Scientific and Clinical Advances Advisory Committee (SCAAC) - agenda

Monday 19 October 2020, 11:00am – 2:30pm

Virtual meeting

Agenda item	Time
1. Welcome, apologies, declarations of interest	11:00am (5')
2. Matters arising Victoria Askew (HFEA)	11:05am (10')
3. Monitoring the effects of COVID on fertility, assisted conception and early pregnancy	11:15am (20')
4. Genome editing – literature review Matthew Mudford (HFEA) Robin Lovell-Badge (The Francis Crick Institute and WHO Expert Advisory Committee) Andy Greenfield (MRC Harwell Institute and The International Commission on the Clinical Use of Human Germline Genome Editing)	11:35pm (20')
5. Update the HFEA's work on treatment add-ons Dina Halai	11:55am (15')
6. Review of traffic light ratings for treatment add-ons Victoria Askew (HFEA) Andy Vail (The University of Manchester)	12:10pm (30')
Lunchbreak	*12:40pm (30')*
7. Review of traffic light ratings for treatment add-ons Victoria Askew (HFEA) Andy Vail (The University of Manchester)	1:10pm (60')
8. Any other business	2:10pm (10')
9. Meeting summary and close	2:20pm (10')

Scientific and Clinical Advances Advisory Committee (SCAAC) – Matters Arising

Monday 19 October 2020

Date and item	Action	Responsibility	Due date	Progress to date
06/06/2020 3.11	The HFEA will update the Committee about COVID-19 research using HFEA data later in the year	Victoria Askew, Policy Manager	Completed	Update included as Appendix A to this paper.
06/06/2020 3.11	The HFEA will update on any outcome studies further into the future.	Victoria Askew, Policy Manager	Ongoing	Update to be given further into the future when outcomes are available.
06/06/2020 3.12	SCAAC agreed to monitor research into the effects of COVID-19 on reproduction or early pregnancy and to discuss the research in a standing agenda item	SCAAC members	Ongoing item at each SCAAC meeting	Standing item added the SCAAC agenda by the executive Committee sent 2 reminders by the executive about their agreement to monitor and highlight research ahead of SCAAC meetings
06/06/2020 4.15 – 4.16	The executive will conduct an immediate update to the treatment add-ons website text in line with the recommendations given by the Committee. The Executive will circulate these website updates to the Committee.	Victoria Askew, Policy Manager Matthew Mudford, Scientific Policy Officer	Completed	Smaller immediate update to the HFEA treatment add-ons webpage completed on 16/07/2020. More extensive update to the HFEA treatment add-ons webpage completed on 24/08/2020, in line with the treatment add-ons project. The Committee was informed of these updates by email on 03/09/2020.

06/06/2020 5.1 – 5.17	The Committee gave a recommendation to the HFEA Statutory Approvals Committee (SAC) regarding the novel process application for the AneVivo device in inter-partner and standard egg donation	Victoria Askew, Policy Manager	Completed	SAC considered the application at the 30/07/2020 meeting. SAC made the decision not to approve this application, in line with the recommendation given by SCAAC. The minutes of the SAC meeting are included as Appendix B to this paper.
06/06/2020 7.2	The executive will circulate information to the Committee about the recent extension to storage limits and will clarify if this law change applies to embryos stored for research purposes	Matthew Mudford, Scientific Policy Officer	Completed	The Committee was informed of the details of the COVID-19 storage extension by email on 03/09/2020.

Annex A – COVID-19 research projects using HFEA register data

There is currently one project that is approved to use HFEA register data in relation to the effects of COVID-19. The HFEA received an application from an ongoing project that had already been approved to use HFEA register data. The aims of the original study are:

1. **develop a clinical prediction model that can estimate the probability of pregnancy (spontaneous or due to treatment) and term singleton live birth for couples undergoing different fertility treatments in Grampian;**
2. **develop a clinical prediction model to predict outcomes in women undergoing IVF treatment in the UK;**
3. **assess the predictive ability of these models and**
4. **externally validate them;**
5. **develop a user-friendly online clinical decision tool based on the models to facilitate management of couples attending the fertility clinic.**

In response to the effects of COVID-19 on the fertility sector the project group created a sub-study using the same dataset as their main project. The aim of this sub study is:

Identifying a strategy for recommencing IVF services after the current state of lockdown by using modelling based on national data

'We are planning an urgent sub-study that will involve the use of the HFEA data and the prediction model that was developed from this project. We will use the model and data to help identify a strategy for recommencing IVF service after the COVID-19 lockdown has been lifted. We will apply the prediction model, developed in the above project, to the 2017 HFEA data to determine the probability of live birth for three scenarios - no delay, 6 month delay and 1 year delay to treatment. This will help determine the impact of delaying IVF on the number of expected live births for different age groups and causes of infertility. This will help make decisions around who should be prioritised for IVF when lockdown is relaxed.'

Annex B – SAC Minutes 30 July 2020

Statutory Approvals Committee - minutes

Authorisation of novel process for Anecova AneVivo Intrauterine Device - London Women's Clinic (centre 0105)

Thursday, 30 July 2020

HFEA, 10 Spring Gardens, London, SW1A 2BU via Teleconference

Committee members	Margaret Gilmore (Chair)	
	Emma Cave	
	Anne Lampe	
	Tony Rutherford	
Members of the Executive	Moya Berry Catherine Burwood	Committee Officer Licensing Manager
Legal Adviser	Sarah Ellson	FieldFisher - LLP
Observers	Dee Knoyle	HFEA Committee Officer

Declarations of interest

- Ruth Wilde declared a conflict of interest and was not present during the discussion of this item.
- The other members of the committee declared that they had no conflicts of interest in relation to this item.

The committee had before it:

- 9th edition of the HFEA Code of Practice
- Standard licensing and approvals pack for committee members

The following papers were considered by the committee:

- 2020-06-08 Authorisation for a novel process paper presented to the Scientific and Clinical Advances Advisory Committee (SCAAC) and annexures
  - Annex A: Novel process application - IVF using the AneVivo device in interpartner and standard egg donation
  - Annex B: Supporting Information
  - Annex C: Novel Processes Authorisation Decision Tree
- 2020-06-08 SCAAC meeting minutes

The following papers were tabled at the meeting following the request of the committee:

- 2015-08-27 Statutory Approvals Committee (SAC) meeting minutes

1. Consideration of application

1.1. The committee noted that the HFEA had received an application for the authorisation of a novel process for the use of Anecova AneVivo Intrauterine Device. The application relates to the extension of a current authorised process and if approved would allow the device to be used between different women. This would allow the eggs donated by a female partner or donor to be inserted into a second partner or recipient for incubation. The committee noted that the process is currently only authorised for use in a single woman.

1.2. The HFEA has delegated the authorisation of novel processes to the Statutory Approvals Committee (SAC), advised by the opinion of the Scientific and Clinical Advances Advisory Committee (SCAAC) on whether there is evidence that a process is not safe or not effective.

Initial authorisation application

1.3. The committee noted that the initial novel process authorisation application was received and approved in 2015. This was for the intrauterine culture of gametes and embryos (including insertion and removal of device, followed by transfer of embryo(s) to the same woman).

1.4. SCAAC advised the committee that:

- The use of intrauterine culture devices constituted a novel process.
- The process applied for fell within two licensable activities: processing gametes and processing embryos.
- The evidence provided gave no indication that the process is unsafe.
- They did not see any evidence to suggest that intrauterine culture of gametes/embryos using a device such as the Anecova AneVivo would not be effective. However, it did not feel that there was sufficient clinical data to say whether the process has a greater or lesser efficacy than that of traditional IVF methods.

1.5. The application was approved, by majority, by SAC at its meeting on 27 August 2015. They specified that it is possible that the process might offer no improvement in efficacy and might add an unnecessary cost to patients, and any patient information provided by clinics should highlight

this. In addition, information on the HFEA website should draw attention to the fact that the process has not yet been subject to a clinical trial, and its efficacy is therefore not known.

1.6. In February 2018, SCAAC reviewed an outcomes report provided by the applicant which resulted in them requesting clarification about the hypothesis and data in order for them to decide if approval of this process should remain. A representative from the applicant centre attended a SCAAC meeting in October 2018, and again in January 2019. SCAAC suggested that additional data would still be needed in order for it to review whether intrauterine culture should remain on the list of approved novel processes. A further outcomes report is due to be submitted to the HFEA by the end of 2020.

Current authorisation application

1.7. The committee noted that this application to extend the current authorised process, was considered by SCAAC on 08 June 2020. The committee noted that SCAAC were asked to consider the following:

- Whether the process outlined in the application is sufficiently different from the processes currently authorised as to be considered 'novel'
- Whether there is evidence that this process is not effective
- Whether there is evidence that this process is not safe

1.8. The committee noted that SCAAC had advised that there appears to be no evidenced benefit in extending the use of this device into more than one woman. Until a clear benefit has been established, SCAAC would not recommend proceeding with this extension as there are potential risks that cannot be quantified due to a lack of evidence.

2. Decision

2.1. The committee had regard to its Decision Tree. They were satisfied that the proposed process was to be used to carry out a licensed activity and therefore the administrative requirements were met.

2.2. The committee sought the advice of the legal adviser on the questions that it had to address following SCAAC's consideration, and also took note of legal advice provided previously, at the 27 August 2015 meeting.

2.3. The committee noted that the questions considered by SCAAC were: (a) is there evidence to suggest the process is not safe; and (b) is there evidence to suggest that the process is not effective. In contrast, the decision tree states that the questions for the committee to consider are: (a) is the process safe; and (b) is the process effective. The committee did not feel that these questions were the same. The legal adviser advised that the novel process in this case involves processing gametes and embryos in the course of providing treatment services. Thus, it relates to licences granted under section 11(1)(a) and paragraph 1 of schedule 2 to the Human Fertilisation and Embryology Act 1990, to which, by virtue of section 14A(2), the conditions required by schedule 3A must apply. By paragraph 11(b) of schedule 3A, one of the requirements is that the processing of gametes and embryos must comply with Annex II, Part B, of Directive 2006/86 EC, and paragraph 1 of part B of Annex II states that the processing procedures "must not render the tissues or cells clinically ineffective or harmful to the recipient". This is why the test for SCAAC is

expressed as it is and legally the questions to be considered by this committee are essentially the same as those that had been considered by SCAAC.

2.4. Having reviewed the advice from SCAAC, the committee noted that there were a number of potential safety risks associated with the process. These included the potential for the device to become lost whilst inserted in the uterus and the unknown likelihood of this occurring; that using the device in two women doubles the risk of infection; and that there is evidence from animal models that increased manipulation of embryos around the time of transfer causes programming effects in offspring, such as birth weight and long-term development. The committee therefore decided that there was insufficient evidence provided to determine the safety of using Anecova AneVivo Intrauterine Device in more than one woman.

2.5. With regard to efficacy, the committee noted the evidence review on the outcomes report that had been carried out by SCAAC in February 2018. The committee noted that SCAAC had raised concerns that there was a lack of hypothesis and the data was insufficient, and it was noted that the protocol used in the outcomes report was different from the protocol in the original application, which in itself raised a risk.

2.6. The committee also noted SCAAC's rebuttal of the applicant's claim that the process is not intended to increase live birth rate but is instead intended to mimic a more 'natural' environment, reduce the exposure to synthetic in vitro culture media and give some psychological benefits to patients. SCAAC advised that the device does not mimic 'natural' development as the embryo would usually be in the fallopian tubes in the early stages of development, rather than the womb.

2.7. The committee therefore decided that there was insufficient evidence provided to determine the effectiveness of using Anecova AneVivo Intrauterine Device in more than one woman.

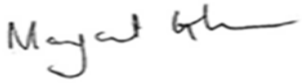
2.8. In conclusion, the committee agreed that there was a lack of evidence with regard to safety and efficacy of the proposed novel process and decided to refuse approval of the application.

2.9. The committee strongly recommended that the further evidence, due to be received in December 2020, which should include details of the validation and evaluation of the Anecova AneVivo Intrauterine Device, is dealt with urgently in order that further clarification on the safety and efficacy of this process, in use between more than one woman, and in general, can be provided.

3. Chair's signature

3.1. I confirm this is a true and accurate record of the meeting.

Signature



Name

Date

18 August 2020

Genome editing

Strategic delivery:	☒ The best care – effective and ethical care for everyone ☐ The right information – to ensure that people can access the right information at the right time ☐ Shaping the future – to embrace and engage with changes in the law, science and society		
Details:			
Meeting	Scientific and Clinical Advances Advisory Committee		
Agenda item	4		
Paper number	SCAAC (19/10/2020) 004		
Meeting date	19 October 2020		
Author	Matthew Mudford, Scientific Policy Officer		
Output:			
For information or recommendation?	For recommendation		
Recommendations	The committee is asked to: • advise the executive if they are aware of any other recent developments; and • discuss potential clinical applications of this technology and identify particular concerns or issues that should be highlighted; and • review whether any outputs from the HFEA are required.		
Resource implications	None		
Implementation date	NA		
Communication(s)	To be determined		
Organisational risk	☒ Low	☐ Medium	☐ High
Annexes	None		

1. Introduction

1.1. The HFEA are the Government regulator responsible for ensuring that all research centres which use human embryos are abiding by the law. One of the core regulatory principles, defined by the Human Fertilisation and Embryology (HFE) Act 1990, is to “ensure that all licensed research by the centre meets ethical standards, and is done only where there is both a clear scientific justification and no viable alternative to the use of embryos”.

1.2. The HFE Act was amended in 2001 to allow human embryonic research, only to "(a) increase knowledge of the developing embryo; (b) increase knowledge about serious disease, or (c) enabling any such knowledge to be applied in developing treatments for serious disease”. As technology has advanced, particularly in the last decade, the potential for genome editing to contribute to these research aims has become clear.

1.3. Genome editing research using human gametes and embryos has already improved our understanding of gene function, DNA-repair mechanisms, early human development and genomic rearrangements; mutations such as deletions that change the gene content of a genome or the arrangement of the genes on a genome. Genome editing techniques can be used to study the relationship between genes and diseases, and to explore the possibility of disease prevention or treatment.

1.4. Genome editing can either be used on germline cells to induce inheritable changes or on somatic cells (all other cells) to induce non-inheritable changes. The latter is much closer to clinical implementation. The great potential for somatic-tissue editing to treat disease is clear and raises few ethical concerns or obstacles as long as patient safety remains paramount. It is the ability to create inheritable changes to the human genetic code, (germline gene editing or heritable human genome editing), that has raised so many concerns. The transfer of genome edits to future generations amplifies the potential risk and makes the long-term consequences much harder to anticipate.

1.5. Arguably the greatest advance in both inheritable and non-inheritable genome editing has been the development of CRISPR Cas9. CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats and is a system adapted from a defence mechanism used by prokaryotes, silencing the genes of invading viruses by cleaving the viral nucleic acids. In genome editing, CRISPR is used to target a specific gene and together with an enzyme called Cas9 forms a complex (CRISPR Cas9) that can, with a high degree of precision, cut a target gene out of the genome which can then be replaced with another gene. This means that CRISPR Cas9 has the potential to be used to avoid the inheritance of diseases, by removing and replacing a defective gene.

1.6. Following the discovery of CRISPR Cas 9 the technology advanced quickly, becoming cheaper, easily scalable and more widely available. In April 2015, a study was published (Liang P et al., 2015) in which the researchers carried out changes in the human genome of non-viable human embryos using CRISPR-Cas9. They demonstrated that it was possible to cleave the mutated gene responsible for beta-thalassaemia in a human embryo. Unfortunately, when they attempted to replace the defective gene, the efficiency of the replacement process, called homologous recombination directed repair (HDR), was low and the resulting edited embryos were mosaic. The paper demonstrated the significant risk posed by limited specificity and fidelity. The research alerted the global scientific community to the

capability, limitations and risks of the technology and highlighted the imminent ethical, social, legal and safety implications.

1.7. In the UK, regulation has had to keep up with the speed of the scientific advancements and the complexity of the multidisciplinary considerations. The HFEA has had to consider the repercussions of genome editing while allowing important germline research under strict conditions. The HFE Act 1990 ensures that all research centres make embryonic research applications to The HFEA and these must be approved by the Licence Committee before the projects can commence. Genetically modified embryos have never been allowed to be used in treatment and cannot be grown in culture for more than 14 days. Even within those boundaries, embryological research in the UK has been able to demonstrate the potential for clinical application.

1.8. In 2016, for the first time, the HFEA granted a license to a project using CRISPR Cas9 technology to study genetically modified embryos at the Francis Crick Institute. Only a handful of UK centres have so far followed suit in applying for such a license.

1.9. The development of CRISPR Cas 9 technology meant that, globally, genome editing became simpler, more accurate and more affordable. In the scientific literature there have been hundreds of studies on germline gene editing in animal embryos in the last few years. Such studies on human embryos have remained relatively rare due to the complex ethical considerations.

1.10. In November 2018, Chinese scientist He Jiankui announced to the world the birth of twins whose genomes had been edited during IVF. Their genomes had been edited using CRISPR Cas9 with the goal of decreasing their lifetime risk of contracting HIV. The was international condemnation of the scientific, ethical, moral and regulatory standards that had been flouted.

1.11. Despite all the scientific progress of recent years, it is not yet widely felt that the on-target effectiveness of the gene-editing process can outweigh the off-target risk. Off-site targeting results in unintended point mutations, deletions, insertions, inversions and translocations, the consequences of which are extremely hard to predict and so are ultimately unmanageable.

1.12. In addition to the scientific hurdles, social, legal and bioethical obstacles remain. There is yet to be widely endorsed proposal where the use of germline gene editing would be acceptable in treatment. There is great diversity of opinion which reflect the complexity of the considerations. However, some support is growing among bioethicists, physicians and the wider population that for couples who are at significant risk of having offspring with devastating genetic disorders such as myotonic dystrophy, it may be permissible to use genome editing to give them a healthy child once the risk becomes acceptable. There is currently no clear regulatory pathway to realise that ambition but several large international organisations are exploring whether there could or should be.

2. Recent regulatory developments

2.1. There have been several publications in the last year which pull together the best evidence and international collaborators to tackle the problem of how to construct a regulatory pathway towards the clinical application of germline genome editing.

2.2. 'Heritable Human Genome Editing', (HHGE) from the International Commission on the Clinical Use of Germline Editing has only just been published in September 2020. It considers whether, from a scientific perspective, genome editing methodologies could be developed sufficiently to permit responsible use. It identifies potential applications for the technology,

discusses pathways towards clinical use and defines the mechanisms for scientific governance which would be required. The report acknowledges that each country with the capability of using germline genome editing will need to establish its own regulatory framework, in line with its unique regulatory structures. It highlights the need for new models of international cooperation if these regulatory advancements are to be achieved. Some of the key scientific recommendations are:

2.2.1. No pregnancy should be established with a human embryo that has undergone editing until it is possible to make accurate genomic changes without undesired edits. Before any attempt to establish a pregnancy with an embryo that has undergone genome editing, preclinical evidence must demonstrate that heritable human genome editing can be performed with sufficiently high efficiency and precision to be clinically useful.

2.2.2. Use of human genome editing should be limited to diseases that cause serious morbidity or premature death. The edit should be limited to a substitution of a pathogenic genetic variant for a genetic sequence known in the population to not be disease-causing. No embryos without the disease-causing genotype should be subjected to genome editing and transfer so as to avoid any associated risk. This should only be done when the prospective parents have poor options as the chances of having unaffected embryos is low.

2.2.3. A proposal for clinical use should also include plans to evaluate human embryos prior to transfer using developmental milestones until the blastocyst stage and a biopsy at the blastocyst stage. The biopsy must demonstrate the existence of the intended edit in all biopsied cells and no evidence of unintended edits at the target locus or off-target sites.

2.3. The International Commission on the Clinical Use of Germline Editing recommended that an International Scientific Advisory Panel be established with a diverse, multidisciplinary membership and should include independent experts who can assess the scientific evidence of safety and efficacy of both genome editing and associated assisted reproductive technologies.

2.4. Also published in the last year are the reports from the meetings of the World Health Organisation's Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. The World Health Organization (WHO) has established a global, multi-disciplinary expert panel to examine the scientific, ethical, social and legal challenges associated with human genome editing. The committee is tasked with advising and making recommendations on appropriate institutional, national, regional and global governance mechanisms for human genome editing. It is consulting with a wide range of stakeholders and has identified strategies to engage with both the scientific community and the lay audience so that information can be exchanged and societal views can be understood.

2.5. The commitee recommended that the WHO develop a registry of relevant planned and ongoing research. Anyone from government, academia, industry or community labs involved in genome editing research would be mandated to register and receive a unique identifier for their project. Funding would only be given on the condition that the research would be registered and only registered research could be published in journals. Failure to register would be considered as a fundamental violation of the principle of responsible stewardship of science.

2.6. The Committee also agreed that "it would be irresponsible at this time for anyone to proceed with clinical applications of human germline genome editing". They requested that all those

conducting or aware of research into genome editing of human germline cells and embryos to engage with the Committee immediately so as to better understand the technical environment and the governance arrangments.

2.7. The most significant outcome of the third meeting (a fourth is still to come) was an agreement as to the tools and guidance that would be required to develop a governance framework which could be implemented in different contexts.

3. Conclusions

3.1. The last SCAAC review of studies using genome editing techniques on human and animal embryos was presented to the committee in 2017. That was prior to the birth of the genetically modified twins which changed the global conversation about genome editing research. Complex ethical, social, legal and safety considerations have been brought to the fore.

3.2. There is potential for disease prevention and treatment but we must be acutely aware of the limitations and repercussions of the technology. Currently, the benefits do not outweigh the risks. For now, it would be irresponsible for anyone to proceed with clinical applications of human germline genome editing. However, where there is potential for genome editing to prevent serious disease or morbidity, a regulatory pathway could be established. It would require a multidisciplinary approach and international collaboration such as is being demonstrated by the WHO. The priority should be to minimise risks of research and progress gradually until the technology becomes precise enough to justify the first treatments.

4. Recommendations

4.1. The committee is asked to note this update and:

- advise the executive if they are aware of any other recent developments; and
- discuss potential clinical applications of this technology and identify particular concerns or issues that should be highlighted; and
- review whether any outputs from the HFEA are required.

5. References

Daley, G., Lovell-Badge, R., Steffan, J. (2019) *After the Storm — A Responsible Path for Genome Editing* New England Journal of Medicine, 380:897-899

Liang, P., Xu, Y, Zhang, X. et al. (2015) *CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes*, Protein & Cell; 6(5):363-372

Nuffield Council on Bioethics (2018) *Genome Editing and Human Reproduction*

Tuerlings, E. (2020) *WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing - Background Paper*

WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing (2020) *WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing - Report of the First Meeting*

WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing (2020) *WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing - Report of the Third Meeting*

International Commission on the Clinical Use of Human Germline Gene Editing (2020) *Heritable Human Genome Editing*

Department of Health and Social Care (2018) *Government Response to the House of Commons Science and Technology Committee's Third Report of Session 2017-19, 'Genomics and Genome Editing in the NHS'*

Review of traffic light ratings for treatment add-ons – October 2020

Strategic delivery:	☒ The best care – effective and ethical care for everyone ☐ The right information – to ensure that people can access the right information at the right time ☐ Shaping the future – to embrace and engage with changes in the law, science and society
Details:	
Meeting	Scientific and Clinical Advances Advisory Committee
Agenda item	6 and 7
Paper number	HFEA (19/10/2020) 006
Meeting date	19 October 2020
Author	Victoria Askew, Policy Manager
Output:	
For information or recommendation?	For recommendation
Recommendation	The committee is asked to: • consider the quality of evidence for each treatment add-on based on the findings from an independent assessor at annex A; and • agree and recommend traffic light categories for each treatment add-on based on the outcome of live birth rate; and • recommend information about outcomes other than live birth rate (time to pregnancy, miscarriage rates, risk of ovarian hyperstimulation syndrome) to be included on the HFEA website for each of the treatment add-ons • recommend whether the removal of PGT-A for day 3 embryos from the HFEA's traffic light rated list of add-ons is appropriate

Resource implications	In budget		
Implementation date	Recommendations will be considered by the HFEA for implementation in due course		
Communication(s)	Communication of revised traffic light ratings if any change in a Clinic Focus and HFEA website update		
Organisational risk	☒ Low	☐ Medium	☐ High
Annexes	Annex A: Treatment add-ons traffic light ratings review Annex B: Independent reviewer report		

1. Introduction

1.1. Treatment add-ons are optional extras, offered on top of the main fertility treatment such as in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI), that claim to improve patients' chances of having a baby. They're sometimes emerging techniques that may have shown some promising results in initial studies, or they may have been around for a number of years but haven't necessarily been proven to improve live birth rates. The HFEA has been concerned about the use of treatment add-ons for some years, and published a consensus statement co-signed by ten leading professional and patient fertility groups, outlining agreed principles on how add-ons should be offered ethically in clinical practice in the UK.

1.2. Since Spring 2017, the HFEA has published patient information on the most commonly available add-ons, currently 11 in number, each assigned with a traffic light rating agreed by the SCAAC reflecting the evidence of the effectiveness of the add-on (as measured by increasing a patient's chances of having a baby) and the safety of the add-on.

1.3. The HFEA agreed that these were the treatment add-ons that patients most need information about, but this is not the complete list of additional treatments that patients may be offered on top of the main fertility treatment. The list of add-ons that the HFEA currently provides patient information on with a traffic light rating are

- Artificial egg activation
- Assisted hatching
- Elective freeze-all
- Endometrial scratching
- Hyaluronate enriched medium (eg EmbryoGlue)
- Intracytoplasmic morphologic sperm injection (IMSI)
- Intrauterine culture
- Physiological intracytoplasmic sperm injection (PICSI)
- Preimplantation genetic testing for aneuploidy (PGT-A)
- Reproductive immunology
- Time-lapse incubation and imaging

1.4. Information is also provided for DNA fragmentation which may be offered to patients in several clinics. There is no traffic light rating for DNA fragmentation as after consulting with an andrology expert, SCAAC decided (at its October 2018 meeting) that this was not feasible, as DNA fragmentation is a diagnostic test and does not directly influence live birth rate.

1.5. HFEA work on treatment add-ons continues to develop over time. In August 2020 the HFEA treatment add-ons webpage was updated to give more information to patients about each of the treatment add-ons, what the traffic light ratings mean and the evidence that is used to decide these ratings.

1.6. And in that same month, we introduced an application form for medical professionals, academics or patient organisations to propose that the HFEA reviews the evidence for a treatment add-on if they are concerned that it is being offered to patients in a UK licensed clinic:

- with the claim that it will increase live birth rate; and
- without conclusive evidence of its safety or effectiveness at improving the live birth rate; and
- it is not already listed in our the HFEA's traffic-light rated list of add-ons; and/or

- there is evidence that an add-on treatment is unsafe or ineffective.

1.7. The HFEA will use the information submitted to help us consider whether to include the proposed add-on in a future assessment. The HFEA's traffic-light rated list of add-ons are annually reviewed for evidence of their effectiveness for increasing live birth rate and safety.

1.8. Lastly, the existing traffic light ratings and the recommendations made in this paper do not consider risks and concerns that are specific to a treatment add-on being used during the current COVID-19 pandemic. For example, there are additional risks associated with reproductive immunology being used in a patient's treatment during the COVID-19 pandemic that would need to be taken into consideration. These risks are additional to the effectiveness and safety concerns discussed in this paper.

2. Traffic light system

2.1. A traffic light system is used alongside our patient information to give a quick, visual indication of whether the add-on is supported by good quality evidence for use in clinical practice or not, for the purpose of increasing live birth rate. The traffic light ratings of the 11 treatment add-ons assessed so far are:

Traffic light rating	Definition	Add-ons currently under this rating
 Red	No evidence to show that it is effective and safe	Assisted hatching PGT-A (day 3 and day 5) IMSI PICSI Intrauterine culture Reproductive immunology tests and treatment
 Amber	There is a conflicting body of evidence for this add-on, further research is required	Artificial egg activation calcium ionophore Elective freeze all cycles Embryo glue Endometrial scratching Time-lapse imaging
 Green	There is more than one good quality RCT which shows that the procedure is effective and safe	*n/a - These treatment add-ons may be routinely used in fertility treatments. It is not current HFEA policy to include 'green' add-ons in this review list.*

2.2. The current traffic light rating system for treatment add-ons was first agreed in 2017. The appropriateness of this current traffic light system will be reviewed by the HFEA Board in due course as part of a wider review of this policy.

2.3. To account for new evidence that arises from randomised clinical trials (RCTs) conducted investigating treatment add-ons, the list of treatment add-ons and their assigned traffic light ratings are reviewed annually to determine whether the traffic light rating should change. Traffic

light ratings could both be promoted to a higher rating (e.g. red to amber or amber to green) or demoted (e.g. amber to red).

2.4. During the treatment add-on traffic light rating review that took place at the October 2019 SCAAC meeting, the committee gave the recommendation that PGT-A for day 5 embryos should be demoted from an amber rating to a red rating. In response to this change, the HFEA received feedback that the exclusive focus on live birth rate in the traffic light assessment process meant that other demonstrable benefits of PGT-A may have been ignored.

2.5. At the June 2020 SCAAC meeting the Committee re-reviewed the evidence from the October 2019 SCAAC meeting to determine if the information published on the HFEA website for PGT-A should be revised to include advice to patients about outcomes other than live birth rate. The Committee recommended including advice for patients that secondary outcomes from some RCTs had suggested that PGT-A may be beneficial for certain categories of women, particularly older women, in relation to a potential reduction in miscarriage.

2.6. Going forward, traffic light ratings will continue to reflect the evidence that a treatment add-on is able to increase the chances of having a baby (a live birth). However, should the independent reviewer report that RCTs for treatment add-ons highlight significant outcomes in addition to live birth rate (time to pregnancy, miscarriage rates, risk of ovarian hyperstimulation syndrome) these will be considered by the committee to determine if there is any additional advice that should be given to patients.

3. Independent assessment of the quality of evidence

3.1. In order to categorise the treatment add-ons under consideration, it is necessary not only to identify the published evidence around each treatment add-on, but also to assess the quality of that evidence. For this reason, we seek 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.

3.2. New research (the published evidenced) in the form of RCTs were identified for five of the 11 add-ons on the HFEA's traffic light rated list of add-ons.

3.3. The independent reviewer reassessed the traffic light ratings in light of the additional studies published since the last review (conducted in October 2019).

3.4. Critical review of studies included assessment of risk of bias from allocation method, blinding, selective reporting, unexplained attrition, unplanned interim analysis and other miscellaneous errors in the design, conduct or reporting of results.

3.5. The findings of this assessment for each add-on and the independent reviewer's recommended ratings can be found at Annex A, alongside the current traffic light rating agreed previously in consultation with the committee, last in October 2019. The assessments made by the independent reviewer are from a methodological perspective without expertise in the clinical or scientific context

[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.

3.6. The independent reviewer's original report can be found at Annex B

4. Recommendations

4.1. The committee is asked to:

- consider the quality of new evidence for each treatment add-on based on the findings from an independent assessor at annex A; and
- agree and recommend traffic light categories for each treatment add-on based on the outcome of live birth rate; and
- recommend information about outcomes other than live birth rate (time to pregnancy, miscarriage rates, risk of ovarian hyperstimulation syndrome) to be included on the HFEA website for each of the treatment add-ons.
- recommend whether the removal of PGT-A for day 3 embryos from the HFEA's traffic light rated list of add-ons is appropriate

Annex A: Treatment add-ons traffic light ratings review

1. Artificial egg activation calcium ionophore

Current traffic light category		Traffic light category recommended by independent reviewer - October 2020
 Amber	There is a conflicting body of evidence for this add-on, further research is required	No new studies were reviewed as part of October 2020 review.

1.1. Artificial egg activation calcium ionophore was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned an amber traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

1.2. No RCTs for this treatment add-on were identified that had been published since the last review in October 2019. For this reason, the traffic light rating for assisted hatching will not be reviewed at this meeting.

2. Assisted hatching

Current traffic light category		Traffic light category recommended by independent reviewer - October 2020
 Red	No evidence to show that it is effective and safe.	No new studies were reviewed as part of October 2020 review.

2.1. Assisted hatching was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned a red traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

2.2. No RCTs for this treatment add-on were identified that had been published since the last review in October 2019. For this reason, the traffic light rating for artificial egg activation calcium ionophore will not be reviewed at this meeting.

3. Elective freeze all cycles

Current traffic light category		Traffic light category recommended by independent reviewer - October 2020	
 Amber	There is a conflicting body of evidence for this add-on, further research is required	 Amber	There is a conflicting body of evidence for this add-on, further research is required

3.1. Elective freeze all cycles was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned an amber traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

3.2. Independent reviewer comments:

3.3. *The previous review in 2017 included four randomised trials, although one had been retracted following "results of an investigation" due to "serious methodological flaws". Two were from the same team as each other covering 'normal' and 'high' responders to stimulation. Both suggested slightly increased rates of ongoing pregnancy with the freeze-all policy but interpretation was limited by insecure allocation and other sources of bias. The remaining trial studied couples undergoing ICSI following unexplained, recurrent implantation failure in at least three previous ICSI cycles using fresh embryo transfer. Results were promising but the trial used (predictable) alternation rather than randomisation, leaving high risk of selection bias. The high number of embryos transferred in each cycle (>2 in each trial arm) may also limit applicability to the UK setting.*

3.4. *The current update incorporates four trials published in leading general medical journals that all appear to be methodologically strong: Shi 2018, Vuong 2018, Wei 2019 and Stormlund 2020. All four studies were at low risk of bias and sample sizes ranged from 460 participants (Stormlund 2020) to over 2000 (Shi 2018).*

3.5. *Shi 2018 and Wei 2019 considered good prognosis couples (e.g. first treatment cycle, maternal age <35 years, good number of available high grade oocytes or embryos). The main differences between these studies were that Shi 2018 selected and froze two day 2 or day 3 embryos for transfer whereas Wei 2019 selected and froze day 5 or 6 embryos and used single blastocyst transfer.*

3.6. *Vuong 2018 similarly selected good prognosis couples but explicitly where the woman did not have polycystic ovary syndrome (PCOS). This trial selected and froze Day 3 embryos for a policy of double embryo transfer.*

3.7. *Stormlund 2020 randomised earlier to incorporate the opportunity to reduce risk of OHSS by using a gonadotrophin releasing hormone agonist to trigger final oocyte maturation. Pragmatic comparison used a conventional trigger but allowed for those allocated to fresh transfer who were at high risk of OHSS to delay until a frozen cycle. Single blastocyst transfer was the policy in both groups.*

3.8. *All four trials reported on live birth following the first transfer cycle. Three found little difference but Wei 2019 reported a large and statistically significant benefit of the freeze-all approach with a confidence interval that did not overlap with that of Shi 2018 despite the similarity of the population. The effect size was also larger than the upper limits of the other two studies. Confirmatory study would be required to ascertain whether this was an anomalous result or a true reflection of the effect in single blastocyst transfer.*

3.9. *Unfortunately, only Vuong reported on outcomes beyond the first transfer cycle, which are arguably more relevant for this intervention. They did not identify any effect on the numbers of participants achieving an ongoing pregnancy within 12 months of randomisation but did report an unsurprising and highly statistically significant average delay of 1.4 months to pregnancy when not attempting a fresh transfer cycle.*

3.10. ***Recommendation: Amber***

4. Endometrial scratching

Current traffic light category		Traffic light category recommended by independent reviewer - October 2020	
Amber	There is a conflicting body of evidence for this add-on, further research is required	Amber	There is a conflicting body of evidence for this add-on, further research is required

4.1. Endometrial scratching was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned an amber traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

4.2. **Independent reviewer comments:**

4.3. *The previous review included 19 RCTs, reporting on more than 4000 participants, with substantial variation in populations, clinical protocols and duration of follow-up for outcomes. Eleven studies of women undergoing IUI or natural cycles were of generally poor quality but surprisingly consistent in estimating clinical benefit of scratching. Seven studies of women undergoing IVF or ICSI cycles were less optimistic and the more recent, larger and higher quality studies did not suggest any benefit.*

4.4. *This review further considers Olesen 2019, which randomised a further 304 participants undergoing IVF/ICSI cycles in a well-designed and clearly reported study. Women had experienced at least one previous implantation failure of top quality embryos or blastocysts. Live birth rate was higher in the scratch group but not statistically significantly so. Important to note is that there was no trend ('dose-response') in effect size according to the number of previous implantation failures despite the abstract highlighting a single subgroup comparison. This study adds a little but does not contradict the previous review suggesting little or no effect in those women undergoing transfer cycles.*

4.5. *During the review process the results of two further studies became available. A Dutch trial (van Hoogenhuijze 2020, in press) randomised nearly 1000 women undergoing IVF with at least one previous failed embryo transfer. A single scratch was performed in the mid-luteal phase of the cycle preceding transfer. Their reported live birth rate was 24% vs 19% in the following fresh transfer cycle.*

4.6. *A large UK study (Metwally 2020, in preparation) randomised 1048 women under 38 years old who were undergoing a first IVF/ICSI treatment cycle. Intervention was also during the mid-luteal phase of the preceding cycle. Their results were strikingly similar to those of Lensen 2019.*

4.7. *Taken together, there are now several large and well-designed trials with consistent results that exclude any major benefit or detriment of the endometrial scratch procedure in women undergoing embryo transfer. A small benefit remains possible, with an odds ratio of 1.3, for example, translating into an increase in live birth rates from 35% to 41%.*

4.8. *If the committee considers it to be biologically plausible that the intervention may affect implantation differentially between IVF/ICSI and IUI/natural cycles, then consideration could be given to providing separate ratings for the two clinical populations.*

4.9. ***Recommendation: Amber***

5. Hyaluronate enriched medium (eg EmbryoGlue)

Current traffic light category		Traffic light category recommended by independent reviewer - October 2020
 Amber	There is a conflicting body of evidence for this add-on, further research is required	No new studies were reviewed as part of October 2020 review.

5.1. Hyaluronate enriched medium was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned an amber traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

5.2. No RCTs for this treatment add-on were identified that had been published since the last review in October 2019. For this reason, the traffic light rating for hyaluronate enriched medium will not be reviewed at this meeting.

6. Intracytoplasmic morphologic sperm injection (IMSI)

Current traffic light category		Traffic light category recommended by independent reviewer - October 2020	
 Red	No evidence to show that it is effective and safe.	 Red	No evidence to show that it is effective and safe.

6.1. IMSI was introduced to the HFEA's traffic light rated list of add-ons in October 2018 and was assigned a red traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

6.2. **Independent reviewer comments:**

6.3. *The previous review considered seven studies including three standard (parallel design) randomised trials and one within-participant (randomised sibling oocytes) comparison. The only suggestion of possible benefit came from a small, well-designed trial by Setti 2013, who reported improved ongoing pregnancy rate using IMSI in fertile men where the female partner was older (at least 37 years), with the hypothesis that older eggs may be less able to repair DNA damage. The studies of infertile men did not suggest any benefit.*

6.4. *The current update adds the trial of 150 couples by Mangoli 2019. Couples had infertile men and healthy women aged under 38 years. The trial appears at high risk of bias with unclear reporting of allocation concealment, blinding and outcome definition. Taken at face value there appears to be an increase of borderline statistical significance in live birth rate when using IMSI: OR (95% CI) = 2.2 (1.0 to 4.6) but it is unclear whether the authors counted the number of women giving birth*

or the number of babies born. With a policy of double embryo transfer the relevance to the UK setting may be questioned.

6.5. ***Recommendation: Red for infertile men***

7. Intrauterine culture

Current traffic light category		Traffic light category recommended by independent reviewer - October 2020
Red	No evidence to show that it is effective and safe.	No new studies were reviewed as part of October 2020 review.

7.1. Intrauterine culture was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned a red traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

7.2. No RCTs for this treatment add-on were identified that had been published since the last review in October 2019. For this reason, the traffic light rating for intrauterine culture will not be reviewed at this meeting.

8. Physiological intracytoplasmic sperm injection (PICSI)

Current traffic light category		Traffic light category recommended by independent reviewer - October 2020
Red	No evidence to show that it is effective and safe.	No new studies were reviewed as part of October 2020 review.

8.1. PICSI was introduced to the HFEA's traffic light rated list of add-ons as in October 2018 and was assigned a red traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

8.2. No RCTs for this treatment add-on were identified that had been published since the last review in October 2019. For this reason, the traffic light rating for PICSI will not be reviewed at this meeting.

9. Pre-implantation genetic testing for aneuploidy (PGT-A)

Current traffic light category		Traffic light category recommended by independent reviewer - October 2020
PGT-A (day 3)		
 Red	No evidence to show that it is effective and safe.	No new studies were reviewed as part of October 2020 review.
PGT-A (day 5)		
 Red	No evidence to show that it is effective and safe.	Not reviewed as part of October 2020 review.

9.1. PGT-A for day 3 embryos was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned a red traffic light rating by the Committee. No changes have been made to this traffic light rating since then. PGT-A for day 5 embryos was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned a red traffic light rating by the Committee, this rating was changed to a red traffic light by the Committee in October 2019.

9.2. No RCTs for this treatment add-on were identified that had been published since the last review in October 2019. For this reason, the traffic light rating for PGT-A (day 3 and day 5) will not be reviewed at this meeting.

9.3. PGT-A is currently separated into traffic light ratings for day 3 and day 5 embryos. It is proposed that the rating for day 3 embryos be removed as this a redundant practice.

10. Reproductive Immunology

Current traffic light category		Traffic light category recommended by independent reviewer - October 2020	
Reproductive Immunology		Steroids	
 Red	No evidence to show that it is effective and safe.	 Amber	There is a conflicting body of evidence for this add-on, further research is required
		Intravenous immunoglobulins (IVIG)	
		 Red	No evidence to show that it is effective and safe.
		Intralipids	

Amber	There is a conflicting body of evidence for this add-on, further research is required

10.1. Reproductive immunology was introduced to the HFEA's traffic light rated list of add-ons as an umbrella term covering all reproductive immunology treatments in February 2017 and was assigned a red traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

10.2. It is now proposed that reproductive immunology be broken down by treatment type and an individual traffic light rating be allocated to each type. It should be noted that no publications investigation TNF-a blocking agents were identified for inclusion in this review and therefore a traffic light rating has not been recommended.

10.3. Reproductive immunology is a complicated issue within the current context of the COVID-19 pandemic. The professional advice from the British Fertility Society (BFS), the Association of Reproductive and Clinical Scientists (ARCS) and the Royal College of Obstetricians and Gynaecologists (RCOG) is that the use of empirical treatments of uncertain efficacy and safety, including immunosuppressive treatments, should be avoided.

10.4. Independent reviewer comments:

10.5. Steroids

10.6. *The nine studies of steroids considered quite different populations depending on the proposed mechanism of action.*

10.7. *Wiser 2010 studied a small number of women with a poor response to stimulation in a previous cycle of treatment. They found a marked increase in live birth rates for women given 75 mg oral dehydroepiandrosterone (DHEA) daily for a number of weeks prior to starting stimulation. The study was unblinded with unclear allocation concealment. Kara 2014 similarly gave DHEA to 200 women with diminished ovarian reserve in an unblinded study. They recorded almost identical clinical pregnancy rate between groups. Narkwichean 2017 undertook a feasibility and proof of concept study in 60 women undergoing their first IVF/ICSI cycle and with predicted diminished ovarian reserve. This study also used DHEA but incorporated matching placebo in a seemingly well designed and conducted trial. They observed slightly higher success amongst the control group.*

10.8. *Fawzy 2013 studied over 300 women with previous unexplained implantation failures. The intervention consisted of oral prednisolone 20 mg/day from the day of stimulation with 1mg/kg/day subcutaneous low molecular weight heparin (LMWH) from the day after oocyte retrieval until the day of pregnancy test (if negative) or week 8 of pregnancy. The authors reported a large increase in ongoing pregnancy but this study was unblinded and, more importantly, used entirely predictable alternation rather than randomisation to allocate participants. Results are therefore unreliable. Tartagni randomised 100 women with repeated IUI failures but normal ovarian reserve. They undertook a placebo-controlled trial of 75 mg oral DHEA daily for eight weeks prior to starting ovulation induction. They reported a higher live birth rate in the active group, most of which could be ascribed to more miscarriages in the control group.*

10.9. *The remaining four studies each targeted particular groups with different aims. Fan 2016 studied 130 women with antinuclear antibody who had experienced a previous implantation failure. Treatment consisted of prednisolone 10mg daily plus aspirin 100mg daily from 3 months before ovulation induction until clinical pregnancy. The trial was unblinded and unclear regarding allocation concealment. A large difference in clinical pregnancy was reported.*

10.10. *Taiyeb 2017 studied 240 men with anti-sperm antibodies. Treatment consisted of following a course of tapering prednisolone repeated in each of three menstrual cycles prior to IVF/ICSI. There was risk of bias from both unclear allocation concealment and blinding processes and methodological issues with post-randomisation exclusions. Reconstruction of an intention to treat comparison suggested a small and non-statistically significant advantage of treatment on clinical pregnancy rate.*

10.11. *Yeganeh 2017 studied over 200 women with PCOS with the aim of reducing the risk of OHSS. Intervention consisted of methylprednisolone: 1g intravenous on the days of oocyte retrieval and embryo transfer plus 16mg oral daily from the first day of stimulation through to pregnancy testing. This was another unblinded study at high risk of bias regarding allocation concealment but reported very similar clinical pregnancy rate in each group.*

10.12. *Most recently, Liu 2018 undertook a study of 450 women undergoing their first IVF cycle with no history of recurrent miscarriage who experienced raised progesterone levels on the third or fourth day of gonadotrophin stimulation. They compared 0.75mg daily oral dexamethasone with no treatment in another unblinded study. They reported very similar outcomes in the fresh transfer cycle. Follow-up for two years of all frozen transfers suggested an advantage of intervention for the outcome of cumulative live birth.*

10.13. ***Recommendation: Amber, or red for most if separating populations***

10.14. **Intravenous immunoglobulins (IVIG)**

10.15. *Two studies were reviewed. Stephenson 2010 randomised 77 participants with idiopathic secondary recurrent miscarriage in a double-blind, placebo controlled trial. IVIG was delivered at a dose of 500mg/kg two to three weeks before the next anticipated menstrual period and then every four weeks for up to 6 cycles or until reaching 18 to 20 weeks gestation. The size of study ruled out very little: live birth odds ratio (95% CI) was 1.2 (0.47 to 2.9); consistent with the intervention more than doubling or halving the odds of success.*

10.16. *Christiansen 2014 conducted a study of similar size in a similar patient population. The main difference was that IVIG was first given on confirmation of pregnancy by repeated biochemical testing. A total of eight infusions were given up to week 15 of gestation at a dose of approximately 25g for those up to 75kg of weight and 35g for heavier women. Results were also very similar with live birth odds ratio (95% CI) of 1.2 (0.51 to 2.9).*

10.17. ***Recommendation: Red***

10.18. **Intralipids**

10.19. *This review included three studies. Dakhly 2016 randomised nearly 300 participants with secondary recurrent miscarriage who were undergoing IVF to IV infusion on the day of oocyte retrieval or matching placebo. Unfortunately this was a poorly reported study with scope for serious bias in the allocation and blinding processes. It was conducted with a policy of*

transferring two or three embryos. The reported result was a marked increase in live birth rate with intervention: OR (95% CI) = 2.1 (1.3 to 3.5).

10.20. *Singh 2019 studied about 100 women with recurrent implantation failure undergoing IVF. Infusions were given immediately following oocyte retrieval and again one hour after embryo transfer. This too was a poorly reported study at risk of bias from both allocation concealment and blinding. It was also conducted with a policy of transferring two or three embryos when available. The reported result was a marked increase in live birth rate with intervention: OR (95% CI) = 3.3 (1.2 to 8.8).*

10.21. *Al-Zebeidi 2019 studied nearly 150 women with unexplained recurrent implantation failure undergoing ICSI. Infusions in this study were given at the time of embryo transfer and again at the time of pregnancy testing. This too was a poor study at risk of bias from allocation concealment and with no attempt at blinding. A double embryo transfer policy was used with three embryos allowed for older women. Again the reported live birth result favoured intervention but this time without reaching statistical significance: OR (95% CI) = 1.4 (0.57 to 3.4).*

10.22. ***Recommendation: Amber***

11. Time-lapse incubation and imaging

Current traffic light category		Traffic light category recommended by independent reviewer - October 2020	
Amber	There is a conflicting body of evidence for this add-on, further research is required	Amber	There is a conflicting body of evidence for this add-on, further research is required

11.1. Time-lapse incubation and imaging was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned a red traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

11.2. Independent reviewer comments:

11.3. *Time lapse incubation involves two distinct processes. The ability to leave the embryo undisturbed during repeated assessment may be beneficial to the development process. Independently, the additional information available through time-lapse imaging may bring benefits for embryo selection. Trials fall into three broad categories evaluating the effect on clinical success of: i) the environment for embryo development; ii) the embryo selection process; and iii) the combined effect of the two. I have therefore reviewed these separately below. One further study was included for review. Wang 2016 was available only in abstract form and reports prediction modelling of which morphokinetic factors may be predictive of good blastocyst development. 150 single embryo transfers were then prospectively studied to 'validate' the model but it is unclear who was eligible and what comparison was made. At the time of writing, a request for the full manuscript has not been answered*

11.4. Trials of environment

11.5. *Only Kirkegaard 2012 considered this comparison. However, this was a study of safety rather than of effectiveness. Embryos were repeatedly removed from the time-lapse incubator to allow blinded assessment, thereby negating any putative benefit of the stable environment whilst retaining any possible detriment of frequent light exposure. The authors concluded no difference (and therefore no evidence of lack of safety) in embryo development. The design randomised oocytes apparently without regard to sibling dependence and therefore contains no information on clinical effectiveness.*

11.6. **Trials of the selection process**

11.7. *Two studies considered this comparison: Goodman 2016 and Kovacs 2019. Each studied couples undergoing autologous IVF cycles with intended fresh transfer. All embryos were incubated in the same way with randomisation to whether the additionally available morphokinetic data were used in the embryo selection process. Whereas Goodman 2016 transferred an average of nearly two embryos per participant the policy within Kovacs 2019 was elective single embryo transfer in each group. Neither study was large, with just 461 participants in total. Unfortunately both were potentially subject to serious bias from the allocation processes described, more clearly so with Kovacs 2019.*

11.8. *Both studies reported a statistically non-significant benefit using the time lapse data within their selection algorithms.*

11.9. **Trials of environment and selection**

11.10. *Four studies considered this comparison to varying extents. Kahraman 2013 studied a small number of women (<40 per group) with good prognosis undergoing elective single blastocyst transfer. Rubio 2014 studied over 850 similarly good prognosis women. Their study differed in that decisions regarding the timing (approx. 75% Day 3) and number (mean 1.9) to transfer were taken independently of the study. Later outcomes for this trial's participants, including live birth, were reported separately in Insua 2017. Both studies were at high risk of bias for allocation concealment and Rubio 2014 additionally suggested there may be scope for serious bias in their study with some patients re-allocated due to personal preference.*

11.11. *Alhelou 2018 studied over 400 women with a broader range of prognosis (e.g. no age limit) using single or double blastocyst transfer according to availability and patient preference. Unfortunately they used alternation rather than randomisation, casting serious doubt on their findings.*

11.12. *Yang 2018 studied 600 women with good prognosis but in a design that mixed comparisons. All embryos were initially placed in the time lapse incubator for the first three days. Comparison was then between application of time-lapse data to select a single embryo for transfer, or continued incubation in a standard incubator with single blastocyst selection based on standard morphological criteria.*

11.13. *The two largest studies, Rubio 2014 and Yang 2018 reported contrasting results: statistically significant benefit and detriment respectively. The other two reported small and not statistically significant differences in favour of their time lapse arms. However, the poor quality of study design and reporting prevents reliable interpretation of any of these studies.*

11.14. ***Recommendation: Amber***

Annex B: Independent reviewer report

Traffic Light System for Treatment Add-ons

Prof Andy Vail, October 2020

INTRODUCTION

The HFEA website provides patients with digestible information on treatment add-ons in the form of a 'traffic light' system. The purpose of this report is to inform the Scientific and Clinical Advances Advisory Committee's deliberations on updating this information. In particular, further recent trials have been identified to supplement current reviews of three add-ons: elective freeze all; IMSI; and endometrial scratch. Trials have also been identified to include new reviews of the effectiveness of time lapse incubation and reproductive immunology, including use of steroids, IV immunoglobulin and intralipids.

The aim of the work reported below was to critically appraise, interpret and summarise the reports of these studies provided for consideration by the HFEA.

METHOD

Dina Halai, Scientific Policy Manager, provided references and hyperlinks to identified studies for consideration. All studies for update of current reviews were published since 2019. Studies for the new reviews were published since 2010.

Critical review of studies included assessment of risk of bias from allocation method, blinding, selective reporting, unexplained attrition, unplanned interim analysis and other miscellaneous errors in the design, conduct or reporting of results. Where it appeared overly simplistic to categorise all studies of a specific add-on together, results have been stratified in the results presented below.

To calculate odds ratios, published results were re-calculated applying the intention to treat (ITT) principle and using two-sided confidence intervals. As these were being interpreted as indicative rather than inferential, no technical adjustments were applied for multiple testing, covariate adjustment or planned interim analyses. Odds ratios were calculated for the latest clinical outcome presented. That is, live birth rate was first choice, followed by ongoing, clinical, unspecified or biochemical pregnancy. An odds ratio greater than 1.0 implies benefit of the add-on under study.

RESULTS

Updates to existing reviews

1. Elective freeze all

The previous review in 2017 included four randomised trials, although one had been retracted following "results of an investigation" due to "serious methodological flaws". Two were from the same team as each other covering 'normal' and 'high' responders to stimulation. Both suggested slightly increased rates of ongoing pregnancy with the freeze-all policy but interpretation was limited by insecure allocation and other sources of bias. The remaining trial studied couples undergoing ICSI following unexplained, recurrent implantation failure in at least three previous ICSI cycles using fresh embryo transfer. Results were promising but the trial used (predictable) alternation rather than randomisation, leaving high risk of selection bias. The high number of embryos transferred in each cycle (>2 in each trial arm) may also limit applicability to the UK setting.

The current update incorporates four trials published in leading general medical journals that all appear to be methodologically strong: Shi 2018, Vuong 2018, Wei 2019 and Stormlund 2020. All four studies were at low risk of bias and sample sizes ranged from 460 participants (Stormlund 2020) to over 2000 (Shi 2018).

Shi 2018 and Wei 2019 considered good prognosis couples (e.g. first treatment cycle, maternal age <35 years, good number of available high grade oocytes or embryos). The main differences between these studies were that Shi 2018 selected and froze two day 2 or day 3 embryos for transfer whereas Wei 2019 selected and froze day 5 or 6 embryos and used single blastocyst transfer.

Vuong 2018 similarly selected good prognosis couples but explicitly where the woman did not have polycystic ovary syndrome (PCOS). This trial selected and froze Day 3 embryos for a policy of double embryo transfer.

Stormlund 2020 randomised earlier to incorporate the opportunity to reduce risk of OHSS by using a gonadotrophin releasing hormone agonist to trigger final oocyte maturation. Pragmatic comparison used a conventional trigger but allowed for those allocated to fresh transfer who were at high risk of OHSS to delay until a frozen cycle. Single blastocyst transfer was the policy in both groups.

All four trials reported on live birth following the first transfer cycle. Three found little difference but Wei 2019 reported a large and statistically significant benefit of the freeze-all approach with a confidence interval that did not overlap with that of Shi 2018 despite the similarity of the population. The effect size was also larger than the upper limits of the other two studies. Confirmatory study would be required to ascertain whether this was an anomalous result or a true reflection of the effect in single blastocyst transfer.

Unfortunately only Vuong reported on outcomes beyond the first transfer cycle, which are arguably more relevant for this intervention. They did not identify any effect on the numbers of participants achieving an ongoing pregnancy within 12 months of randomisation but did report an unsurprising and highly statistically significant average delay of 1.4 months to pregnancy when not attempting a fresh transfer cycle.

Current rating amber.
Recommendation: amber (only one of four high quality studies suggested benefit and this may be an anomaly or a genuine result of the different clinical context)

2. Intracytoplasmic morphologically selected sperm injection (IMSI)

The previous review considered seven studies including three standard (parallel design) randomised trials and one within-participant (randomised sibling oocytes) comparison. The only suggestion of possible benefit came from a small, well-designed trial by Setti 2013, who reported improved ongoing pregnancy rate using IMSI in fertile men

where the female partner was older (at least 37 years), with the hypothesis that older eggs may be less able to repair DNA damage. The studies of infertile men did not suggest any benefit.

The current update adds the trial of 150 couples by Mangoli 2019. Couples had infertile men and healthy women aged under 38 years. The trial appears at high risk of bias with unclear reporting of allocation concealment, blinding and outcome definition. Taken at face value there appears to be an increase of borderline statistical significance in live birth rate when using IMSI: OR (95% CI) = 2.2 (1.0 to 4.6) but it is unclear whether the authors counted the number of women giving birth or the number of babies born. With a policy of double embryo transfer the relevance to the UK setting may be questioned.

Current rating red.
Recommendation: red (experimental: little evidence to support use) for infertile men. The new study is insufficiently persuasive on its own to justify a change.

3. Endometrial Scratching

The previous review included 19 RCTs, reporting on more than 4000 participants, with substantial variation in populations, clinical protocols and duration of follow-up for outcomes. Eleven studies of women undergoing IUI or natural cycles were of generally poor quality but surprisingly consistent in estimating clinical benefit of scratching. Seven studies of women undergoing IVF or ICSI cycles were less optimistic and the more recent, larger and higher quality studies did not suggest any benefit.

This review further considers Olesen 2019, which randomised a further 304 participants undergoing IVF/ICSI cycles in a well-designed and clearly reported study. Women had experienced at least one previous implantation failure of top quality embryos or blastocysts. Live birth rate was higher in the scratch group but not statistically significantly so. Important to note is that there was no trend ('dose-response') in effect size according to the number of previous implantation failures despite the abstract highlighting a single subgroup comparison. This study adds a little but does not contradict the previous review suggesting little or no effect in those women undergoing transfer cycles.

During the review process the results of two further studies became available. A Dutch trial (van Hoogenhuijze 2020, in press) randomised nearly 1000 women undergoing IVF with at least one previous failed embryo transfer. A single scratch was performed in the mid-luteal phase of the cycle preceding transfer. Their reported live birth rate was 24% vs 19% in the following fresh transfer cycle.

A large UK study (Metwally 2020, in preparation) randomised 1048 women under 38 years old who were undergoing a first IVF/ICSI treatment cycle. Intervention was also during the mid-luteal phase of the preceding cycle. Their results were strikingly similar to those of Lensen 2019.

Taken together, there are now several large and well-designed trials with consistent results that exclude any major benefit or detriment of the endometrial scratch procedure in women undergoing embryo transfer. A small benefit remains possible, with an odds ratio of 1.3, for example, translating into an increase in live birth rates from 35% to 41%.

If the committee considers it to be biologically plausible that the intervention may affect implantation differentially between IVF/ICSI and IUI/natural cycles, then consideration could be given to providing separate ratings for the two clinical populations.

Current rating: amber
Recommendation: amber (contradictory evidence overall but small positive effect would be consistent with the best quality, recent evidence).

New Reviews

1. Time lapse incubation systems

Time lapse incubation involves two distinct processes. The ability to leave the embryo undisturbed during repeated assessment may be beneficial to the development process. Independently, the additional information available through time-lapse imaging may bring benefits for embryo selection. Trials fall into three broad categories evaluating the effect on clinical success of: i) the environment for embryo development; ii) the embryo selection process; and iii) the combined effect of the two. I have therefore reviewed these separately below. One further study was included for review. Wang 2016 was available only in abstract form and reports prediction modelling of which morphokinetic factors may be predictive of good blastocyst development. 150 single embryo transfers were then prospectively studied to 'validate' the model but it is unclear who was eligible and what comparison was made. At the time of writing, a request for the full manuscript has not been answered.

1 (i). Trials of the environment

Only Kirkegaard 2012 considered this comparison. However, this was a study of safety rather than of effectiveness. Embryos were repeatedly removed from the time-lapse incubator to allow blinded assessment, thereby negating any putative benefit of the stable environment whilst retaining any possible detriment of frequent light exposure. The authors concluded no difference (and therefore no evidence of lack of safety) in embryo development. The design randomised oocytes apparently without regard to sibling dependence and therefore contains no information on clinical effectiveness.

1 (ii). Trials of the selection process

Two studies considered this comparison: Goodman 2016 and Kovacs 2019. Each studied couples undergoing autologous IVF cycles with intended fresh transfer. All embryos were incubated in the same way with randomisation to whether the additionally available morphokinetic data were used in the embryo selection process. Whereas Goodman 2016 transferred an average of nearly two embryos per participant the policy within Kovacs 2019 was elective single embryo transfer in each group. Neither study was large, with just 461 participants in total. Unfortunately both were potentially subject to serious bias from the allocation processes described, more clearly so with Kovacs 2019.

Both studies reported a statistically non-significant benefit using the time lapse data within their selection algorithms.

1 (iii). Trials of environment and selection

Four studies considered this comparison to varying extents. Kahraman 2013 studied a small number of women (<40 per group) with good prognosis undergoing elective single blastocyst transfer. Rubio 2014 studied over 850 similarly good prognosis women. Their study differed in that decisions regarding the timing (approx. 75% Day 3) and number (mean 1.9) to transfer were taken independently of the study. Later outcomes for this trial's participants, including live birth, were reported separately in Insua 2017. Both studies were at high risk of bias for allocation concealment and Rubio 2014 additionally suggested there may be scope for serious bias in their study with some patients re-allocated due to personal preference.

Alhelou 2018 studied over 400 women with a broader range of prognosis (e.g. no age limit) using single or double blastocyst transfer according to availability and patient preference. Unfortunately they used alternation rather than randomisation, casting serious doubt on their findings.

Yang 2018 studied 600 women with good prognosis but in a design that mixed comparisons. All embryos were initially placed in the time lapse incubator for the first three days. Comparison was then between application of time-lapse data to select a single embryo for transfer, or continued incubation in a standard incubator with single blastocyst selection based on standard morphological criteria.

The two largest studies, Rubio 2014 and Yang 2018 reported contrasting results: statistically significant benefit and detriment respectively. The other two reported small and not statistically significant differences in favour of their time lapse arms. However, the poor quality of study design and reporting prevents reliable interpretation of any of these studies.

Recommendation: amber (contrasting and poor quality evidence that cannot rule out either detriment or benefit of the intervention)

2. Reproductive Immunology

2(i). Steroids

The nine studies of steroids considered quite different populations depending on the proposed mechanism of action.

Wiser 2010 studied a small number of women with a poor response to stimulation in a previous cycle of treatment. They found a marked increase in live birth rates for women given 75 mg oral dehydroepiandrosterone (DHEA) daily for a number of weeks prior to starting stimulation. The study was unblinded with unclear allocation concealment. Kara 2014 similarly gave DHEA to 200 women with diminished ovarian reserve in an unblinded study. They recorded almost identical clinical pregnancy rate between groups. Narkwichean 2017 undertook a feasibility and proof of concept study in 60 women undergoing their first IVF/ICSI cycle and with predicted diminished ovarian reserve. This study also used DHEA but incorporated matching placebo in a seemingly well designed and conducted trial. They observed slightly higher success amongst the control group.

Fawzy 2013 studied over 300 women with previous unexplained implantation failures. The intervention consisted of oral prednisolone 20 mg/day from the day of stimulation with 1mg/kg/day subcutaneous low molecular weight heparin (LMWH) from the day after oocyte retrieval until the day of pregnancy test (if negative) or week 8 of pregnancy. The authors reported a large increase in ongoing pregnancy but this study was unblinded and, more importantly, used entirely predictable alternation rather than randomisation to allocate participants. Results are

therefore unreliable. Tartagni randomised 100 women with repeated IUI failures but normal ovarian reserve. They undertook a placebo-controlled trial of 75 mg oral DHEA daily for eight weeks prior to starting ovulation induction. They reported a higher live birth rate in the active group, most of which could be ascribed to more miscarriages in the control group.

The remaining four studies each targeted particular groups with different aims. Fan 2016 studied 130 women with antinuclear antibody who had experienced a previous implantation failure. Treatment consisted of prednisolone 10mg daily plus aspirin 100mg daily from 3 months before ovulation induction until clinical pregnancy. The trial was unblinded and unclear regarding allocation concealment. A large difference in clinical pregnancy was reported.

Taiyeb 2017 studied 240 men with anti-sperm antibodies. Treatment consisted of following a course of tapering prednisolone repeated in each of three menstrual cycles prior to IVF/ICSI. There was risk of bias from both unclear allocation concealment and blinding processes and methodological issues with post-randomisation exclusions. Reconstruction of an intention to treat comparison suggested a small and non-statistically significant advantage of treatment on clinical pregnancy rate.

Yeganeh 2017 studied over 200 women with PCOS with the aim of reducing the risk of OHSS. Intervention consisted of methylprednisolone: 1g intravenous on the days of oocyte retrieval and embryo transfer plus 16mg oral daily from the first day of stimulation through to pregnancy testing. This was another unblinded study at high risk of bias regarding allocation concealment but reported very similar clinical pregnancy rate in each group.

Most recently, Liu 2018 undertook a study of 450 women undergoing their first IVF cycle with no history of recurrent miscarriage who experienced raised progesterone levels on the third or fourth day of gonadotrophin stimulation. They compared 0.75mg daily oral dexamethasone with no treatment in another unblinded study. They reported very similar outcomes in the fresh transfer cycle. Follow-up for two years of all frozen transfers suggested an advantage of intervention for the outcome of cumulative live birth.

Recommendation: amber, or red for most if separating populations (generally little high quality evidence with nothing replicated consistently). Most promise from Tartagni (repeated IUI failures) and Liu (raised progesterone response).

2(ii). Intravenous immunoglobulins (IVIG)

Two studies were reviewed. Stephenson 2010 randomised 77 participants with idiopathic secondary recurrent miscarriage in a double-blind, placebo controlled trial. IVIG was delivered at a dose of 500mg/kg two to three weeks before the next anticipated menstrual period and then every four weeks for up to 6 cycles or until reaching 18 to 20 weeks gestation. The size of study ruled out very little: live birth odds ratio (95% CI) was 1.2 (0.47 to 2.9); consistent with the intervention more than doubling or halving the odds of success.

Christiansen 2014 conducted a study of similar size in a similar patient population. The main difference was that IVIG was first given on confirmation of pregnancy by repeated biochemical testing. A total of eight infusions were given up to week 15 of gestation at a dose of approximately 25g for those up to 75kg of weight and 35g for heavier women. Results were also very similar with live birth odds ratio (95% CI) of 1.2 (0.51 to 2.9).

Recommendation: red (experimental, no evidence to support use). Two consistent results despite different delivery of intervention but too small to rule benefit in or out).

2(iii). Intralipids

This review included three studies. Dakhly 2016 randomised nearly 300 participants with secondary recurrent miscarriage who were undergoing IVF to IV infusion on the day of oocyte retrieval or matching placebo. Unfortunately this was a poorly reported study with scope for serious bias in the allocation and blinding processes. It was conducted with a policy of transferring two or three embryos. The reported result was a marked increase in live birth rate with intervention: OR (95% CI) = 2.1 (1.3 to 3.5).

Singh 2019 studied about 100 women with recurrent implantation failure undergoing IVF. Infusions were given immediately following oocyte retrieval and again one hour after embryo transfer. This too was a poorly reported study at risk of bias from both allocation concealment and blinding. It was also conducted with a policy of transferring two or three embryos when available. The reported result was a marked increase in live birth rate with intervention: OR (95% CI) = 3.3 (1.2 to 8.8).

Al-Zebeidi 2019 studied nearly 150 women with unexplained recurrent implantation failure undergoing ICSI. Infusions in this study were given at the time of embryo transfer and again at the time of pregnancy testing. This too was a poor study at risk of bias from allocation concealment and with no attempt at blinding. A double embryo transfer policy was used with three embryos allowed for older women. Again the reported live birth result favoured intervention but this time without reaching statistical significance: OR (95% CI) = 1.4 (0.57 to 3.4).

Recommendation: amber (poor quality studies suggest benefit but no high quality evidence).

DISCUSSION

Caution is required as the assessments above are made from a methodological perspective without expertise in the clinical or scientific context. Many post-hoc but biologically plausible rationales could be put forward to 'lump' or 'split' categories presented above.

REFERENCES: Reviewed studies (Bold indicates references added for 2019 update)

Adjunct	Study	DOI/reference
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
	Magdi 2017	10.1016/j.fertnstert.2017.04.020
	Shi 2018	**10.1056/NEJMoa1705334**
	Vuong 2018	**10.1056/NEJMoa1703768**
	Wei 2019	**10.1016/S0140-6736(18)32843-5**
	Stormlund 2020	**10.1136/bmj.m2519**
IMSI	De Vos 2013	10.1093/humrep/des435
	Leandri 2013	10.1111/j.2047-2927.2013.00104.x
	Setti 2013	10.1016/j.ejogrb.2013.09.006
	Marci 2013	10.1186/1742-4755-10-16
	Kim 2014	10.5653/cerm.2014.41.1.9
	Cassuto 2014	10.1016/j.rbmo.2013.08.013
	La Sala 2015	10.1186/s12958-015-0096-y
	Mangoli 2019	**10.1111/and.13340**
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	10.1016/j/ejogrb.2015.08.025
	Mahey 2015	10.1016/j.fertnstert.2015.07.1163
	Maged 2016	10.1177/1933719115602776
	Goel 2017	10.1007/s10815-017-0949-8
	Mak 2017	10.1016/j.rbmo.2017.04.004
	Aleyamma 2017	10.1016/j.ejogrb.2017.05.005
	Helmy 2017	10.1002/ijgo.12178
	Senocak 2017	10.1016/j.jogoh.2017.09.003
	Ashrafi 2017	10.1111/jog.13401
	Maged 2018	10.1002/ijgo.12355
	Frantz 2019	10.1093/humrep/dey334
	Lensen 2019	10.1056/NEJMoa1808737
	Olesen 2019	**10.1016/j.fertnstert.2019.08.010**
	van Hoogenhuijze 2020	**NL5193/NTR 5342**
	Metwally 2020	**ISRCTN 23800982**
Time Lapse	**Kirkegaard 2012**	**10.1007/s10815-012-9750-x**
	Goodman 2016	**10.1016/j.fertnstert.2015.10.013**
	Kovacs 2019	**10.1016/j.ejogrb.2018.12.011**
	Kahraman 2013	**10.1177/205891581200300204**
	Rubio 2014	**10.1016/j.fertnstert.2014.07.738**
	Insua 2017	**10.1016/j.fertnstert.2017.06.031**
	Alhelou 2018	**10.1016/j.repbio.2017.12.003**
	Yang 2018	**10.1093/humrep/dey047**
	Wang 2016	**J Reprod Med 61(5):254-262**
Steroids	**Wiser 2010**	**10.1093/humrep/deq220**
	Fawzy 2013	**10.1007/s00404-013-3020-8**
	Kara 2014	**10.1016/j.ejogrb.2013.11.008**
	Tartagni 2015	**10.1186/s12958-015-0014-3**
	Fan 2016	**10.1111/aji.12559**
	Narkwichean 2017	**10.1016/j.ejogrb.2017.09.006**
	Taiyeb 2017	**10.1007/s12020-017-1446-7**

	Yeganeh 2017	**10.1080/01443615.2017.1346593**
	Liu 2018	**10.1111/cen.13824**
IV Immunoglobulin	**Stephensen 2010**	**10.1093/humrep/deq179**
	Christiansen 2014	**10.1111/1471-0528.13192**
Intralipids	**Dakhly 2016**	**10.1016/j.ijgo.2016.06.026**
	Singh 2019	**10.1016/j.ejogrb.2019.06.007**
	Al-Zebeidi 2019	**10.1080/09513590.2019.1631280**