“ADD-ONS” IN MEDICALLY ASSISTED REPRODUCTION TREATMENTS

A guide for those seeking fertility care

European Committee on Organ Transplantation (CD-P-TO)

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French edition: *Traitements adjuvants dans le cadre d'un parcours d'assistance médicale à la procréation. Guide à l'usage des personnes présentant des troubles de la reproduction*

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Introduction

Many people face difficulties when trying to have children and may need professional advice and medical help. The reasons for seeking fertility care are many and diverse and concern both men and women. While medically assisted reproduction techniques, such as intrauterine sperm insemination, *in vitro* fertilisation or the use of donor oocytes, sperm and embryos, are well established and have been shown to be effective for many infertility problems, up to 35 % of all these treatments will not succeed, even after several attempts. On the other hand, medically assisted reproduction is a rapidly developing and highly innovative field and this has led to the availability of many new techniques in fertility clinics, although some of these treatments or procedures have no or little proven evidence of effectiveness and/or safety.

A treatment "add-on" is an optional, non-essential treatment that may be

offered in addition to proven fertility treatments. It can be defined as a procedure that, for most patients seeking medically assisted reproduction treatment, is not necessary for the fertility treatment as such. A wide range of add-ons are on offer for medically assisted reproduction, including various tests, drugs, equipment, complementary or alternative therapies, laboratory and surgical interventions. They are added to the standard medically assisted reproduction treatment and typically claim to improve the chances of becoming pregnant and having a baby, reduce the risk of miscarriage and/or shorten the time to pregnancy. Some of these treatments are known to be ineffective, but they are still promoted. For others, it is not known if they are effective or even safe to use. Most often, patients are asked to pay extra for these treatments. With the increasing availability of information about treatment add-ons online and the influence of market forces on their availability and healthcare dynamics, patients can easily become overwhelmed and struggle to make informed decisions.

This booklet provides a short overview of the different add-on treatments offered by clinics, for anyone considering medically assisted reproduction (Table 1). It does not cover all the add-ons available, but provides links to recommended websites and documents where more information can be found about which

treatments have been shown to be safe and effective according to current knowledge, and for which indications. The aim is to support patients being offered new intervention options to help them choose safe and effective treatments both in terms of outcome and patient well-being, according to their individual needs. The booklet outlines some of the treatment add-ons available so that if they are offered one of them, patients can ask their healthcare providers the right questions, such as why it is being offered and if it may be of benefit for them specifically, so they can make informed decisions.

Many people facing infertility problems and trying to conceive through medically assisted reproduction are offered new procedures or techniques, presenting them with the overwhelming choice of finding the right course of treatment for their specific case. This booklet provides information and resources to help make informed decisions in such cases.

It is important to remember that research is ongoing, and new and additional evidence is collected and published all the time. All evidence needs to be evaluated on a regular basis and may change the current recommendations in the future.

This booklet has been prepared by the Council of Europe's **European Committee on Organ Transplantation (CD-P-TO)**, composed of internationally recognised experts, in collaboration with the **European Society of Human Reproduction and Embryology (ESHRE)**.

When is it appropriate to use a certain treatment?

Some of the treatments listed in this booklet may be appropriate and well-established therapeutic options for patients with certain medical conditions but not appropriate for general use in all fertility patients.

For example, when there is a risk of ovarian hyperstimulation syndrome, an elective freeze-all cycle may be offered. In such cases, rather than transferring one or two fresh embryos a few days after the oocyte collection, all resulting embryos after fertilisation are frozen and later thawed and transferred to the patient's womb. Similarly, intracytoplasmic sperm injection (ICSI) may be appropriate to fertilise oocytes for couples with severe male factor infertility (e.g. a low sperm count, abnormally shaped sperm or sperm that don't move normally, etc.), but should not be used for all patients.

Other treatments, including autoimmune treatments or glucocorticoids, may be necessary for patients with specific medical conditions, but these options are not recommended as a means of improving fertility outcomes in healthy patients.

Clinics and fertility specialists should always discuss the available treatment options with their patients and, basing themselves on established treatments

Not all treatment options are appropriate for all patients. For some add-ons, evidence proving their effectiveness or even their safety may be lacking. Make sure to ask the right questions to the team offering you fertility treatments!

that have proven diagnostic or therapeutic value, advise them which would be most appropriate in their specific case. The advice given and procedure selected should be tailored to the cause of infertility and the age of the patient.

Treatments for which strong evidence of safety and/or effectiveness is lacking should only be offered in a research setting. Patients should not be charged extra to take part in research, including clinical trials.

Where to find evidence of safety and effectiveness

At all times, clinics or healthcare providers offering any add-on treatments should provide evidence of the effectiveness and safety of any treatment they offer.

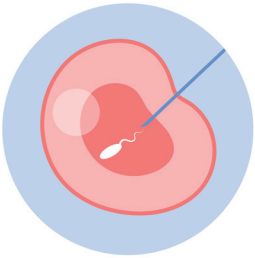
To assist in this, several organisations regularly review the existing data evaluating the effectiveness of existing treatment add-ons in improving treatment outcomes and/or their safety or risk factors, when they exist. Some of them are:

HFEA: the UK Human Fertilisation and Embryology Authority has developed a rating system for add-ons in medically assisted reproduction, that shows the current evidence, based on scientific literature searches, of the safety and effectiveness of several different treatments/procedures – https://www.hfea.gov.uk/.

Cochrane: the Cochrane organisation has published a guide (*Special Collection: In vitro fertilisation – effectiveness of add-ons*) on its website which reviews some of the current add-ons (currently 11 Cochrane reviews), assessing the background and available evidence for specific medically assisted reproduction add-ons – https://www.cochranelibrary.com/collections/doi/SC0000046/full.

ESHRE: the European Society for Human Reproduction and Embryology has reviewed the scientific literature on over 40 add-on procedures that are currently available in clinics and that are claimed to increase the effectiveness of medically assisted reproduction treatment. The aim was to find evidence of whether the procedure has been shown to be safe to use and determine its impact (whether positive or negative). The results and recommendations have been summarised in a recommendation document and can be found at: https://www.eshre.eu/ (see also Table 1.).

Treatment add-ons and recommendations



For the purpose of this booklet, treatment add-ons can be categorised as follows:

Not recommended: of significant potential risk and/or high financial cost and with uncertain benefits. These should either not be used in medically assisted reproduction treatments or used only in the context of an ongoing research study, in which case they should not result in additional costs for the patient. The clinician should provide this information.

Not recommended for routine clinical use: of low risk, with possible or uncertain benefits. These may be used after informed counselling on the related risks and benefits, and at no extra cost to the patient.

Can be recommended/may be considered for use: of no apparent risk, and with possible benefits for general use or in specific patient groups.

The table below shows a summary of recommendations for frequently offered treatments, currently considered as add-ons (ESHRE 2023). There is a vast number of diverse treatments on offer, most of which are not currently recommended for clinical use for most fertility patients. A comprehensive explanation of each of the treatments below can be found at the ESHRE web page "Good practice recommendations on add-ons in reproductive medicine".

Table 1. **Recommendations regarding procedures offered during fertility treatment (non-exhaustive list)**

Not recommended *Should not be used for fertility treatments. Not shown to be effective and/or may be potentially detrimental*
Acupuncture, Chinese and herbal medicine and other complementary therapies
Adjuncts (metformin, growth hormone, testosterone, dehydroepiandrosterone [DHEA], aspirin, indomethacin and sildenafil) before or during ovarian stimulation
Antioxidant therapy
Assisted hatching of the embryo
Flushing of the uterus (embryo culture supernatant, seminal plasma)
Endometrial receptivity tests
Glucocorticoids
Growth factor-supplemented embryo culture medium
Intracytoplasmic sperm injection (ICSI; only recommended for male factor infertility)
Immunomodulating treatments, such as intralipid, intravenous immunoglobulin (IVIG), recombinant human leukaemia inhibitory factor (rh-LIF), peripheral blood mononuclear cells (PBMCs), and tumour necrosis factor inhibitors (anti-TNF)
In vitro activation of dormant follicles (IVA)
Administration of platelet-rich plasma (PRP) into the ovary
Administration into the uterus of granulocyte colony-stimulating factor (G-CSF), human chorionic gonadotropin (hCG) hormone, or PRP
Mitochondrial replacement therapy for oocyte quality "boosting"
Peripheral blood tests for immune parameters and uterine natural killer (uNK) cell-testing
Stem cell therapy for premature ovarian insufficiency or diminished/poor ovarian reserve
Time-lapse imaging (TLI)

Not recommended for routine clinical use *These treatments have not been shown to be effective, but are considered to be of lower risk*
Artificial oocyte activation (however, it can be considered in some situations - see below)
Artificial sperm activation (however, it can be considered in some situations - see below)
Clinical *in vitro* maturation (IVM) of oocytes and rescue-IVM or natural cycle IVF/M
DuoStim
Elective freeze-all (however, it can be considered in some situations - see below)
Endometrial scratching
Intracytoplasmic morphologic sperm injection (IMSI)
Intravaginal or intrauterine culture devices
KIR and HLA genotyping
Magnetic-activated sperm cell sorting (MACS)
Mitochondrial DNA load measurement
Non-invasive preimplantation genetic testing (niPGT)
Physiological intracytoplasmic sperm injection (PICSI)
Preimplantation genetic testing for aneuploidy (PGT-A)
Screening hysteroscopy (however, it can be considered in some situations - see "Can be recommended/may be considered for use", below)
Sperm DNA damage testing
Sperm hyaluronic binding assay (HBA)

Can be recommended/may be considered for use
Intracytoplasmic sperm injection (ICSI), for patients with male factor infertility
Artificial oocyte activation, may be used for cases of complete activation failure (0% 2PN), very low fertilisation (< 30% fertilisation) or globozoospermia
Artificial sperm activation, may be used for patients with primary or secondary total asthenozoospermia which is not the result of axonemal structure defects
Hyaluronic acid, may be used as addition to embryo transfer media
Microfluidics systems, may be used for sperm selection and preparation
Elective freeze-all cycle, for patients with risk of ovarian hyperstimulation syndrome
Screening hysteroscopy, for patients with recurrent implantation failure

Take-home messages

As a patient undergoing or seeking medically assisted reproduction treatment, it is common to feel pressured by the hope of having a child and overwhelmed by the many different procedures offered by clinics. In addition, the information provided by clinics and websites about the necessity and potential benefits of certain procedures can be overstated, and the additional costs are not always clear.

Patients should never be exposed to unnecessary risks (physical or emotional) or to ineffective treatments.

Due to a lack of well-conducted research studies, there is often little consensus about which strategies are genuinely effective in increasing live births after medically assisted reproduction. Sometimes there may not be enough evidence to fully prove the benefits of certain medically assisted reproduction add-ons, but also not enough to completely dismiss them.

Clinicians who prescribe interventions based on weak evidence should inform patients about the limited knowledge and the risks of potential, yet unidentified, adverse effects.

This booklet serves as a guide to the current evidence for many of the add-on treatments being offered by fertility clinics today, as well as a resource for further information. By reading it,

patients will be better equipped to ask fertility clinics and healthcare providers about the procedures, their relevance to their specific situation, and any associated risks or additional costs. This will help them make informed decisions about which options best suit their needs.

Many people face difficulties when trying to have children and may need professional advice and medical help. A wide range of add-on treatments are on offer for medically assisted reproduction, including various tests, drugs, equipment, complementary or alternative therapies, as well as laboratory and surgical interventions. With so many options available, it is easy for patients to become overwhelmed and find it difficult to make an informed decision.

This booklet provides a short overview of the different add-on treatments offered by clinics for those considering medically assisted reproduction procedures and provides information about which treatments have been shown to be safe and effective according to current knowledge, and for which indications. It has been prepared by the Council of Europe's European Committee on Organ Transplantation (CD-P-TO), composed of internationally recognised experts, in collaboration with the European Society of Human Reproduction and Embryology (ESHRE).

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