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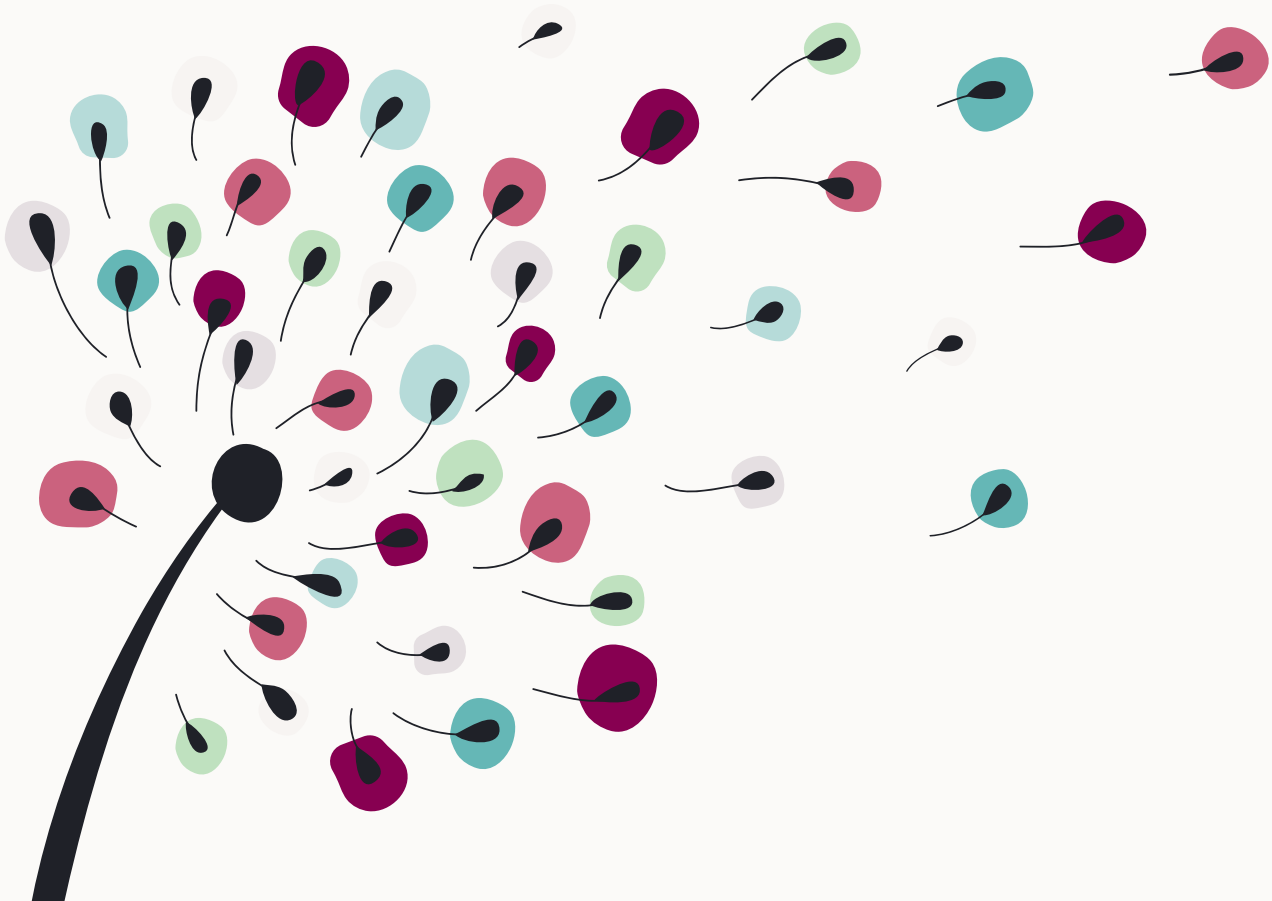
A guide to using IVF add-ons rationally and effectively



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How to use your IVF add-ons rationally and effectively



By Dr Thanos Papathanasiou,
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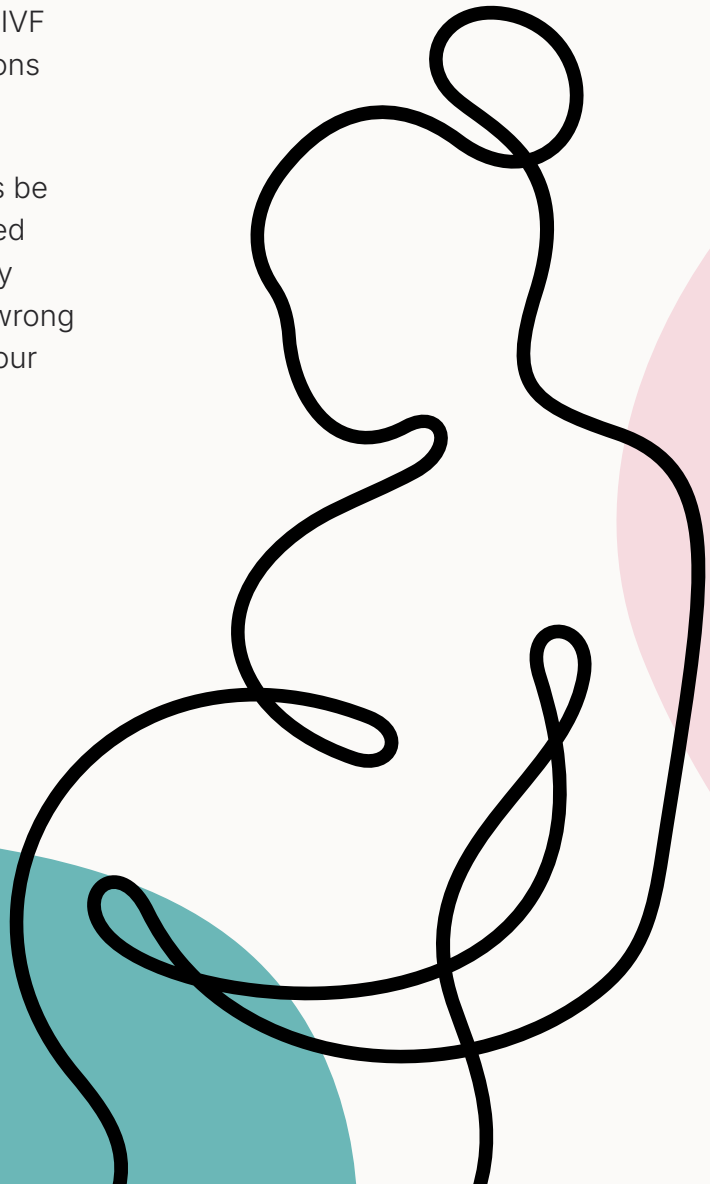
Advances in IVF treatment and technology offer a multitude of add-on options for your IVF experience. However, navigating these options can be challenging, even daunting.

Unfortunately, IVF treatment may not always be successful, even when everything has looked very promising. When this happens, it is only natural to try to understand what has gone wrong and what else could be done to maximise your future success.



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When should I start thinking about using add-ons?

Our advice is to be selective with what add-ons you consider for your first treatment. IVF (with or without ICSI) already addresses several fertility problems, such as low sperm, damaged tubes, ovulation problems or endometriosis. For most couples, IVF already provides a better chance of having a baby compared to trying to conceive naturally.

If your first IVF has not worked, it will still have provided important feedback on performance of the eggs, sperm and the lining of the womb. For example, you will know whether your ovaries have made enough eggs, if the eggs and sperm joined easily, or if you made good-quality embryos.

This knowledge, combined with advice from our fertility specialists, will help you fine-tune and optimise your subsequent cycles.

It is important to remember that while many IVF add-ons have been found to work for some patients, they do not have a rigorous evidence base to support wider use and are still under ongoing scrutiny and research.

For more information, read the add-ons section on the **HFEA website** (www.hfea.gov.uk/treatments/treatment-add-ons/).



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IVF add-ons available at Bourn Hall

Add-on	Test or Intervention	Focus on	Fresh cycle	Frozen cycle	Self-funded (private)	NHS
PGT-A	Test and intervention	Female age Egg - Sperm - Embryo	●	●	●1	
Hysteroscopy	Test	Endometrium	●	●	●1	●
EMMA-ALICE	Test	Endometrium	●	●	●1	●
ERA	Test	Endometrium		●	●	●
EmbryoGlue	Intervention	Endometrium	●	●	●1	
Injectable progesterone	Intervention	Endometrium	●	●	●1	After embryo transfer
Progesterone monitoring during stimulation	Test	Endometrium	●		●1	
Progesterone levels before transfer	Test	Endometrium		●	●1	
IMSI	Intervention	Sperm	●		●1	
ZyMot	Intervention	Sperm	●		●1	
Time-lapse (GERI)	Intervention	Embryo	●		●1	
Endometrial scratch	Intervention	Endometrium	●	●	●	●
Sperm DNA fragmentation (COMET) test	Test	Sperm	●		●1	●
Immune treatments	Intervention	Endometrium	●	●	●	
Growth hormone	Intervention	Egg Endometrium	●		●	
Blood thinners	Intervention	Endometrium	●	●	●1	
Assisted hatching	Test	Female age, frozen embryo	●	●	●	

1= *Means the add-on can be considered even for the 1st Self-funded IVF cycle, after discussion with your Bourn Hall fertility specialist.*

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Which add-ons are suitable for me?

Women aged under 37 with good-quality embryos

If you are under 37 years old undergoing IVF, and you have previously created good-quality embryos, we would suggest that you think about add-ons that focus on the endometrium (the lining of the womb).

As there are numerous add-ons that affect the lining of the womb, consider the following when deciding which to use:

Is your next cycle a fresh or a frozen one?

Some add-ons are only applicable to a certain type of cycle.

Should you aim for an add-on test or an add-on intervention?

If you are at the beginning of your IVF journey and you had one or two failed embryo transfers, you may be more inclined to try an intervention in an empirical way, to see if it makes a positive difference. Most interventions are easy to add to your treatment plan and overall will not delay your treatment.

If you experience significant difficulties with IVF - say, more than a couple of failed transfers - you may wish to consider an IVF add-on test.

Most testing can be performed one to two months before your actual cycle and the results can be available to fine-tune your upcoming IVF cycle.It is also important for you to have some answers why your IVF journey is not so easy. Tests are typically performed once, and their recommendations apply to all future cycles.

What is the medical advice?

If you are considering any add-ons, please discuss them with our fertility specialists. They will help you understand what we know - and what we don't know - about them, how effective and safe they may be in your case.

What is the cost?

Depending on the technology used, some add-ons are more expensive than others. Therefore, cost also needs to be considered in your final decision-making. Our finance advisers or Patient Support team will happily provide you with transparent pricing in advance of your next cycle.

After receiving the necessary information by our specialists, you will be asked to sign a consent form for the particular add-on(s), to ensure that you have understood the advice received and you are happy to use them.

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Over 35 years and satisfactory egg reserve (or good-quality blastocysts)

If you are over 35, you are likely to make a significant proportion of embryos that are genetically abnormal. These abnormal embryos will typically not implant successfully or may subsequently miscarry. In women over 35 years old, therefore, we think more about the 'embryo' factor.

This is where preimplantation genetic testing for aneuploidy (PGT-A) becomes an attractive option. PGT-A involves testing your individual embryos to find out which ones are genetically normal. Only the normal ones are then transferred as frozen-thawed during a subsequent cycle, and these embryos have a high chance of becoming babies. In practical terms, as long as you have a 'normal' embryo for transfer, with PGT-A you should expect to be as successful as a younger woman who is under 35 years old.

An additional benefit of PGT-A is that you can still aim to transfer single embryos, because each has a high chance of success. This makes your IVF cycle safer, as you minimise the medical risks associated with a multiple pregnancy.

There are some requirements though; you need to make good quality blastocyst embryos to undergo PGT-A. If you have not had IVF already, you don't know for certain if you can make blastocysts, so it is important that you have a reasonable egg reserve. Hopefully, this will help you harvest enough eggs so that the embryos can be cultured to the blastocyst stage.

There is also a chance that after PGT-A, you will have no 'normal' embryos for transfer (this is more common with women in their forties). Even in this case though, you will have more confidence to decide what to do next; you may well decide to create and test more embryos, and you will have also avoided an 'unnecessary' transfer.

We offer PGT-A packages that will allow you to move swiftly through egg retrievals. In addition, you also have the option to combine PGT-A and endometrial optimisation. It is worth remembering that the lining of the womb could still be a contributor in older women having IVF.

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Concerns with embryo quality

If you struggle to make good-quality embryos, you need to take a hard look at the egg and the sperm.

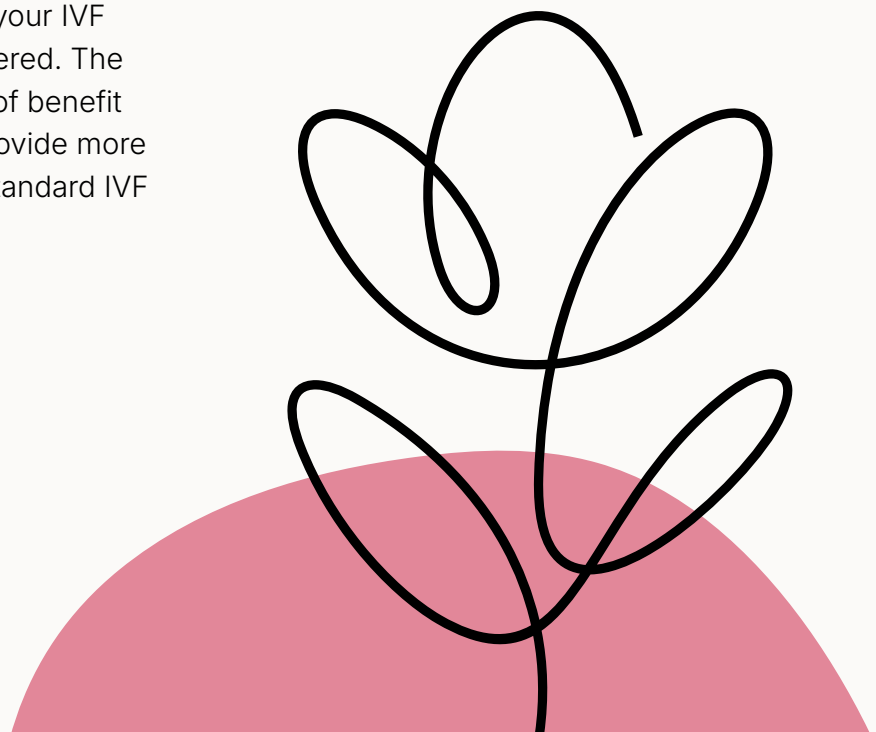
It is easier to investigate the sperm further. You could consider a sperm DNA fragmentation test, to understand how much the sperm contributes to embryo quality issues; in such cases you may find substantially high DNA damage. ICSI, or IMSI, may help when the sperm is contributing to low-quality embryos as will using our time-lapse incubator GERI. Male supplements may also help.

If the female partner is over 35 years old, or there is history of PCOS, this may suggest that the egg is contributing to embryo quality issues. Lifestyle optimisation may help with PCOS, as well as certain supplements. Growth hormone can help improve the egg quality for some women. Modifications to your IVF drug protocol could also be considered. The time-lapse GERI incubator may be of benefit to some embryos and is likely to provide more feedback on embryo quality than standard IVF incubators.

If you repeatedly create embryos that are not of high quality, it is important that you also take onboard the reflection and input from our consultants. We have substantial expertise within our medical function, and we are used to dealing with particularly challenging cases. Many patients come to us after having had failed treatments elsewhere.

Our team of embryologists and fertility experts are here to help you and are available to consider your individual care.

We wish you the very best for your IVF journey.



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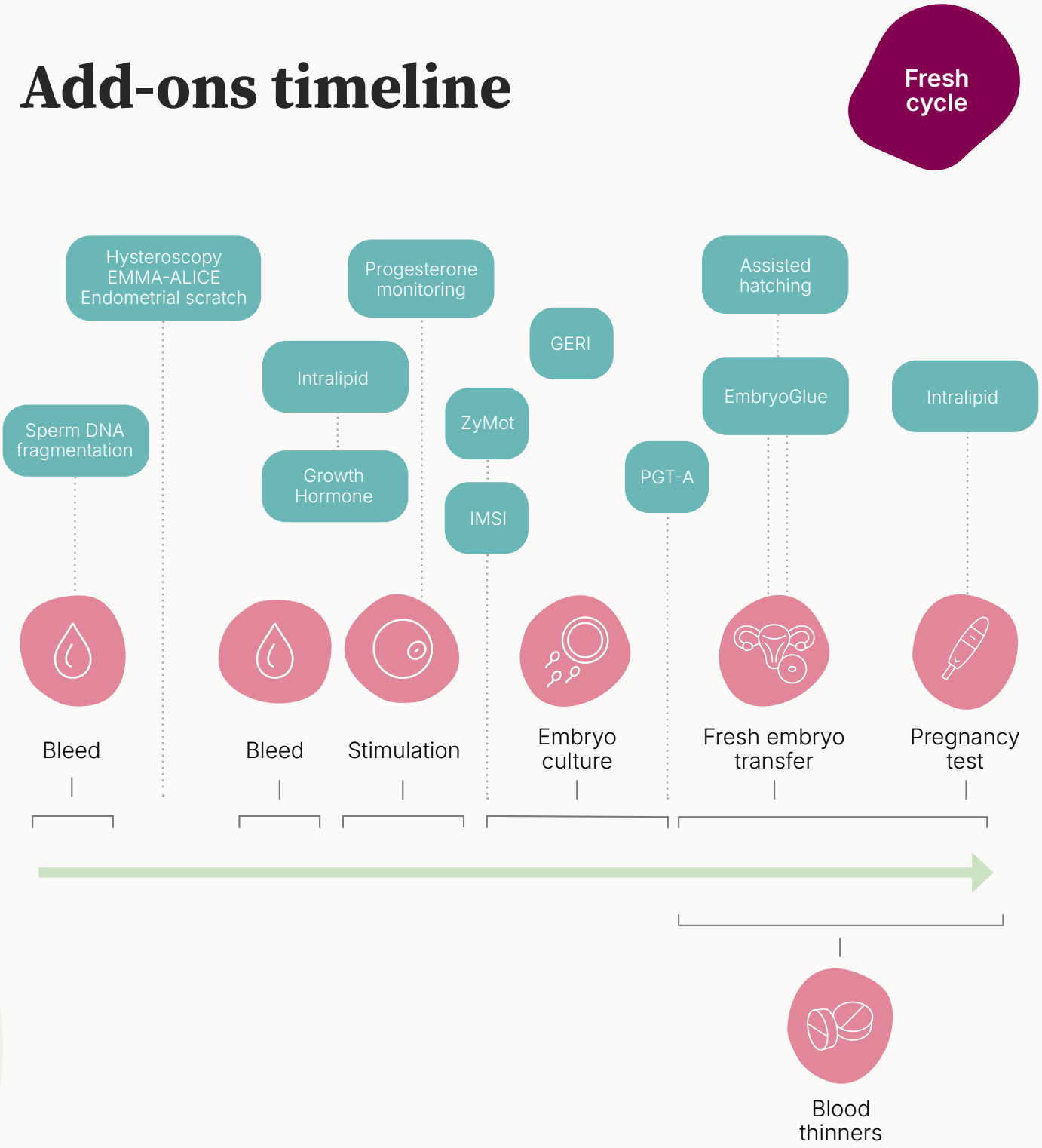
Add-ons timeline



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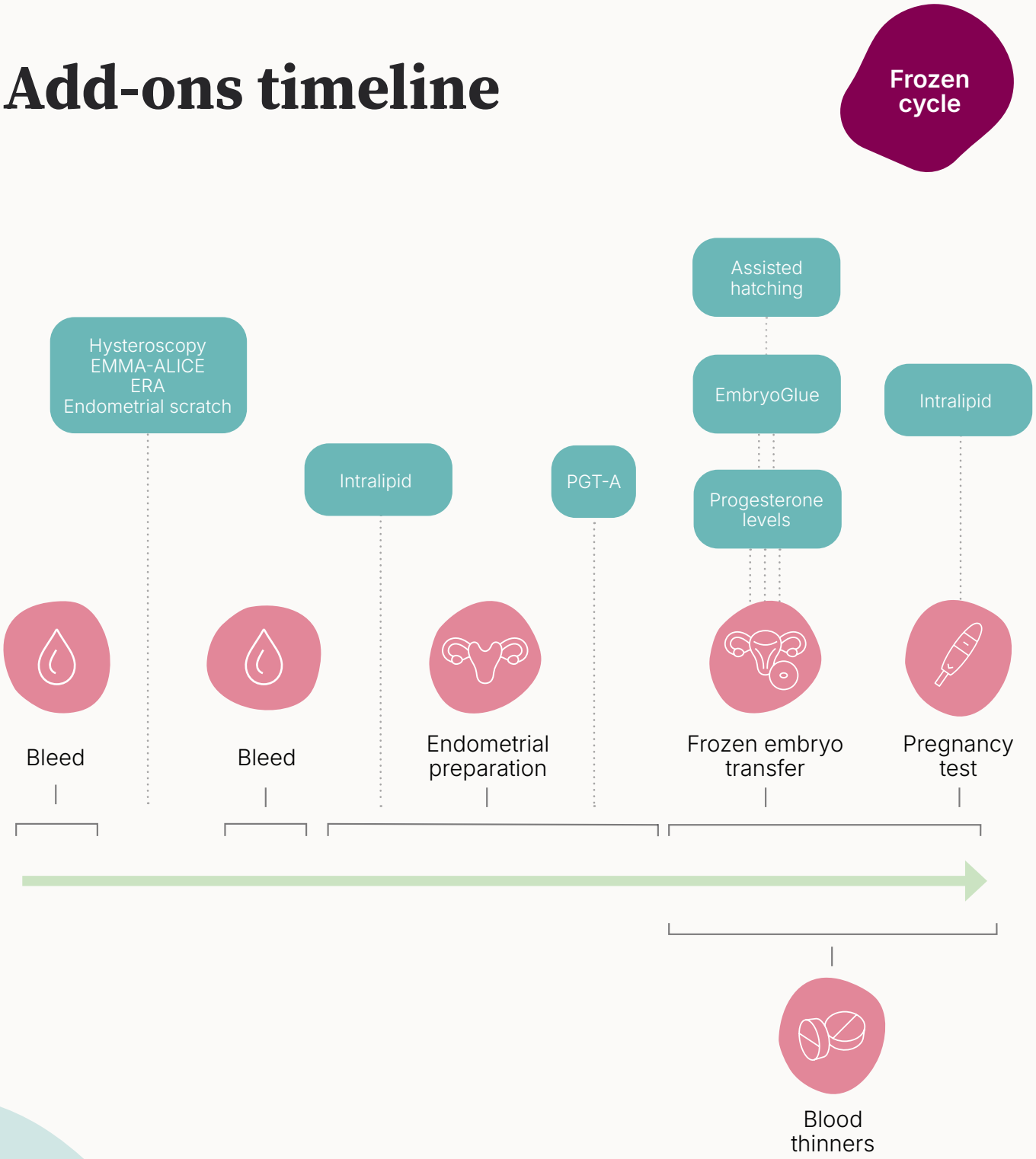

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Add-ons in detail

Over the following pages we have outlined each of the options with how they work, who they are appropriate for and the science behind them

Add-on	How does it work?	Who does it benefit?	The science
PGT-A	• Identifies your best embryos before transfer, by taking a small sample of each blastocyst embryo for genetic analysis	• Women over 35 years of age • Women who have had a previous miscarriage, especially those known to have been caused by chromosomal imbalance • Women who have had repeated implantation failure • Anyone who aims to avoid multiple pregnancy because of medical or personal reasons • Available at Bourn Hall Cambridge only	• Typically, no more than half of the embryos created during IVF are genetically normal (euploid). Women over 35 make fewer euploid embryos • PGT-A identifies euploid embryos and thus helps avoid potentially 'unnecessary' transfers
Hysteroscopy	• It investigates the cavity of the womb with a camera, aiming to confirm normality and exclude polyps, scars or cavity-protruding fibroids	• Persistently thin lining • Previous failed embryo transfer • Scans suggests an abnormality within the cavity of the womb • Women with frequent and/or heavy bleeding • Available at Bourn Hall Cambridge and Essex (Wickford)	• Hysteroscopy is the 'gold standard' check for the anatomy of the cavity of the womb. It may find a problem when simpler tests, such as scans, have not. Some conditions identified by hysteroscopy can be treated to optimise implantation and reduce the risk of miscarriage or problems arising from the placenta in advanced pregnancy
EMMA-ALICE	• It involves taking a sample of the lining of the womb, aiming to identify 'hidden' issues in the lining of the womb	• Previous failed embryo transfer	• **EMMA** checks for imbalance in the flora (microbiome) of the lining of the womb. If an imbalance is identified, specific treatment may optimise the lining • **ALICE** checks for low-grade infection of the lining of the womb (chronic endometritis). If infection is identified, specific antibiotic treatment can be offered

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Add-ons in detail

Add-on	How does it work?	Who does it benefit?	The science
ERA	• It may help identify the best day for frozen embryo transfer	• Planning a frozen embryo transfer (preferably when on oestrogen and progesterone medication) • Previous failed frozen embryo transfer (preferably when on oestrogen and progesterone medication)	• ERA works on the theory that the 'window' of implantation is not the same for every woman. By taking a small sample from the lining of the womb the month before the transfer, more insight can be offered how to plan precisely the right medication and dates of the actual transfer
EmbryoGlue	• Helps the embryo attach to the lining of the womb	• Planning a fresh embryo transfer (particularly single embryo transfer) • Also suitable for frozen embryo transfer (with the exception of fully hatched blastocysts)	• There is evidence that embryo glue helps with fresh embryo transfers. We do not know yet for certain if it helps with frozen embryos. For not clear reasons, it also appears to be of less benefit when donor eggs have been used for making the embryos
Injectable progesterone	• Injectable progesterone tends to produce high levels of progesterone in the blood in the overwhelming majority of women undergoing IVF. Although injectable progesterone can be opted for instead of the usual vaginal progesterone (self-funding patients only), it can also be used as an add-on (added to the vaginal progesterone on the day of embryo transfer)	• Previous IVF with bleeding well before the date of the pregnancy test • Any concerns about progesterone levels around the time of embryo transfer	• Some research suggests that a minority of women may have low progesterone levels around the time of embryo transfer and before the date of the pregnancy test. This is more established for women who undergo frozen embryo transfer using oestrogen and vaginal progesterone medications
Progesterone monitoring during stimulation	• If progesterone levels at the end of stimulation are high, then the fresh transfer is cancelled, and the embryos are frozen for subsequent use	• Fresh IVF cycle • Available at Bourn Hall Cambridge only	• If progesterone levels rise significantly during stimulation, the lining of the womb may mature earlier than normal, which would make it less receptive to the embryo. In these cases, it may be better not to transfer the best embryo straight away but, instead, prepare a new lining during a subsequent month

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Add-ons in detail

Add-on	How does it work?	Who does it benefit?	The science
Progesterone levels before transfer	• Low progesterone levels around the time of transfer may result in lower chances of implantation	• Frozen embryo transfer using oestrogen and progesterone medication	• There is evidence that, during frozen cycles, some women have low progesterone levels despite using standard vaginal progesterone medication. In these women, adding extra progesterone may help with implantation. Most of the research has focused on frozen cycles where hormonal medication has been used (not when the natural cycle is use
IMSI	• Incredibly powerful magnification is used to help select the best sperm to be injected into the egg	• Any case of low sperm where sperm injection (ICSI) has been recommended before, generally not suitable for surgically recovered sperm • Previous failed treatment after ICSI • Previous low embryo quality after ICSI • Available at Bourn Hall Cambridge and Essex (Wickford)	• The use of a high-strength microscope allows the embryologists to identify with more confidence the most normal-looking sperm
Zymot	• Sperm preparation device that separates sperm of the highest quality and motility for use in fertility treatments	• High levels of Sperm DNA fragmentation • Previous failed ICSI cycles • Are undergoing PGT-A cycles • Have recurrent implantation failure or recurrent miscarriage	• Conventional sperm preparation methods use centrifuges and density gradients to separate motile sperm from immotile sperm, which places stress on sperm and may lead to increased DNA damage • With ZyMot, the semen sample is loaded into the device and the motile sperm swim through a selective membrane filter. The media containing just these most motile sperm is removed by the embryologist for use in treatment
Time-lapse (GERI)	• A highly specialised Incubator with individual chambers and inbuilt cameras generates a video of embryo development	• Anyone having a fresh cycle • Anyone concerned about embryo quality • Available at Bourn Hall Cambridge and Essex (Wickford) • Provides you with video recording of your embryos' development	• The time-lapse GERI incubator allows continuous monitoring of the embryos during culture. It provides a constant, uninterrupted environment for embryos to grow. These unique features enable the embryologists to identify embryos with unusual or negative developmental features. GERI may also help grow better embryos in some cases
Endometrial scratch	• 'Scratching' the lining of the womb before IVF may improve the receptivity of the lining to the embryo	• Previous failed embryo transfers	• While researching the lining in the past, it was realised that the mechanical disturbance of the lining could itself improve implantation. The 'scratch' effect may improve the blood or promote immune balance of the lining

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Add-ons in detail

Add-on	How does it work?	Who does it benefit?	The science
Sperm DNA fragmentation (COMET) test	• It helps understand the degree of sperm damage • It may help decide if there is a benefit for ICSI even when the sperm numbers are normal (contrary to usual practice of doing IVF with normal sperm)	• Poor embryo quality after IVF or ICSI • Previous/recurrent early miscarriage • Previous failed cycles • Before considering switching to donor or surgically recovered sperm	• Sperm with high degree of DNA damage may reduce the success of IVF treatment, impair embryo development and be implicated in early miscarriages. Some men with normal sperm numbers on the conventional semen analysis may still have a high degree of DNA damage
Immune treatments	• They may address immune imbalance in the lining of the womb	• Previous failed cycles • Fresh or frozen embryo transfer • Some women who are prone to autoimmunity	• Medication such as the lipid drip (intralipids) or steroid tablets have been used to address immune problems of the lining • While some clinics advocate testing for immune imbalance, we use an empirical approach (if it is agreed to use an immune treatment, it is simply added to the IVF treatment plan)
Growth hormone	• This injectable medication may improve the responsiveness of the ovary to IVF stimulation • It may help grow the lining of the womb	• Low numbers of eggs collected during IVF • Low egg reserve • Low embryo quality • Thin lining of the womb	• Growth hormone may have an energising effect on the ovaries during IVF, which may rasult in more eggs or better-quality embryos. • It may also have an enhancing effect on the lining of the womb

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Add-ons in detail

Add-on	How does it work?	Who does it benefit?	The science
Blood thinners	• Blood thinner injections may improve blood flow in the lining of the womb	• Previous miscarriage • May be suitable after previous failed embryo transfers	• Certain clotting conditions can predispose to miscarriage or problems arising from the placenta in advanced pregnancy; this can be alleviated by using blood thinners. On the other hand, it is debated whether blood thinners help with failed implantation • Some clinics advocate testing for clotting conditions. However, there are uncertainties around the usefulness of testing, so we often prefer an empirical approach (if it is agreed to use a blood thinner, it is simply added to the IVF medication prescription)
See an andrologist	• A specialist andrologist may help to identify ways to improve sperm quality.The andrologist may also be able surgically extract sperm from the testes when there is no fresh sperm available	• Low sperm or no sperm • High sperm DNA fragmentation • Low embryo quality • Previous failed cycles (no obvious explanation) • Vasectomy • Varicocele	• The andrologist may identify a treatable cause of low sperm. This could improve the success of IVF or even the chances of natural conception
Laser-assisted hatching	• Using a precision laser, we create a gap in the outer shell of the embryo (zona pellucida), which allows it to hatch out. This is essential for successful implantation in the womb	• Those who have experienced failed embryo implantation • Women of advanced maternal age • Anyone using frozen/thawed embryos • This add-on is delivered through our Cambridge clinic	• To implant successfully, the embryo must hatch out of its protective shell. This process occurs naturally in the womb, but if it does not, it may result in some unsuccessful treatments. There is some evidence to suggest that the zona pellucida may be hardened by the IVF process itself, and especially by freezing/thawing process. Women of advanced maternal age may also experience this issue

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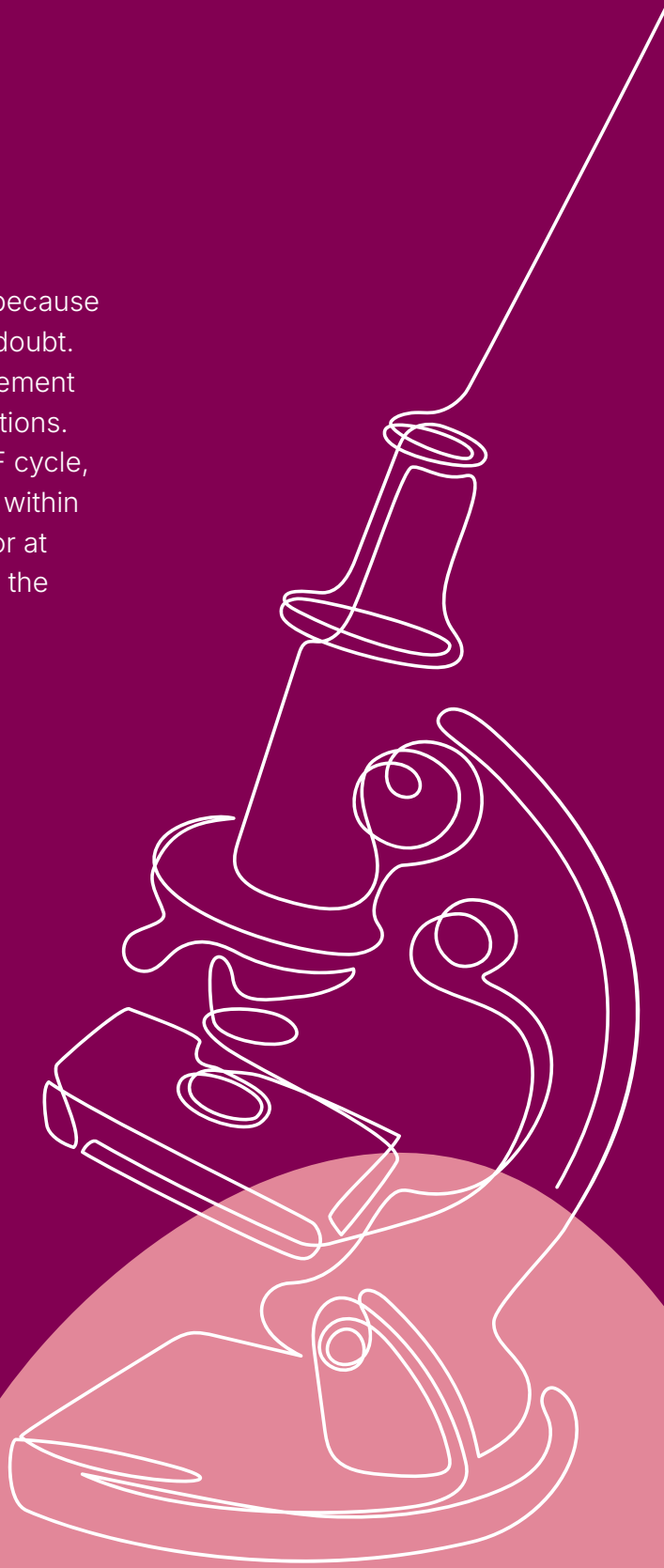
NHS-funded IVF and add-ons

The NHS does not support routine use of IVF add-ons, because their efficacy (and safety) has not been proven beyond doubt. However, the NHS rules do allow you to add a private element to your NHS-funded treatment under certain strict conditions. As a rule of thumb, you cannot modify your standard IVF cycle, even if you are willing to pay for doing so. However, it is within your rights as a patient to add a private element before or at the end of your IVF cycle, as long as you are happy with the information received to make a choice about it.

Advice from the regulator (HFEA)

The UK's regulator, the Human Fertilisation and Embryology Authority (HFEA) advises against routine use of various IVF add-ons, although it acknowledges that some may have a place for selected indications. We advise that, before committing to using add-ons, you visit the **HFEA website** (www.hfea.gov.uk/treatments/treatment-add-ons/).



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