

International Federation of Fertility Societies

Global Standards of Infertility Care

Therapies used to enhance ART success rates - “Add-ons”

Standard - 20

Name	Therapies used to enhance assisted conception treatment success rate
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Introduction

The goal of IFFS Practice Standards is to provide policy and decision-makers and the clinical and scientific community with a set of recommendations that can be used as a basis for developing or revising institutional or national guidelines on selected practice recommendations for infertility practice.

The document addresses minimal standards of practice but does not provide rigid guidelines but rather gives recommendations that provide the basis for rationalizing the provision of infertility services in view of the most up-to-date information available.

Because country situations and programme environments vary so greatly, it is inappropriate to set firm international guidelines on infertility practice. However, it is expected that institutional and national programmes will use these guidance documents for updating or developing their own infertility guidelines in the light of their national health policies, needs, priorities and resources. The intent is to help improve access to, quality of, and safety of infertility and assisted conception services. These improvements must be made within the context of users’ informed choice and medical safety.

Adaptation is not always an easy task and is best done by those well-acquainted with prevailing health conditions, behaviours, and cultures.

Rationale

Couples seeking help to achieve a pregnancy through assisted reproduction (ART) access information from many sources and make choices about a variety of medical and non medical interventions in addition to “standard” treatment in order to maximise their likelihood of success. Matthiesen et al (2011) found significant association between stress indices and ART outcome which may lead patients to seek remedies additional to conventional treatment. In Vitro fertilisation (IVF) practitioners have also introduced a range of adjuncts to complement the ART process, often without good quality evidence to support their use, in an attempt to increase success rates. The range of adjunct treatments now in common use extends from relatively harmless therapies to complex interventions with potential risk either woman or offspring. Additionally, they may raise the cost of treatment substantially. Usadi and Merriam (2015) comment on the increasing use of “off-label” drugs in infertility practice without evidence of efficacy and potential risks in pregnancy if not discontinued. Legro (2015) points out the use of “off-label” products has become “ubiquitous” with infertility practice and as such acts as a disincentive for appropriate evaluation. The objective of this paper is to review the evidence for the benefit of adjuvant therapy to ART and provide guidance to practitioners as to their use.

Scope

This paper provides guidance in the use of adjuvant therapies in assisted conception procedures including IVF/ICSI. Procedures for the prevention or minimisation of Ovarian Hyperstimulation Syndrome are not included in this review. It has been assumed that culture to blastocyst forms part of standard treatment.

Definition

Adjuvant therapy is defined as any procedure or agent additional to the standard therapy that improves the success of the treatment.

For the purposes of this guidance standard therapy includes

- Ovarian suppression and stimulation
- Oocyte maturation trigger
- Fertilisation with or without ICSI
- Embryo culture in vitro with or without extension to blastocyst
- Embryo transfer
- Luteal phase support

Recommendations

Antioxidants

There is no evidence to support the use of antioxidants as an adjuvant in IVF used for female infertility. There is evidence for improved outcome in IVF when the indication is male infertility but this is based on 18 live births from 116 participants in three trials dating back twenty years. *On the currently available evidence the use of antioxidants as an adjunct to routine IVF practice is not recommended.*

Acupuncture

The evidence does not support the use of Acupuncture as an adjunct to IVF. *The use of acupuncture as an adjunct to routine IVF practice is not recommended.*

Alternative therapies

There is some evidence of benefit with the use of acupuncture in combination with Chinese Herbal Medicine – Whole System Chinese Herbal Medicine (CHM) in improving outcome of IVF treatment. However the quality of the evidence is low and should be tested in well conducted appropriately powered RCTs before it can be routine recommended. *Currently there is insufficient evidence to recommend alternate therapies or CHM as an adjunct to routine IVF practice.*

Vitamin D

There is no evidence that Vitamin D supplements improve outcome in IVF. However *it is recommended that women planning infertility treatment comply with current recommendations for dietary intake of 600 IU increasing to 1500–2000 IU when pregnancy is established.* Furthermore, practitioners' attention is drawn to those patients who may be at particular risk of Vitamin D deficiency for example those with increased skin pigmentation or who for cultural reasons limit skin exposure.

Time lapse imaging (TLI)

There is evidence that the processes associated with Time Lapse Imaging (TLI) are beneficial to embryo culture and may improve clinical outcomes. However, *there is currently insufficient evidence to recommend TLI as routine practice for embryo selection.* Further research is warranted and adequately powered clinical trials indicated.

Assisted hatching

There is no evidence that Assisted Hatching (AH) by whichever method improves outcome when applied to a general IVF population. There is some evidence that AH may improve outcome when applied to a sub group of patients who have recurrent implantation failure but appropriately powered, well conducted RCTs are necessary to confirm this. *Assisted Hatching is not recommended as an adjunct to routine IVF practice.*

Pre-implantation Genetic Screening (PGS)

Rapidly evolving technology and improved efficiency with these techniques may change the future application of this technology to IVF. However, until adequately powered RCTs are undertaken with relevant comparisons together with economic evaluation, it is premature to recommend PGS/PGTa as part of IVF management in any context. *The application of PGS/PGTa as an adjunct to routine IVF practice is not recommended.*

In vitro maturation (IVM)

This is another area in which techniques have evolved and outcomes improved. IVM is currently applicable in cases at high risk of ovarian hyperstimulation syndrome (OHSS) and fertility preservation for cancer patients. *The application of IVM in cases at risk of OHSS needs to be tested by prospective RCTs before it can be routinely recommended in this setting. IVM is not recommended as an adjuvant to routine IVF practice. The use of IVM*

in fertility preservation programmes should be undertaken as part of a research programme with monitoring and reporting of long term outcomes.

Bed rest after embryo transfer

There is no evidence to recommend a particular approach to this intervention. *Bed rest after embryo transfer is not recommended.*

Embryo adhesion compounds

There is no evidence to support the use of adhesions compounds to improve embryo implantation. *The use of adhesions compounds as an adjuvant to IVF is not recommended.*

Endometrial injury

There is conflicting evidence regarding the possible benefit of this intervention. There is evidence of benefit in a sub group of patients with recurrent implantation failure in IVF. Further research is indicated to investigate the putative mechanisms. *Currently there is insufficient evidence to recommend endometrial injury as an adjuvant to routine IVF practice.*

Heparin

The currently available data does not support the routine use of heparin, however, this adjuvant therapy may be of benefit in those cases with recurrent implantation failure although this remains to be proven in large RCTs. *The routine use of Heparin is not recommended.*

Intravenous Immunoglobulin therapy (IVIg)

Benefit has been shown in one RCT (n=82) in a subgroup of patients with recurrent IVF failure. The meta-analysis by Clark of three studies including the Sher trial also showed benefit although the total number of participants was 172 with 32 births. There was heterogeneity between the trials and the last trial was conducted in 2000. Polanski's recent review also drew attention to the poor quality of the trials. We conclude there may be benefit for a sub group of patients with recurrent implantation failure but this requires to be tested by a well conducted appropriately powered RCT before this therapy can be recommended for this sub group. *There is no evidence to support the use of this adjuvant in routine IVF practice and it is not recommended in this setting.*

Anti TNF α

There have been no prospective RCTs undertaken to evaluate this therapy as an adjuvant to improve implantation. *This treatment is not recommended.*

Glucocorticoids

There is insufficient evidence to recommend the use of glucocorticoids as an adjuvant to improve ovarian response to stimulation or to improve implantation. *This treatment is not recommended.*

Vasodilators including Sildenafil

There is no evidence from prospective RCTs to support the use of pharmacological vasodilators in improving implantation. *These adjuvant treatments are not recommended.*

Aspirin

There is insufficient evidence to recommend the use of Aspirin as a routine adjuvant to improve ovarian response to stimulation or to improve implantation. *This treatment is not recommended.*

DHEA

DHEA may affect IVF in two ways either by enhancing response to stimulation in patients known to be poor responders or by influencing implantation through improved embryo quality. The evidence to date is inconsistent for both these outcomes, the quality of the evidence is generally poor and the trials small in size. *Large randomized prospective trials are needed before DHEA can be recommended as a routine adjuvant or to support ovarian stimulation in women with diminished ovarian reserve.*

Testosterone

There is evidence of benefit in enhancing ovarian response in poor responders based on three small RCTs. The benefit of this adjuvant should be tested in an adequately powered RCT before it is recommended as an adjuvant in poor ovarian responders. There is no evidence to support its use in normal ovarian responders. *Testosterone is not recommended as part of routine IVF practice.*

Growth Hormone

There is evidence of benefit in enhancing ovarian response in poor responders based on four small RCTs. The benefit of this adjuvant should be tested in an adequately powered RCT before it is recommended as an adjuvant in poor ovarian responders. There is no evidence to support its use in normal ovarian responders. *Growth Hormone is not recommended as as part of routine IVF practice.*

Granulocyte Colony Stimulating Factor (GCSF)

There is good quality evidence from one RCT for improvement in live births following the addition of Granulocyte Colony Stimulating Factor (GCSF) to culture media. *This finding should be confirmed through further large trials before recommending its general use.*

Intravenous Lipid therapy

There is no evidence to support the use of this adjuvant as a treatment to improve implantation. *This treatment is not recommended.*

Lymphocyte immunotherapy

There is no evidence to support the use of this adjuvant as a treatment to improve implantation. *This treatment is not recommended.*

