development. There was also variation in product and protocol, with embryos spending from at least ten minutes to four hours in the transfer medium. Only one study reported adequate allocation concealment. All the RCT claimed to have blinded both clinician and patient to the allocated intervention but for three of these this information had been obtained by Cochrane Reviewers rather than from the source report. Several of the RCT were at high risk of bias. Three adapted or stopped on the basis of interim analyses and one, conducted without ethical approval, appeared to contain previously published data, suggestive of unplanned interim analyses. A fifth RCT appeared to have both post-randomisation exclusions and pre-randomisation inclusions. All studies apart from the first, Morbeck 2007, found qualitatively in favour of embryo glue. The methodologically strongest study, Urman 2008, found significantly increased live birth rate.

5. Endometrial scratching

Background

Endometrial scratch is currently rated as amber. Early results suggest that this technique could increase pregnancy rates. The independent reviewer was in agreement with this assessment as there was consistent, moderate quality evidence supporting the use of endometrial scratching. The committee is therefore asked to agree that endometrial scratching will be categorised as amber.

Current traffic light category (also recommended by independent reviewer):

Independent reviewer comments:

"Eleven studies, comprising ten randomised trials (RCT) and one prospective, patient-preference design, were reviewed. There was substantial variation in eligibility criteria: different studies targeted groups undergoing expectant management, controlled ovarian stimulation, IUI and IVF/ICSI; with and without requirement for multiple previous implantation failures; and with follow-up ranging from one cycle to six months. Three RCT included a 'placebo procedure' to attempt blinding of the patient to allocation. Two of these three, and one additional trial, described an adequate method of allocation concealment to guard against selection bias. Otherwise, there were no particular risks of bias from loss to follow-up, selective reporting or other sources. Only two trials reported live birth. Results were consistent despite the diversity of eligibility criteria, clinical protocols and outcomes reported, with odds ratio (OR) ranging from 1.3 to 4.4."

6. Intrauterine culture

Background

Intrauterine culture is currently rated as red. This technique is currently being offered by one clinic in a clinical trial setting. There is not enough evidence to show that intrauterine culture improves births rates and is safe. This assessment was mirrored by the independent reviewer who recommended a red traffic light rating. The committee is therefore asked to confirm that intrauterine culture will be categorised as red.

Current traffic light category (also recommended by independent reviewer):

Independent reviewer comments:

"Only one study, Blockeel 2015, was reviewed. This was a clinical, experimental design in which sibling oocytes were non-randomly assigned to four different conditions ranging from zero to three days of '*in utero* culture system'. The embryos that were cultured *in vivo* were selected at least as often as being of sufficient quality for transfer but the nature of the design cannot inform regarding relative clinical outcomes. Results therefore show early promise but there is no clinical evidence to make a recommendation for practice".

7. Preimplantation genetic screening (PGS)

Background

PGS currently has an amber traffic light rating. The proposed patient information on this topic explains that there is no evidence that PGS carried out on embryos biopsied on day 3 is effective and it may even reduce success rates. There are three studies which assess PGS on embryos biopsied on day 5 or 6 and these suggest that PGS may improve success rates. However further research is required to confirm these findings. The independent reviewer recommended a red traffic light rating for PGS on the basis that it may cause harm when carried out on day 3 embryos, and there is very little evidence looking at PGS on day 5 embryos. The committee is therefore asked to agree a final traffic light rating for PGS.

Current traffic light category:

Traffic light rating recommended by independent reviewer:

Independent reviewer comments:

"a) Day 3 embryo - Eight studies, comprising seven RCT and one, three-group cohort comparison, were reviewed. Most assessed blastocyst transfer during the fresh cycle, but one RCT, Mastenbroek 2007, allowed up to three cycles. This study was also the only one to attempt blinding of clinician and patient, and one of only two to report an adequate method of allocation concealment. There were several serious methodological risks of bias, including early and repeated randomisation. The first and methodologically strongest study found significant detriment. Subsequent studies, with a variety of eligibility criteria, found similar results.

b) Day 5 embryo - Three RCT were reviewed. All studies considered a single fresh transfer cycle and employed assisted hatching on day 3 in both groups to facilitate PGS of the blastocyst. Yang 2012 used elective single embryo transfer (eSET) in both groups of women with no previous IVF attempts. Forman 2013 compared eSET in the PGS group with double embryo transfer (DET) in the controls. Scott 2013, from the same research team, compared DET on day 6 in the PGS group with day 5 DET in the controls. Yang 2012 did not report allocation concealment but attempted to blind patients to their intervention. The other two studies concealed allocation in open-label studies. Yang 2012 and Scott 2013 both reported significantly better outcome with PGS, whereas Forman reported non-significantly fewer on-going pregnancies. Results overall show early promise but the three RCT (two from one group) ask different questions. There is little clinical evidence to make a recommendation for practice".

8. Reproductive immunology

Background

The committee has previously agreed a red traffic light rating for reproductive immunology. The committee considered a detailed literature review on this topic in 2015[3] and concluded that there is insufficient data from well-designed randomised controlled trials to support the safety and efficacy of immune therapies in IVF. Reproductive immunology treatments are used to suppress the body's natural immunity and there are risks attached to these treatments. The committee is therefore asked to confirm that reproductive immunology will have a red traffic light rating.

Current traffic light category:

Findings from evidence assessment:

The independent reviewer did not assess evidence around reproductive immunology because the committee has recently considered this topic in detail.

9. Time-lapse imaging

Background

The committee has previously agreed an amber traffic light rating for time-lapse imaging. This committee considered this topic in detail in 2015 when three experts presented their Cochrane review findings and an assessment of the evidence in this area. The committee heard that there is insufficient evidence of difference in live birth rates, miscarriage, still birth or clinical pregnancy rates between time-lapse imaging and conventional incubation. The committee noted in 2015 that time-lapse incubators are high quality incubators even without using an algorithm to analyse time-lapse images. Many clinics are already committed to using this technology which may confound clinical trials in this area. The committee are asked to confirm that time-lapse imaging will have an amber traffic light rating.

Current traffic light category:

Findings from evidence assessment:

The independent reviewer did not assess evidence on time-lapse imaging because the committee has recently considered this topic in detail.

[3] Scientific and Clinical Advances Advisory Committee Paper. Reproductive Immunology Update 2015. http://www.hfea.gov.uk/docs/2015-02-04_SCAAC_-_Reproductive_immunology.pdf

Studies reviewed by the independent reviewer

Adjunct	Study	DOI/reference
Intrauterine Culture	Blockeel 2015	doi:10.1093/humrep/dep005
Artificial Egg Activation	Meerschaut 2012	doi:10.1093/humrep/des097
	Aytac 2015	dx.doi.org/10.1016/j.fertnstert.2015.07.1163
Endometrial Scratching	Raziel 2007	10.1016/j.fertnstert.2006.05.062
	Karimzadeh 2009	10.1111/j.1479-828X.2009.01076
	Narvekar 2010	10.4103/0974-1208.63116
	Abdelhamid 2012	10.1007/s00404-013-2785-0
	Gibreel 2013	10.1111/j.1447-0756.2012.02016.x
	Parsanezhad 2013	IRCT:2012082510657NI
	Zarei 2014	IRCT:2012070810210NI
	Wadhwa 2015	J Hum Reprod Sci 2015;8(3):151-8.
	El Khayat 2015	dx.doi.org/10.1016/j/ejogrb.2015.08.025
	Mahey 2015	dx.doi.org/10.1016/j.fertnstert.2015.07.1163
	Maged 2016	10.1177/1933719115602776
Embryo Glue	Morbeck 2007	NCT005882250
	Mahani 2007	EMHJ 2007;13(4):876-80.
	Friedler 2007	10.1093/humrep/dem220
	Korosec 2007	RBM0 2007;15(6):701-7.
	Hazlett 2008	10.1016/j.fertnstert.2007.05.063
	Urman 2008	10.1016/j.fertnstert.2007.07.1294
	Dittmann-Muller 2009	Hum Reprod 2009;24 Suppl 1:167.
	Fancsovits 2015	10.1007/s00404-014-3541-9
	Singh 2015	10.4103/0974-1208.170398
PGS (Day 3)	Mastenbroek 2007	NEJM 2007;357:9-17.
	Hardarson 2008	10.1093/humrep/den217
	Staessen 2008	10.1093/humrep/den367
	Blockeel 2008	RBMO 2008;17(6):848-54.
	Meyer 2009	10.1016/j.fertnstert.2008.02.162
	Schoolcraft 2009	10.1016/j.fertnstert.2008.05.029
	Sher 2009	10.1016/j.fertnstert.2008.11.029
	Debrock 2010	10.1016/jfertnstert.2008.10.072
PGS (Day 5)	Yang 2012	Molec Cytogen 2012;5:24
	Forman 2013	10.1016/j.fertnstert.2013.02.056
	Scott 2013	10.1016/j.fertnstert.2013.04.035
Freeze All	Aflatoonian 2010	10.1007/s10815-010-9412-9
	Shapiro 2011a	10.1016/j.fertnstert.2011.05.050
	Shapiro 2011b	10.1016/j.fertnstert.2011.02.059
Assisted Hatching: Fresh	Sagoskin 2007	10.1016/j.fertnstert.2006.07.1498
	Ge 2008fresh	RBMO 2008;16(4):589-96.
	Balakier 2009	10.1016/j.fertnstert.2008.07.1729
	Hagemann 2010	10.1016/j.fertnstert.2009.01.116
	Kutlu 2010young	10.1007/s10815-010-9431-6
	Kutlu 2010old	10.1007/s10815-010-9431-6
	Razi 2013	Iran J reprod Med 2013;11(12):1021-6.
	Shi 2016	10.1177/1933719116641764
	Chang 2016	F&S 2016;106(3) Suppl:e314
Assisted Hatching: Frozen	Balaban 2006	10.1093/humrep/del097
	Ge 2008froz	RBMO 2008;16(4):589-96.
	Valojerdi 2010	10.1016/j.rbmo.2009.11.002
	Fang 2010	10.1016/j.fertnstert.2009.08.014
	Wang 2016	10.3892/br.2016.716
	Knudtson 2016	F&S 2016;106(3) Suppl:e141

Annex B: Final patient information on treatment add ons

Treatment add ons

Your clinic may offer you additional treatments on top of your main treatment such as IVF or ICSI. This page will explain what some of the most common treatment add ons are and how effective they are. For more detailed information, you may want to contact a clinic to discuss this further with a specialist. Some of these add ons are also offered on the NHS.

What are add ons?

Add ons are optional extras that you may be offered on top of your normal fertility treatment, often at an additional cost.

They're often emerging techniques that may have shown some promising results in initial studies but haven't necessarily been proven to improve pregnancy or birth rates.

Some clinics may include certain add ons with their treatment packages as standard whilst others charge separately.

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, look for these symbols:



What do the ratings mean?

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 RCTs and follow up studies to be sure a new procedure is effective and safe.

We have given a treatment a green tick if good quality research has been done and shows a positive effect.

We have used a question mark where there is a growing body of evidence but further research is required.

Where we have shown an exclamation mark, studies show that this treatment is either not effective or does not have enough evidence to show it is effective and safe.

Artificial egg activation – calcium ionophore

Traffic light symbol: amber (tbc)

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.

Assisted hatching

Traffic light symbol: red (tbc)

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.

Elective freeze all cycles

Traffic light symbol: amber (tbc)

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.

Find out more about the risks of fertility treatment

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.

Find out more about embryo freezing

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.

Embryo glue

Traffic light symbol: green (tbc)

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%.

Endometrial scratching

Traffic light symbol: amber (tbc)

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.

Intrauterine culture

Traffic light symbol: red (tbc)

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 not enough 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.

Pre-implantation genetic screening (PGS)

Traffic light symbol: amber (tbc)

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?

PGS carries the same risks as PGD, which you can read about here. However, PGS may have some additional 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 improve success rates 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.

Find out more about PGS

Find out more about blastocyst embryos

Reproductive immunology tests and treatment

Traffic light symbol: red (tbc)

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 (eg 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.

Time-lapse imaging

Traffic light symbol: amber (tbc)

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.

NHS choices has further information on the evidence for time-lapse imaging here: http://www.nhs.uk/news/2013/05May/Pages/Time-lapse-technique-may-boost-success-rate-of-IVF.aspx