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

Monday 6th October 2025

Date	Action	Responsibility	Due date	Progress to date
09/06/2025	Publish a statement on the website to highlight the updated guidance on GLP-1 issued by the MHRA.	Dharmi Deugi, Scientific Policy Officer	06/10/2025	Text has been published to the website: Explore fertility treatments | HFEA
09/06/2025	Commission an expert literature review on evidence of the use of intrauterine and intraovarian infusion/injection of PRP as a treatment add-on.	Rebecca Taylor, Scientific Project Manager	06/10/2025	An expert literature review has been commissioned. This will be brought to the October SCAAC for an official rating.
09/06/2025	Publish a statement on the website highlighting that both the HFEA and the MHRA are looking into the use of intrauterine and intraovarian infusion/injection of PRP.	Molly Davies, Policy Manager (Scientific)	06/10/2025	Text has been published to the website.
09/06/2025	Authority to consider including tests in the definition of a treatment add-on the HFEA will provide information on. If approved, an expert literature review on microbiome testing and sperm DNA fragmentation should be commissioned.	Molly Davies, Policy Manager (Scientific)	06/10/2025	The Authority approved amending the definition of a treatment add-on to include tests. Microbiome testing and sperm DNA fragmentation will be brought to a future meeting of the SCAAC for an official rating.
09/06/2025	Review and update patient information on the website to highlight: • Any potential risks associated with the use of donor eggs and for surrogates. • The role of preconception health in outcomes for ART patients.	Rebecca Taylor, Scientific Project Manager	06/10/2025	Text has been published to the website on the following pages: • Risks of fertility treatment • Donating your eggs • Reciprocal IVF

HFEA's Annual Horizon Scanning Meeting 2025 - Notes

Details

Date:	1st July 2025, 14:00 – 17.00 CEST
Venue:	Paris, France
Attendees:	**Tim Child (TC) – UK – Meeting Chair** Nuno Costa-Borges (NCB) – Spain Christine Rondanino (CR) – France Eduardo Gerardo Mendizábal-Ruiz (EGMR) – Mexico Emre Seli (ES) – USA Cathy Herbrand (CH) – UK Claus Yding Andersen (CYA) – Denmark Sourima Biswas Shivhare (SBS) – UK Nikica Zaninovic (NZ) – USA Laura Rienzi (LR) – Spain Jacques Cohen (JC) – USA Rod Mitchell (RM) – UK Eoghan Cunnane (EC) – Ireland Verena Nordhoff (VN) – Germany Aisling McMahon (AM) – UK Ranveig Svenning Berg (RSB) – UK Stephen Troup (ST) – UK Alison Campbell (AC) - UK Sonia Herraiz (SH) – Spain Sebastiaan Mastenbroek (SM) – The Netherlands Seppe Segers (SS) – Belgium
Executive:	Dharmi Deugi (DE) - HFEA Dina Halai (DH) - HFEA Rebecca Taylor (RT) – HFEA Ruby Relton (RR) - HFEA
Minutes drafted by:	Dharmi Deugi (DD) – HFEA

1. Welcome and apologies

1.1. The HFEA convenes the Horizon Scanning Meeting every year with the aim to discuss the latest developments in fertility treatment and human embryo research, to identify new topics and anticipate future implications and issues that will impact the sector over the coming years. By identifying these issues, the HFEA can be aware of potential license applications and prepare, if necessary, a policy position or relevant patient information. The meetings are also a valuable opportunity to compare hot topics and issues on the horizon which could affect the fertility sector in different countries, and to share learnings.

1.2. The focus of the conversations are on topics that are further on the horizon. This meeting focused on three hot topics:

- The application of mitochondrial donation for non-disease related use;
- In vitro spermatogenesis for male fertility preservation;
- Future uses of robotics and automation in fertility treatment.

1.3. Each topic was introduced by an invited expert speaker followed by a round-table discussion with attendees contributing their thoughts, concerns, and perspectives.

2. HFEA Update

2.1. To introduce the recent work of the HFEA and give an indication of the state UK fertility sector, RR provided a brief update of the recent and upcoming HFEA publications, including:

- Main findings of the **Family formations in fertility 2022 report** (published in November 2024);
- Main findings of the **National patient survey 2024** (published in March 2025);
- Main findings of the **Fertility treatment 2023: trends and figures report** (published in June 2025);
- Updates to the **HFEA's data dashboards** (formally launched in January 2024);
- Updates on Register research projects, including the launch of the **HFEA's Data research newsletter.**

2.2. DD introduced the HFEA's horizon scanning function and processes, including an overview of the HFEA's **Scientific and Clinical Advances Advisory Committee (SCAAC)** and their ongoing workplan.

3. Future use of mitochondrial donation: Going beyond preventing inherited disease?

3.1. The speaker, Dr Nuno Costa-Borges (NCB) is an embryologist by background and Scientific Director at Embryotools in Spain. NCB was lead author of a **pilot study on mitochondrial replacement therapy (MRT) for infertility** published in early 2025.

3.2. NCB presented on:

- The biological rationale for the use of MRTs to treat infertility linked to poor oocyte quality.

- The scientific evidence supporting the use of MRTs to treat infertility linked to poor oocyte quality.
- Whether patients facing infertility should have the same access to MRTs as those with mitochondrial DNA (mtDNA) mutations.
- The UK as a global reference for safe, ethical and regulated implementation of MRTs.

3.3. The speaker and attendees made the following comments:

- The evidence base for the efficacy of this technique is from animal studies where oocytes that don't make it to the blastocyst stage are able to overcome this problem through MRT. Although the **pilot study** was undertaken on a small cohort and the technique is not 100% effective, it is feasible. The study also offers important insights into the chances of maternal mtDNA reversal.
- Researchers of the pilot study have committed to an 18-year follow-up agreement with the hospital, which is located in Greece. If the results are encouraging, the Greek Authority which authorised the research may consider regulating the technique on a case-by-case basis.
- Regarding the indications for treatment, it was highlighted that indications may include patients undergoing a final cycle following fertilisation failure or repeated embryo developmental arrest.
- Reasons for mtDNA reversal are unknown, though there is deemed to be a greater risk of reversion when MRT is used for the prevention of mitochondrial disease due to the potential of carry over following mtDNA replacement, rather than infertility related MRT. Having for example a 25% reversal rate would have major repercussion for disease related MRT but not for infertility.
- A study in Ukraine that has not been published found less than 1% carry over when using MRT for infertility. Another study also found similar results.
- Other issues, include mtDNA sources, regulation of donation and donor surveillance. Sources of mtDNA include oocytes, though there are questions as to whether patients would donate oocytes for infertility related MRT.
- There is already a reason for the use of MRT for disease prevention. However, when using MRT for embryonic arrest related infertility, caution should be taken as the cause of infertility could be related to something else. It was also noted that embryonic arrest has not been well investigated.
- Overall, there is limited evidence of efficacy as well as lack of data for both infertility and disease related MRT. Further research should be undertaken to identify patient populations, as well as to build evidence on efficacy, safety and feasibility, including considerations for cost. In addition, data collection and publication should be more transparent.

4. Emerging techniques in male fertility preservation: The role of in vitro spermatogenesis

4.1. The speaker, Dr Chistine Rondanino (CR) is an Associate Professor from the University of Rouen, France, whose research looks at the molecular mechanisms involved in the initiation of spermatogenesis.

4.2. CR presented on:

- Different techniques for in vitro spermatogenesis using testicular cells, seminiferous tubules or testicular tissue. Concerns with some techniques, such as the reintroduction of tumour cells, as well as zoonosis were also described.

- Evidence from animal and human studies on the in vitro formation of a variety of cells or cell-like components such as, spermatozoa, post-meiotic cells, elongated spermatids, sperm-like cells and spermatocytes
- Limitations and challenges, in relation to protocol optimisation, translation to humans, epigenetics and ethical issues.

4.3. The speaker and attendees made the following comments:

- Majority of the research on in vitro maturation (IVM) has been conducted in animal models due to the scarcity of prepubertal testicular tissue. It is therefore also important to identify the patient population for whom this would be most beneficial due to the quantity of usable tissue that is obtained from patients.
- With animal studies showing significant progress, the IVM approach may be successful in the coming years. In addition, a testicular tissue transplant has taken place in a human recently so there is potential in humans, though this is not properly categorised as several challenges still remain such as eligibility criteria, standardised protocols, including optimisation of transplantation timing and follow-up protocols. Research is also currently exploring the potential of induced pluripotent and embryonic stem cells to generate germ cells, which can be taken from the patient following treatment. Developments in this are progressing and therefore, concerns of using these types of cells may be more significant. Some of these concerns include genetic and epigenetic modifications, selection of desirable traits and the destruction of human embryos.
- A question was raised over whether the cryopreservation of prepubertal testicular tissue should be promoted so that it is available to patients in 20 years time. Cryopreservation of testicular tissue has been happening for over 15 years around the world, and patients are now already coming back wishing to use the tissue.
- There are **ESHRE good practice recommendations** which offer information on considerations for setting up testicular cryopreservation programmes.
- The **ORCHID-NET consortium** focuses on better capturing current practice and coordinating clinical and research activity in fertility preservation in boys and restoration in their adult life.
- Ethical concerns relate to reproductive pressure on the child in later life, taking consent from minors as well as the need for genetic relatedness and whether the risks for wanting a genetically related child/grandchild are worth it. As consent for preservation of prepubertal tissue is taken from the parent(s)/guardian(s) of patients, another concern includes considering whose preferences should be taken into account at the time of consent provision.
- Obtaining consent from young boys can be difficult, because decisions often have to be made before children are able to consent[1]. In situations where the child is not able to consent, the majority of parents make the decision to consent on behalf of their child. There is evidence that patients come back when they are older to ask about tissue status and are happy that they have reproductive possibilities in the future. Children whose parents consented on their behalf are asked to reconsent at 16 to 18 years of age to ensure autonomy, with most being interested in having a family in the future.

[1] In the UK children over 16 are normally considered capable of giving consent. For those under 16, there is no minimum age, but instead an individual child's capacity to consent is assessed. This is known as "Gillick competence".

- Long-term studies to evaluate the impact of different cancer treatments on fertility are being conducted.
- A question was raised about whether we could learn from ovarian tissue freezing which is already being done now.

5. Future uses of Artificial Intelligence in the IVF lab – what are the possibilities?

5.1. The speaker, Dr Eduardo Gerardo Mendizabal-Ruiz is a Professor of Computer Science at the University of Guadalajara and VP Product Development at Conceivable Life Sciences. Professor Mendizabal-Ruiz was lead author of **a study on the first live birth following digitally controlled, remotely operated ICSI** in early 2025.

5.2. EGMR presented on:

- Increasing IVF demand but limited human resources due to global shortages of embryologists as well as bottlenecks due to manual processes.
- Lack of standardization in the lab with persistent differences in laboratory and clinical practices, due to, for example, human errors and subjective decisions.
- Automation of IVF processes could lead to reduction in variability through consistent and repeatable protocols, as well as supporting the scaling of accuracy. Furthermore, remote IVF through automated and cloud-connected robotics can decouple location from expertise, letting embryologists supervise/control numerous labs, including at a distance.
- Risk landscape and mitigation, including technical aspects such as, redundant connectivity, biological considerations, cyber security, and algorithmic bias.

5.3. The speaker and attendees made the following comments:

- There is a need for standardised practices for the use of automation and robotics in the lab. Some processes, such as time lapse systems can be standardised through controlled and quality assured data, though annotation systems need to be fully validated.
- Automated tools will support embryologists and not replace them, preventing burnout and also allowing standardised research protocols. AI gives further information to assist in decision making, though with time we should be able to trust the system and therefore spend less time verifying whether the decision is correct.
- Although progress in automation has been made, introduction into the lab will take longer than we think. For example, ICSI involves 17 distinct steps which need to be considered when automating. Adoption is most likely to be slow with the first prototype clinical model for some automated processes such as dish and sperm preparation could be available within 2 years, however further data is required.
- The security for automated processes conducted through virtual robotics would have to be similar to that in banks.
- Models are only as good as the data that is used to train it. Data is required to train a model; however, the same data may not work across different processes/equipment or clinics. Good quality data is needed to avoid the impact of confounding factors, and a large amount of data is required to find things that are unknown.
- It is important to consider how many cycles a clinic would need to do to reduce costs for patients, taking into consideration risks of the large number of steps required for each process,

the scale of damage if the tool failed, the timescale to repair damage to the machine/clinic/patient, as well as the cost involved to repair the damage.

- Cost reduction will take time and initially there might be more costs as well as the need for more people, especially due to unknowns of the automated systems and reliability. However, overtime costs will be reduced, and processes may be managed by fewer people.
- The black box approach is replaced by the glass box approach where credibility and the drivers of decision making are important from a legal point of view.
- We should start considering the regulation of robotics.

Alternative methods to derive embryonic and embryonic-like stem cells

Details about this paper

Area(s) of strategy this paper relates to:	Supporting scientific and medical innovation
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	5
Paper number:	HFEA (06/10/2025) 005
Meeting date:	06 October 2025
Author:	Molly Davies, Policy Manager (HFEA)
Annexes	Annex A: Developmental paradigm and stem cell classification Annex B: Literature update on alternative methods to derive embryonic and embryonic like stem cells – 2024/25

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • consider the progress of research into alternative methods to derive embryonic or embryonic-like stem cells; • advise the Executive if they are aware of any other recent research developments; • review whether any outputs from the HFEA are required; and • agree to amend the title of this prioritised topic to 'Methods to derive embryonic and extraembryonic stem cells, and their alternatives'.
Resource implications:	Within scope of horizon scanning function.

Implementation date:	The Executive will aim to take forward any recommendations on the topic ahead of the next SCAAC meeting. If title is amended, this topic will be referred to as agreed following publication of committee minutes.
Communication(s):	Minutes of the committee discussion will be published on the SCAAC webpage and communicated to the sector via our Clinic Focus newsletter.
Organisational risk:	Low

1. Background

1.1. The Human Fertilisation and Embryology (HFE) Act gives the HFEA statutory responsibility for research involving the creation, storage, or use of human embryos. Research licences may only be granted if the use of human embryos is considered to be "necessary or desirable" for the purposes set out by the Act (Paragraph 3A(1)(a-c) of Schedule 2). The principal purposes, expanded by the HFE (Research Purposes) Regulations 2001, for embryo research are as follows:

(a) increasing knowledge about serious disease or other serious medical conditions,

(b) developing treatments for serious disease or other serious medical conditions,

(c) increasing knowledge about the causes of any congenital disease or congenital medical condition that does not fall within paragraph (a),

(d) promoting advances in the treatment of infertility,

(e) increasing knowledge about the causes of miscarriage,

(f) developing more effective techniques of contraception,

(g) developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation, or

(h) increasing knowledge about the development of embryos.

1.2. Deriving human embryonic stem cells (hESC) involves isolating the inner cell mass from a blastocyst-stage embryo, requiring an embryo as the source material. Because this process necessitates the use of human embryos, research deriving stem cells from human embryos requires HFEA approval and must fulfil the requirement to be "necessary or desirable" for a permitted purpose.

1.3. When an application is made for an HFEA research licence for a project that will derive human embryonic stem cells, researchers are asked to justify their use of hESC and explain why the same aims/results could not be obtained if banked stem cell lines were used. Examples of embryo research projects that have been licenced by the HFEA can be found on our website.

1.4. Once licenced, the research conducted must then be compliant with HFEA Standard Licence Conditions, Directions, and guidance issued within the Code of Practice. This includes research licence condition R30 which requires a sample of all human embryonic stem cell lines derived as part of the project to be deposited in the UK Stem Cell Bank (UKSCB).

1.5. All UK research involving the use of human ESC lines is expected to comply with the UK Code of Practice for the Use of Human Stem Cell Lines and consider Guidelines for Stem Cell Research and Clinical Translation, published by the International Society for Stem Cell Research (ISCCR).

1.6. In line with the joint position on 'Regulating human embryonic stem cell lines for human application', published by the Human Tissue Authority (HTA), HFEA, and Medicines and Healthcare products Regulatory Agency (MHRA), the HFEA's remit includes the use of embryos in the derivation of stem cell lines but does not extend to the regulation of stem cell lines themselves.

1.7. Historically, embryo research was the only way in which pluripotent stem cells could be derived. However, alternative methods of establishing stem cells with similar features (broadly referred to as hESC-like cells by the Authority, e.g. reprogrammed induced pluripotent stem cells) now exist, avoiding the requirement for human embryos to be used in some research scenarios. These developments, raise the threshold for demonstrating that embryo research to create new hESC remains necessary.

1.8. 'Alternative methods to derive embryonic or embryonic-like stem cells' has been brought to the SCAAC as a standing high priority horizon scanning topic for several years, with the intention of briefing the Authority on the state of research and any implications this may have for licencing.

1.9. As highlighted by members of the SCAAC during their June 2024 meeting, hESC remain the benchmark for pluripotency and are considered the gold standard when comparing quality, functionality and utility of new cells against their embryonic-derived counterparts. They also provide a resource for addressing aspects of early human development that induced pluripotent stem cells (iPSCs) or stem cell-based embryo models (SCBEM) cannot fully recapture. The Committee concluded discussions by agreeing that it was vital that work to derive stem cell lineages through embryo research continues. In February 2025, the SCAAC confirmed that this topic remains of high priority and that research developments will continue to be monitored through the horizon scanning function.

1.10. Annex A provides background information on the developmental paradigm and stem cell terminology. Annex B provides details of the available research on alternative methods to derive embryonic and embryonic-like stem cells published between 1st May 2024 and 31st August 2025, including that relating to extraembryonic cell lines. The Executive notes that this paper is not an assessment of study validity.

2. Summary of research developments

2.1. Research continues to focus on efforts to establish and maintain human pluripotent stem cell populations representative of distinct pluripotent states observed during embryonic development, with much research continuing to focus on the functional roles of molecules in maintaining potency states.

2.2. Since the previous discussion on this topic, advances have been made in establishing alternative human stem cell models, including zygotic genome activation-like cells and totipotent blastomere-like cells which expand the scope of stem cell modelling beyond classic naïve/primed pluripotency (Li *et al.*, 2024). However, maintaining these states stably in long-term culture without impaired developmental potential or genetic and epigenetic aberrations remains a challenge. Key takeaways from hESC research include:

- Following advances made characterising transient eight cell-like cells (8CLS) in naïve hPSC cultures (Mazid *et al.*, 2022; Taubenschmid-Stowers *et al.*, 2022; Yu *et al.*, 2022; Moya-Jódar *et al.*, 2023), the establishment of alternative human stem cells with 'totipotent-like' potential, termed human totipotent blastomere-like cells (hTBLCs), has been reported (Li *et al.*, 2024). Through a two-step conversion process, hPSC were first directed into zygotic genome activation (ZGA)-like cells (ZLCs) which after extended culture transitioned into stable hTBLC lines representative of pre-naïve or 'totipotent-like' cells. When compared with 8CLC, the ZLC

cells were found to more faithfully resemble the transcriptional profile of in vivo eight-cell blastomeres. Independent replication and benchmarking of human cell lines is still required, but these populations provide in vitro models to study early totipotency and zygotic genome activation in humans.

- Research into expanded/extended potential stem cells (EPSC) has shifted towards methodological refinements, including work to establish defined, xeno-free protocols for their derivation and benchmarking of state characteristics (Onfray *et al.*, 2024; Zhao *et al.*, 2025).
- Beyond the existing pluripotent models (formative-totipotent window/XPSC and formative stem cells) (Kinoshita *et al.*, 2021; Yu *et al.*, 2021), no distinct new formative human pluripotent stem cell state has been established. Research has focused on developing improved induction systems to generate human primordial germ cell-like cells directly from established hPSC states without intermediates, with authors suggesting that primed lines may be more germline-competent that previously assumed.
- In parallel, small-molecule and metabolic interventions continue to be explored to promote human PSC towards naïve, formative or primed-like states via epigenetic and metabolic modulation (Cheng *et al.*, 2025). Whilst optimisation of naïve culture media and refinement of conversion pathways have sought to address the ongoing challenges of chromosomal and epigenetic instability.

2.3. In humans, culturable extraembryonic stem cell lines representative of the trophectoderm (TE), hypoblast (induced hypoblast-like cells), extraembryonic mesoderm (EXMCs), and the amnion (amnion-like cells) have been established to varying degrees. Key developments include:

- Human trophoblast stem cell (hTSCs) can be derived from both naïve and primed pluripotent stem cells as well as from embryonic trophoblast populations. Protocols for converting cells from hPSC are becoming increasingly efficient, generating self-renewing cultures. There have also been improvements in deriving primary hTSC from late-gestation placentas.
- As highlighted by experts at the previous SCAAC discussion, it had recently become possible to culture stable hypoblast-like cells (nHyCs) from naïve human pluripotent stem cells (Okubo *et al.*, 2024). Naïve pluripotent stem cells have been shown to differentiate to hypoblast cells in vitro via reversion to a transitional ICM-like intermediate state, dependent upon fibroblast growth factor (FGF) signalling (Dattani *et al.*, 2024).
- Gold-standard criteria for lineage-restricted populations, including extraembryonic mesoderm (EXMCs) and amnion-like cells is not yet established. Understanding of markers, signalling requirements, and passage limits of these models is still in development.

2.4. Technical advances in culture systems, including hydrogels, scaffold engineering (and scaffold-free approaches), and microfluidic gradient systems, are also increasingly improving the accuracy and reproducibility of stem cell research.

2.5. The establishment of novel embryonic and extraembryonic stem cell lines has also improved the accuracy and complexity of stem cell-based embryo models (SCBEM), allowing for improved in vitro study of early embryonic development. Advances have been made across both assembled (those which combine distinct embryonic and extraembryonic cell types) and induced (derived from a single stem cell type) human stem cell models, with preliminary evidence that both approaches can generate integrated structures containing both embryonic and extraembryonic cell types.

2.6. Assembled models utilising both naïve and primed hESC have demonstrated the capacity to self-organise into spatially organised morphogenetic structures (SEMs) which recapitulate features of post-implantation embryos (including those of the epiblast, extraembryonic mesoderm, and trophoblast). In parallel, naïve hESC and extraembryonic cells have been combined to assemble into comprehensive embryo-like models that mimic peri-implantation development, and induced techniques have been shown to produce models from reprogrammed fibroblasts, human naïve ESCs, totipotent-like human eight-cell-like cells, and human extended pluripotent stem cells, some of which show TE-like structures.

2.7. Despite advancements made towards modelling the post-implantation embryo, human SCBEM research remains limited by lack of extraembryonic stem cell lineages, the developmental potential, and stability of the starting cell line. Researchers have argued that continued development of embryonic and extraembryonic stem cell populations that more accurately capture and replicate the pluripotency state transition of cells in vivo is required. This includes understanding the impact of epigenetic memory and genetic stability, differentiation control and functional equivalence, reprogramming efficiency, and scalable production.

2.8. Ethical boundaries and the limited access to embryonic and extraembryonic material additionally restrict research in this field, particularly when investigating the post-implantation stages of development. Recent recommendations to revisit the 14-day rule proposed by the Authority in November 2024, highlight the opportunity to access later developmental stages directly, whilst enabling potential validation and refinement of in vitro models.

2.9. Beyond embryology, hESC and related stem cell models (iPSCs and SCBEM) serve as platforms for disease research, allowing for the recreation of developmental disorders in vitro and enabling genetic research and drug screening. Their capacity to differentiate into different tissue types further allows for their application in regenerative therapy, which has led to the development of patient-specific stem cell treatments and the potential for organ regeneration or functional tissue replacement. Key advances for clinical applications include:

- As of December 2024, Kirkeby et al. (2025) identified that worldwide there were 115 approved clinical trials testing 83 hPSC products. Although trials were initially dominated by those targeting the ocular diseases (specifically RPE for macular degeneration), there are increasing numbers of trials for products targeting immune, cardiac, and endocrine pathologies. No hPSC-derived therapy has yet received full regulatory approval (Kirkeby *et al.*, 2025).
- As the majority of these clinical protocols utilise reprogrammed primed hESC or hiPSC as the source material, companies are thought to be facing challenges related to maintaining stability and safety of cell populations when manufacturing these products at scale.

2.10. To reflect advances in extraembryonic stem cell research, the Executive are proposing that the title of this topic is amended to ‘Methods to derive embryonic and extraembryonic stem cells, and their alternatives’ and that the scope of the topic is expanded to include the monitoring of such developments.

3. Recommendations

3.1. Members are asked to:

- consider the progress of research into alternative methods to derive embryonic or embryonic-like stem cells;
- advise the Executive if they are aware of any other recent research developments;
- review whether any outputs from the HFEA are required; and
- agree to amend the title of this prioritised topic to 'Alternative methods to derive embryonic and extraembryonic stem cells, and their alternatives'.

3.2. A summary of developments presented by this paper and the recommendations given by SCAAC in response will be used to update the HFEA's Licence Committee and those involved with the peer review process when considering research licence applications.

4. References

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5. Annex A: Developmental paradigm and stem cell classification

5.1. Potency describes a cell's ability to self-renew and differentiate into specialised cell types. In vivo, the potency of cells within the embryo is transient, becoming progressively reduced as cells become increasingly specialised.

5.2. Totipotent cells are those which have the capacity to generate all cell types, including both embryonic and extraembryonic tissues:

- From fertilisation (zygote) to cleavage stages (2-8 cells blastomeres), the embryo remains totipotent-like and can broadly contribute to all tissues.

5.3. Pluripotent cells, including those of the inner cell mass (ICM) and the epiblast, can give rise to all cell types of the embryo proper, but not typically to extraembryonic tissues[1]:

- By the morula stage (around 16 cells), the first lineage specification begins, with cells segregating into the ICM and the trophectoderm (TE) of the blastocyst.
- The ICM is pluripotent and produces the epiblast, which forms the embryo proper (embryonic) and amnion (extraembryonic tissue), and the hypoblast (or primitive endoderm) which contributes to the yolk sac and extraembryonic endoderm.

5.4. Lineage-restricted cells are committed to producing only one-specialised cell lineage:

- The TE consists of lineage-restricted cells committed to trophoblast development (extraembryonic), including cytotrophoblast, syncytiotrophoblast and extravillous trophoblast, which together give rise to the placenta, chorion, and other supporting structures.
- In vivo, the trophoblast, hypoblast, and other extraembryonic lineages do not pass through a pluripotent stage, being specified earlier during the first and second lineage restrictions[2].

5.5. In a research context, the term 'embryonic stem cells' (ESCs) typically refers to epiblast-derived pluripotent stem cells isolated from the ICM of the blastocyst and not all cells of embryonic origin. However, when cultured in vitro, the blastocyst forms as a composite structure formed of both embryonic (ICM) and extraembryonic (TE and hypoblast) lineages.

5.6. In vitro, embryo-derived stem cells recapitulate the progression of in vivo cell states across a potency spectrum. Pluripotency states of stem cells are further described as naïve, formative and primed; terms which indicate the molecular and functional state the stem cell is in:

- Naïve pluripotency typically corresponds to the pre-implantation epiblast, reflecting a ground state cell prior to lineage specification. In vitro, such cells have been shown to be induced to specialise into extraembryonic lineages, showing broader plasticity than later cell states.
- Formative pluripotency describes an intermediate state representative of cells of the early post-implantation epiblast, in which markers of naivety have been lost and cells have acquired competence for germ layer differentiation and germline specification.

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[1] There is limited evidence that epiblast cells can give rise to trophoblast cells, and early-stage TE can produce epiblast, suggesting that cells of the human embryo may take longer to become restricted in their potency than previously thought.

[2] The first lineage restriction separates the TE from the ICM, occurring in vivo around 3-4 days post-fertilisation. The second lineage restriction separates the ICM into the epiblast and hypoblast, occurring in vivo around 5-6 days post fertilisation.

- Primed pluripotency reflects cells of the late post-implantation epiblast immediately before gastrulation, where cells retain pluripotency but 'primed' for germ layer specification. These cells have been found to exhibit higher DNA methylation, X-chromosome inactivation in females, and more lineage-specific gene expression.

5.7. Pluripotency state terms can apply to stem cells derived directly from the epiblast of an embryo or generated by reprogramming of somatic cells to form induced pluripotent stem cells (iPSCs). However, these terms are not typically extended to cell lines derived from lineage-restricted extraembryonic cell lineages (for example, hypoblast-derived cells or those taken from the TE). The terminology used for extraembryonic stem cell lines established in vitro is specific to the cell lineage it models and how it has been characterised.

5.8. In humans, ESCs are usually considered to be in a primed pluripotent state when derived from the epiblast. To generate naïve or formative states, primed hESC are typically converted from a primed state through reprogramming; although it is possible to isolate naïve cells directly from human embryo directly under defined conditions. Direct isolation of human formative stem cells from an embryo is limited by the prohibition of embryo research beyond 14-days/appearance of the primitive streak.

5.9. Defining stem cells by state helps compare methods of maintaining and manipulating stem cells. This is because the pluripotent state of a cell will not only require state specific culture system, but also affect how a cell responds to experimental manipulation or differentiation protocol.

6. Annex B: Literature review on alternative methods to derive embryonic and embryonic like stem cells – 2024/25

6.1. Annex B has been circulated to the committee as a separate Excel document, which provides details on the available research on alternative methods to derive embryonic and embryonic-like stem cells published between 1st May 2024 and 26th August 2025. Where possible literature has been grouped under relevant subheadings.

6.2. The topic search strategy, originally developed in PubMed, was adapted for Ovid Medline to align with the methodology developed for the treatment add-ons literature search, and to ensure comprehensive coverage across platforms.

Testicular tissue transplantation to restore fertility in males

Details about this paper

Area(s) of strategy this paper relates to:	Supporting scientific and medical innovation
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	6
Paper number:	HFEA (06/10/2025) 006
Meeting date:	06 October 2025
Author:	Dharmi Deugi, Scientific Policy Officer (HFEA)
Annexes	Annex A – Literature review on testicular tissue transplantation to restore fertility in males – 2024/25

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • consider the progress of research into testicular tissue transplantation to restore fertility in males; • advise the Executive if they are aware of any other recent research developments; and • review whether any outputs from the HFEA are required.
Resource implications:	Within scope of horizon scanning function.
Implementation date:	The Executive will aim to take forward any recommendations on this topic ahead of the next SCAAC meeting.
Communication(s):	Minutes of the committee discussion will be published on the SCAAC webpage and communicated to the sector via our Clinic Focus newsletter.
Organisational risk:	Low.

1. Background

1.1. The cryopreservation of pre-pubertal testicular tissue and/or cells prior to chemotherapy, radiotherapy or other gonadotoxic therapies is an experimental fertility preservation method for children at risk of infertility due to cancer treatment. Since pre-pubertal boys do not produce mature sperm, cryopreservation of immature testicular tissue containing spermatogonial stem cells (SSC) is considered a potential approach to restore natural fertility. The frozen-thawed tissue can then be used for re-transplantation back to the patient when they reach adulthood, in the hope it could generate functional sperm. Testicular tissue transplantation may also be considered as an experimental method for pre-pubertal boys undergoing high-risk treatment for severe haematological disease. Other avenues to restore functionality of cryopreserved tissue (or contained stem cells) include SSC transplantation or in vitro maturation (IVM).

1.2. The clinical aspects of this topic were reviewed by an invited speaker at the October 2023 SCAAC meeting who was asked to address the topic of 'in vitro derived gametes'. The discussion concluded that patients will soon be able to access treatments involving the generation of in vitro derived gametes and therefore the Authority will need to consider how regulation of these 'other categories of cells' may be defined in future legislation. It was also noted that the breadth of methodology in this field raised a variety of legal and ethical questions and areas that may already be considered by existing legislation should be understood. During discussions, it was noted that there are at least three centres worldwide (UK, USA and Belgium) which have obtained or are in the process of obtaining ethical approval to transplant cryopreserved tissue back to the patients as clinical treatment. In February 2024, it was agreed that the topic of testicular tissue transplantation to restore fertility in males should be considered a distinct topic from 'In vitro derived gametes'; it was then added to the SCAAC's horizon scanning prioritisation as a medium priority topic.

1.3. This topic was the subject of one of the talks at the HFEA's Annual Horizon Scanning Meeting (HSM) during the European Society of Human Reproduction and Embryology (ESHRE) 2025 conference. As mentioned in the HSM 2025 notes circulated for this meeting, researchers from Vrije University Brussels (VUB) and Brussels IVF reported on the successful reintroduction of several cryopreserved autologous tissue fragments into an infertile man previously treated with chemotherapy. The production of mature sperm from the grafted tissue will be evaluated in 2026, one year after the transplant. None of the approaches to restore functionality of the cryopreserved tissue are clinically available for patients in the UK at present.

1.4. In the UK, the storage of gametes is a HFEA licensable activity under which the cryopreservation of testicular tissue is an authorised process. Due to regulatory overlap, the HFEA and Human Tissue Authority (HTA) issued a joint statement on ovarian and testicular tissue storage in 2013. Establishments storing tissue containing immature gametes require a licence from both the HFEA and the HTA if the tissue containing the gametes is being stored for future transplant into a recipient, or where the intended future use of the tissue is unknown.

1.5. Several international networks including ORCHID-NET, Nordfertil, and a coordinated network of academic centres (Valli-Pulaski et al., 2019) have been established to focus on this topic. In June 2025, ESHRE published good practice recommendations on fertility preservation involving testicular tissue cryopreservation in children receiving gonadotoxic therapies, providing

guidance on for example, setting up a fertility preservation programme, eligibility criteria and counselling, including the practical aspects of testicular tissue biopsy and cryopreservation.

1.6. Annex A provides details of the available research on testicular tissue transplantation to restore fertility in males published between January 2015 and August 2025. The Executive notes that this paper provides a summary of the findings described in published literature and is not an assessment of study validity.

2. Summary of research developments

2.1. Studies have indicated that germ-cell sensitivity to chemotherapy might be both drug and age dependent, with agents, such as alkylators and platinum drugs being linked to a reduction in SSC or germ-cell counts and DNA damage. In addition, findings point to potential sensitive developmental windows in the immature testis when spermatogonia are highly sensitive to chemotherapy-induced apoptosis. Research also observed that some patients do already present with reduced SSC counts at diagnosis, making early preservation critical. In contrast, some studies report on the maintenance of Sertoli and Leydig cell numbers and function after platinum exposure, suggesting that the preserved somatic niche could support future restoration.

2.2. Oncological safety could be a key challenge as minimal residual disease (MRD) can persist in cryopreserved tissue highlighting the need for MRD screening. Although protective interventions might demonstrate pre-clinical promise, until safety is assured, in-vitro maturation or spermatogonial stem cell-based strategies may be preferred over direct autografting.

2.3. Research has made some promising progress over the last couple of years with increasing number of centres offering programmes for cryopreservation of immature testicular tissue for future use. Even though animal models have been used for majority of the research, with a feasibility study in primates demonstrating the success of this technique in producing functional sperm and live offspring (Fayomi et al., 2019), researchers have started to report advances in human research.

2.4. Whilst there have been no reports of successful mature sperm production in humans, a study has provided evidence of successful survival of testicular tissue in an adult fertile male following autologous transplantation (Jensen et al., 2023). Furthermore, researchers from Vrije University Brussels (VUB) and Brussels IVF have successfully reintroduced several cryopreserved autologous tissue fragments into an infertile man previously treated with chemotherapy. The production of functional mature sperm from the grafted tissue is yet to be confirmed.

2.5. Protocol based advances in terms of testicular tissue cryopreservation and culture are beginning to align around several possible reproducible approaches. For instance, whilst studies on hydrogen encapsulation hint at its potential role in protecting immature testicular tissue during freezing by limiting cryoinjury; modified cryomedia and antioxidant adjuncts such as, liposomes, could be associated with improvements in post-thaw viability and reduction in oxidative markers. Moreover, there are indications that engineered scaffolds and nanoparticle-delivered growth factors may accelerate graft revascularization and enhance early short-term spermatogonial survival after transplantation. In parallel, advanced culture systems are hypothesised to support gonocyte/SSC maintenance and advanced meiotic progression. Though various processes for cryopreservation and culture have shown reproducible benefit in animal models and ex vivo

human tissue, routine clinical use remains limited by safety concerns such as, malignant cell contamination and genomic/epigenomic integrity as well as the need for efficacy validation. Therefore, further research is needed. At the 2025 HSM, it was noted that some clinics are already cryopreserving prepubertal testicular tissue.

2.6. The procedures used for testicular tissue biopsy appear to be safe and well-tolerated with a few studies reporting only minor complications. In addition, there was a long term follow up study reporting no adverse impact on testicular development or pubertal progression.

2.7. Findings hint that patients and their families do value having a fertility preservation option in the future despite its experimental status, though one study explored parent-child disagreements. Despite some reports of anxiety, there are indications that discussing future fertility is acceptable to most paediatric patients when done sensitively, and especially with the use of educational materials. Furthermore, other important aspects include respecting evolving autonomy and also tailoring pathways to the needs of different patient groups.

2.8. Though not within the remit of this topic, it's worth noting that in addition to testicular tissue transplantation, research has also focused on multiple other techniques including SSC-based approaches such as SSC transplantation, as well as IVM. Converging these approaches with innovative techniques, such as tissue engineering and biomaterial which involves for instance, 3D culture systems and bioprinted testis models, are also being explored.

2.9. Overall, despite significant developments, translation of testicular tissue transplantation to humans remains at an experimental stage. Safety, particularly the risk of malignant cell reintroduction and genomic/epigenomic integrity, remain critical barriers. This is in addition to the need to establish eligibility criteria, validated and standardised protocols as well as MRD assays and long-term follow up data.

3. Recommendations

3.1. Members are asked to:

- consider the progress of research into testicular tissue transplantation to restore fertility in males;
- advise the Executive if they are aware of any other recent research developments; and
- review whether any outputs from the HFEA are required.

4. Annex A – Literature review on testicular tissue transplantation to restore fertility in males – 2024/25

4.1. Annex A has been circulated to the committee as a separate Excel document, which provides details on the available research on testicular tissue transplantation to restore fertility in males published between January 2015 and August 2025. Where possible literature has been separated by relevant subheadings.

4.2. The topic search strategy, originally developed in PubMed, was adapted for Ovid Medline to align with the methodology developed for the treatment add-ons literature search, and to ensure comprehensive coverage across platforms.

Rating review for treatment add-ons – Intrauterine and intraovarian platelet rich plasma

Details about this paper

Area(s) of strategy this paper relates to:	Regulating a changing environment
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	7
Paper number:	HFEA (06/10/2025) 007
Meeting date:	06 October 2025
Authors:	Rebecca Taylor, Scientific Policy Manager Molly Davies, Policy Manager
Annexes	Annex A: Evidence decision tree for rating add-ons Annex B: References of reviewed studies Annex C: References of systematic reviews and meta-analyses Annex D: Inclusion criteria and definitions Annex E: Expert statistician independent report

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • consider the quality of evidence for intrauterine and intraovarian platelet rich plasma (PRP) as a treatment add-on based on the findings from an independent assessor; • agree and recommend ratings for each outcome(s) and population(s).
Resource implications:	In budget
Implementation date:	Recommendations will be implemented as soon as feasible

Communication(s):	Updates to the HFEA's website information on treatment add-ons and communication of updates to the sector, patients and public.
Organisational risk:	Low

1. Background

1.1. Treatment add-ons are often non-essential treatments or tests that may be offered in fertility clinics in addition to routine treatment with the claim that they can improve treatment outcomes.

1.2. As with all new treatments, tests or technologies being introduced into reproductive medicine, the HFEA expect the introduction of treatment add-ons into clinics to be preceded by good quality scientific research into the effectiveness and safety of these interventions. However, some treatment add-ons are being offered to patients without any such evidence for effectiveness at increasing live birth rate, safety, or other treatment outcomes. They are frequently offered outside of a research setting and are charged for at an additional cost.

1.3. The HFEA and eight professional and patient bodies have committed to monitor the evidence base for treatment add-ons and their offering in UK clinics in a **consensus statement**.

1.4. Medical professionals, academics or patient organisations can propose that we review the evidence base for a treatment or test 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 the live birth rate or improve other treatment outcomes;
- without conclusive evidence of its effectiveness at improving the live birth rate or other treatment outcomes;
- it is not already listed in our the HFEA's rated list of add-ons; or
- there is evidence that an add-on treatment or test may reduce treatment effectiveness or there are potential safety concerns.

1.5. An application for intrauterine and intraovarian PRP to be considered for the add-ons list was reviewed at the June 2025 meeting, SCAAC members recommended that both are eligible for HFEA ratings.

1.6. Following consideration of the PRP treatment add-ons application at the June 2025 meeting, SCAAC members recommended that both intrauterine and intraovarian PRP could be considered treatments add-ons eligible for an HFEA rating.

1.7. A SCAAC add-ons review panel was convened and identified the following relevant populations and outcomes for intrauterine PRP:

- General population - endometrial thickness, implantation rate, miscarriage rate, live birth rate and ongoing pregnancy rate (OGPR)[1].
- Patients with thin/refractory endometrium - endometrial thickness, implantation rate, miscarriage rate, live birth rate and ongoing pregnancy rate.
- Patients with repeated/recurrent implantation failure (RIF) - endometrial thickness, implantation rate, miscarriage rate, live birth rate and ongoing pregnancy rate.
- Asherman's Syndrome/intrauterine adhesions - endometrial thickness, implantation rate, miscarriage rate, live birth rate and ongoing pregnancy rate.

[1] For the purpose of the treatment add-on ratings, ongoing pregnancy rate has been defined as pregnancy. Where OGPR is recorded in place of LBR, this will be clearly stated on the HFEA website.

- Recurrent pregnancy loss - endometrial thickness, implantation rate, miscarriage rate, live birth rate and ongoing pregnancy rate.

For intraovarian PRP, the panel identified the following populations and outcomes:

- General population - Egg numbers (include MII oocytes or any egg number value), embryo blastocyst formation rates (if available numbers of transferable embryos), live birth rate, ongoing pregnancy rate (sometimes called "sustained implantation").
- Patients with poor/diminished ovarian reserve (POR/DOR)[2] - Egg numbers (include MII oocytes or any egg number value), embryo blastocyst formation rates (if available numbers of transferable embryos), live birth rate, ongoing pregnancy rate (sometimes called "sustained implantation").

2. Literature search – updated process

2.1. The interface MEDLINE (Ovid), along with two clinical trial registries in line with Cochrane (International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov) were used to carry out the literature search[3].

2.2. The literature was first searched for randomised controlled trials (RCTs) and systematic reviews. If fewer than three systematic reviews or RCT studies were identified, then the search was expanded to non-randomised studies of intervention (NRSIs) which are limited to case/cohort/control studies.

2.3. At the February 2017 SCAAC meeting, it was agreed that evidence published in the last 10 years would be sent for review. The literature considered here covers literature published between 1st January 2015 and 6th August 2025.

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 on 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[4]) for each treatment add-on.

3.2. The 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. However, the assessments made by the independent reviewer are from a methodological perspective without expertise in the clinical or scientific context.

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[2] POR/DOR have varying definitions in the literature (as outlined in annex D of the androgen supplementation add-ons paper). In addition, studies looking at "primary ovarian insufficiency" or "premature ovarian insufficiency" both often abbreviated to "POI" have been included as they can be considered a sub-set of POR/DOR.

[3] In line with the decision tree found at Annex A, neither pre-prints nor abstracts are included in the evidence base.

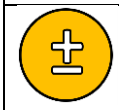
[4] GRADE is an approach for grading the quality of evidence and the strength of recommendations. It was developed by the Grading of Recommendations, Assessment, Development and Evaluation Working Group.

3.3. Findings of the independent assessment for intrauterine and intraovarian PRP treatments can be found within Annex E, with the studies considered provided in Annex B and C. These detail the independent reviewers recommended rating in relation to the HFEA's five-category rating system.

4. The five-category rating system

4.1. The decision tree for determining how evidence will be used by SCAAC when assigning add-ons rating can be found at Annex A.

4.2. The Authority approved a five-category rating system with the following symbols/colours and definitions in July 2022:

	On balance, findings from high quality evidence shows this add-on **is effective at improving the treatment outcome**.
	On balance, it is **not clear whether this add-on is effective at improving the treatment outcome**. This is because there is conflicting moderate/high quality evidence – in some studies the add-on has been found to be effective, but in other studies it has not.
	**We cannot rate the effectiveness of this add-on at improving the treatment outcome** as there is insufficient moderate/high quality evidence.
	On balance, the findings from moderate/high quality evidence shows that **this add-on has no effect on the treatment outcome**.
	There are **potential safety concerns and/or**, on balance, the findings from moderate/high quality evidence shows that **this add-on may reduce treatment effectiveness**.

4.3. Most treatment add-ons on our website will have a rating to indicate whether the evidence shows that the treatment add-on is effective at improving the chances of having a baby for most fertility patients. However, as approved by the Authority, the five-category rating system may also be applied to additional outcomes, such as miscarriage, and outcomes for specific patient groups, such as those diagnosed with male-factor infertility.

5. Considerations and recommendations for rating intrauterine and intraovarian PRP as treatment add-ons

5.1. The ESHRE good practice recommendations on treatment add-ons published in November 2023 conclude that intrauterine and intraovarian PRP should not be recommended for use in ART treatment.

5.2. There is a 2024 Cochrane review on autologous platelet-rich plasma for assisted reproduction, which concludes that the effect of intrauterine or intraovarian administration of PRP on the outcome of ART treatment in infertile women is uncertain.

5.3. In addition, the Evidence Based IVF group at the University of Melbourne in Australia has considered the use of intrauterine and intraovarian PRP (**Platelet Rich Plasma - Ovarian Injection | Evidence-based IVF** and **Platelet Rich Plasma (PRP) for IVF - Uterine Infusion | Evidence-based IVF**). These reviews concluded that the evidence for both intrauterine and intraovarian PRP was "unclear" in relation to their impact on pregnancy, miscarriage and live birth rates.

5.4. 10 systematic reviews and/or meta-analyses assessing the use of intraovarian PRP and 25 systematic reviews and/or meta-analyses for intrauterine PRP in the defined patient groups were identified and are referenced in Annex C. Many of the same RCTs are analysed in the multiple systematic reviews.

Intraovarian PRP

5.5. The Committee is asked to consider the independent reviewers report and the following recommended ratings for intraovarian PRP. This review included 8 studies, listed in Annex B.

Expert review August 2025
 GREY for oocyte numbers for most fertility patients GREY for blastocyst numbers for most fertility patients GREY for live birth rate for most fertility patients GREY for ongoing pregnancy rate for most fertility patients
 GREY for oocyte numbers for poor/diminished ovarian reserve GREY for blastocyst numbers for poor/diminished ovarian reserve GREY for live birth rate for poor/diminished ovarian reserve GREY for ongoing pregnancy rate for poor/diminished ovarian reserve

Intrauterine PRP

5.6. The Committee is asked to consider the independent reviewers report and the following recommended ratings for intrauterine PRP. This review included 25 studies, listed in Annex B.

Expert review August 2025
 GREY for endometrial thickness for most fertility patients GREY for implantation for most fertility patients GREY for live birth rate for most fertility patients GREY for ongoing pregnancy rate for most fertility patients
 GREY for endometrial thickness for thin/refractory endometrium GREY for implantation for thin/refractory endometrium GREY for live birth rate for thin/refractory endometrium GREY for ongoing pregnancy rate for thin/refractory endometrium
 GREY for endometrial thickness for recurrent/repeated implantation failure GREY for implantation recurrent/repeated implantation failure GREY for live birth rate for recurrent/repeated implantation failure GREY for ongoing pregnancy rate for recurrent/repeated implantation failure

	GREY for endometrial thickness for Asherman's syndrome/intrauterine adhesions GREY for implantation for Asherman's syndrome/intrauterine adhesions GREY for live birth rate for Asherman's syndrome/intrauterine adhesions GREY for ongoing pregnancy rate for Asherman's syndrome/intrauterine adhesions
	GREY for endometrial thickness for recurrent pregnancy loss GREY for implantation for recurrent pregnancy loss GREY for live birth rate for recurrent pregnancy loss GREY for ongoing pregnancy rate for recurrent pregnancy loss

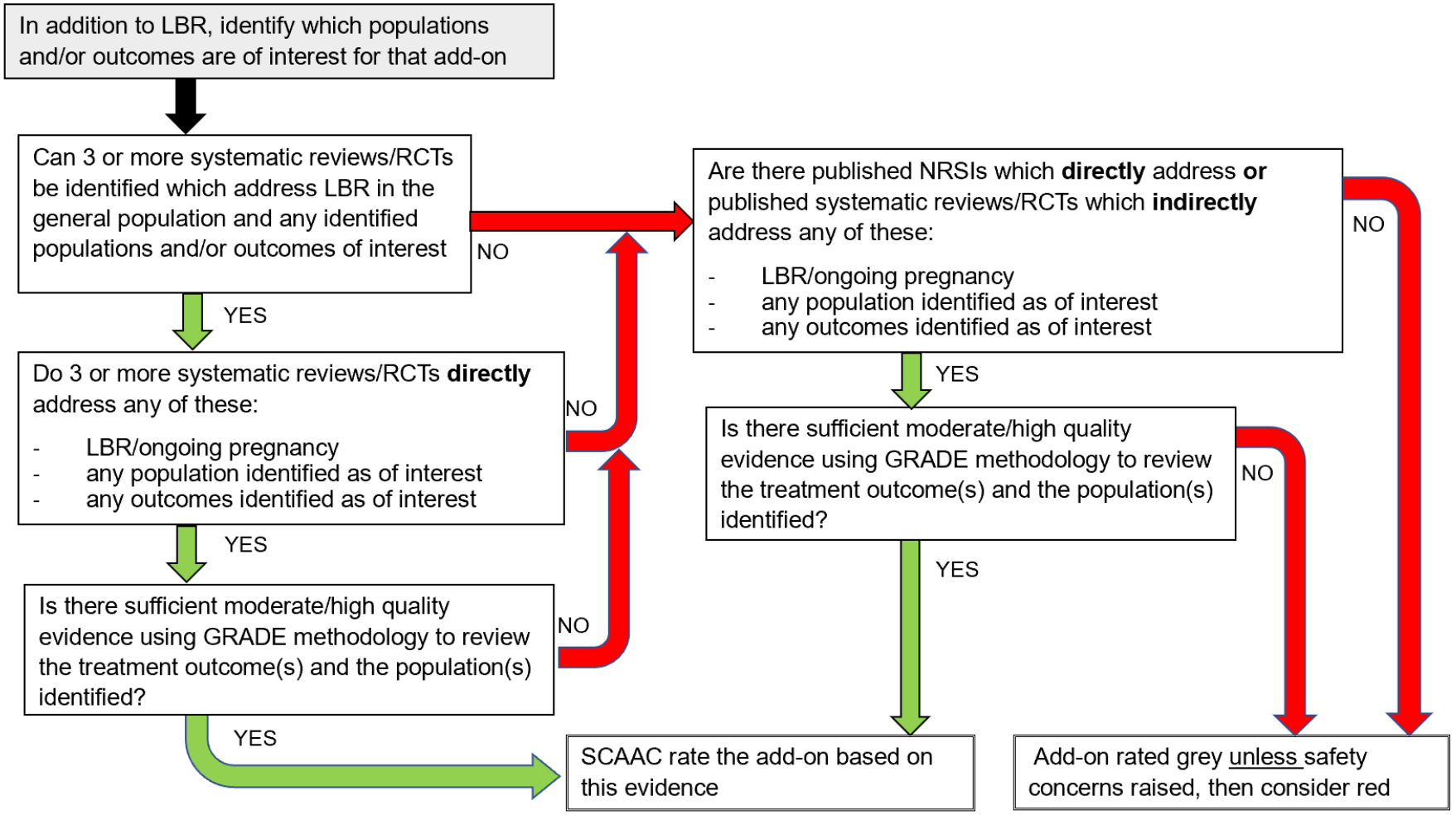
6. Recommendations

6.1.

Members are asked to:

- consider the quality of evidence for intrauterine and intraovarian platelet rich plasma (PRP) as a treatment add-on based on the findings from an independent assessor; and
- agree and recommend ratings for each outcome(s) and population(s).

7. Annex A: Evidence decision tree for rating add-on



8. Annex B: References of reviewed studies

Intraovarian PRP

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Intrauterine PRP

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Intraovarian PRP

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10. Annex D: Inclusion criteria and definitions

10.1. The International Committee for Monitoring Assisted Reproductive Technologies (ICMART) defined the terms poor ovarian responder (POR), poor ovarian response, and diminished ovarian reserve as follows:

- Poor ovarian responder (POR) in assisted reproductive technology: A woman treated with ovarian stimulation for ART, in which at least two of the following features are present: (1) Advanced maternal age (≥40 years); (2) A previous poor ovarian response (≤3 oocytes with a conventional stimulation protocol aimed at obtaining more than three oocytes); and, (3) An abnormal ovarian reserve test (i.e. antral follicle count 5–7 follicles or anti-Mullerian hormone 0.5–1.1 ng/ml (Bologna criteria); or other reference values obtained from a standardized reference population.)
- Poor ovarian response to ovarian stimulation: A condition in which fewer than four follicles and/or oocytes are developed/obtained following ovarian stimulation with the intention of obtaining more follicles and oocytes.
- Diminished ovarian reserve (DOR): A term generally used to indicate a reduced number and/or reduced quality of oocytes, such that the ability to reproduce is decreased. (See ovarian reserve.)

- Ovarian reserve: A term generally used to indicate the number and/or quality of oocytes, reflecting the ability to reproduce. Ovarian reserve can be assessed by any of several means. They include: female age; number of antral follicles on ultrasound; anti-Mullerian hormone levels; follicle stimulating hormone and estradiol levels; clomiphene citrate challenge test; response to gonadotropin stimulation, and oocyte and/or embryo assessment during an ART procedure, based on number, morphology or genetic assessment of the oocytes and/or embryos.

10.2. Under this definition, studies looking at POR may be inclusive of the following patient groups:

- Patients with advanced maternal age (>40) and previous poor ovarian response (<3 oocytes with a conventional stimulation protocol aimed at obtaining more than 3 oocytes);
- Patients with advanced maternal age (>40) and abnormal ovarian reserve (defined as antral follicle count 5-7 follicles, or AMH 0.5-1.1ng/ml [Bologna criteria] or other reference values obtained from a standardized reference population); or
- Patients with poor ovarian response (defined as above) and abnormal ovarian reserve (as above) – note, this would include patients under 40 years old.

10.3. Studies looking at DOR are included in the grouping 'women with poor/diminished ovarian reserve'.

11. Annex E: Independent report of expert statistician

Traffic Light System for Treatment Add-ons: Platelet-Rich Plasma

Andy Vail, September 2025

INTRODUCTION

The HFEA website provides patients with digestible information on treatment add-ons in the form of a rating system. The purpose of this report is to inform the Scientific and Clinical Advances Advisory Committee's (SCAAC) deliberations on updating this information. In particular, this update extends the ratings system to cover intraovarian or intrauterine injection of platelet-rich plasma.

The aim of the work reported below is to critically appraise, interpret and summarise, for consideration by SCAAC, the reports of identified studies.

METHOD

Rebecca Taylor, Scientific Policy Manager, provided references and hyperlinks to identified studies for consideration, categorised by add-on, study design and population under study. I screened and prioritised the studies, including checking of author names against the retraction watch database.

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. To classify a randomised trial as providing moderate/high quality evidence I have applied the default classification of the Cochrane Gynaecology and Fertility review group. Specifically, for a study to be considered in this category it must describe an adequately concealed randomisation process to prevent selection bias. It must also not be identified as at high risk of bias in other regards ('unclear' is acceptable) other than where blinding is unrealistic. Where HFEA specifically requested results for a sub-population of interest, I have presented first the studies addressing the

general population and then studies addressing the specific sub-populations. The extent to which interpretation of sparse results for a sub-population should borrow from the broader information available is addressed on a case-by-case basis.

To calculate odds ratios, published results were re-calculated applying the intention to treat (ITT) principle where possible 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. For studies where possible, 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 for these outcomes implies benefit of the add-on under study. Additional outcomes as requested by HFEA are presented with confidence intervals based on reported means and standard deviations. A difference greater than zero implies a higher mean for the intervention group.

RESULTS

1. Intraovarian Platelet-Rich Plasma (PRP)

The current search identified a total of 27 primary research studies. Searching of reviews identified one further randomised study for consideration. Priority for this report is given to the four randomised trials and four other concurrently controlled studies. The 20 identified 'before and after' studies do not by design give an estimate of treatment effect that is separable from the exact population under study.

1 (i) *General population*

No studies were identified that included a general population of patients undergoing assisted reproduction.

Recommendation: GREY for all outcomes.

1 (ii) *Poor/diminished ovarian reserve*

Three randomised trials assessed intra-ovarian PRP for participants variously defined as having poor or diminished ovarian reserve.

Herlihy 2022 studied 73 women under the age of 38 years. Intervention consisted of a 4cc injection to each ovary on day 3-10 of their menstrual cycle, with controls receiving no intervention. The study was unblinded and reported in abstract form only with inadequate detail to assess allocation processes and other potential sources of bias. They found similar metaphase II (MII) oocyte retrieval in each group, reporting mean (sd) of 3.7 (3.3) versus 3.0 (2.5) (p=0.64) in active and control respectively. They also reported similar mean (sd) of euploid blastocysts as 1.0 (1.7) and 1.0 (1.2). Ongoing pregnancy rate was similar between groups: OR (95% CI) = 1.1 (0.28 to 4.4).

Barrenetxea 2024 randomised 60 women under the age of 42 years and meeting POSEIDON Grade III or IV for poor ovarian reserve. All participants underwent three consecutive retrieval cycles to accumulate oocytes prior to a complete IVF/ICSI cycle followed through to delivery or exhaustion of frozen embryos. Those in the intervention group received an injection of 4ml to each ovary immediately after the first retrieval, whilst those in the control group received matching saline in a fully blinded design. This appears to be a high-quality study reporting concealed allocation and low risk of bias in all domains. They reported a higher mean (sd) number of MII oocytes retrieved in the intervention group: 10.5 (2.2) versus 8.9 (2.1). However, an identical number of participants had blastocysts (22 in each group) and fewer of those in the intervention group had euploid blastocysts (13 versus 16). Despite fewer miscarriages in the intervention group (1 versus 5) there were also fewer live births: OR (95% CI) = 0.40 (0.11 to 1.4).

Barad 2024 studied 34 women under the age of 40 years with primary ovarian insufficiency. This was reported only as a conference abstract. Details of timing and dose were absent but a single injection was given to a randomly selected ovary. They reported that more women developed follicles >4mm in treated than control ovaries. Numbers of oocytes and embryos were reported but overall, rather than by allocated group.

Peng 2025 was identified as a randomised trial by the search strategy but was unfortunately available only in Chinese. Trustworthiness checks suggest that the trial was unregistered and flagged the senior author's name on an article previously retracted for "unreliable data". It would nonetheless be of interest to appraise this manuscript if a translation is available.

Stojkovska 2019 studied 20 women meeting at least two of the three Bologna criteria for poor ovarian reserve who underwent a 3-5ml injection immediately following activation. Comparison was made with a group of 20 women fulfilling similar criteria who did not receive PRP. Division into comparison groups may have been by patient choice but it is unclear how or when eligibility was confirmed given that "only patients where the IVF process was completed with an embryo transfer were included in the study". The numbers of participants contributing to clinical outcomes is unclear as they are not explicitly stated and reported p-values are inconsistent with a sample size of 20 per group. They reported a lower mean (sd) number of MII oocytes retrieved in the intervention group: 1.9 (1.1) versus 3.7 (2.4).

Melo 2020 studied 83 women over the age of 38 years. All participants underwent three consecutive retrieval cycles. Those in the intervention group received monthly 200µl injection to each ovary on day 7-9 of their cycle. Group membership was determined by patient choice, there was no blinding and, unusually, a little under 50% of participants progressed to an IVF/ICSI cycle rather than alternative therapies. All participants were followed up for 12 months. For the 40 participants who progressed to IVF/ICSI, they reported a higher median (range) number of oocytes retrieved in the intervention group: 5 (2 to 9) versus 3 (0 to 6). Overall, despite more miscarriages in the intervention group (6 versus 1) there were also more live births: OR (95% CI) = 4.4 (0.45 to 213).

Keikha 2022 studied 12 women meeting at least two of the three Bologna criteria for poor ovarian reserve. This was an unusual design in several regards. All women underwent two consecutive retrieval cycles with a 4cc injection to the right ovary after the first retrieval. The woman's left ovary provided the "control group" in this within-patient design with no immediate IVF/ICSI undertaken and therefore no clinical outcomes. The post-intervention (right) ovaries produced similar mean (sd) number of oocytes: 1.1 (1.0) versus 1.0 (0.7) but the presented analyses fail to recognise the paired nature of the design.

Yu 2025 studied 74 women over the age of 20 years who had undergone at least two previous controlled ovarian hyperstimulation cycles without producing a single good quality blastocyst. Those in the intervention group received 1ml injections to each of four sites in each ovary during the follicular phase. Group membership was determined by patient choice so there was no blinding and a high risk of selection bias. The intervention group produced more mature oocytes: 6.7 (4.2) vs 4.9 (4.8). This carried through to more blastocysts - 1.7 (1.5) vs 0.5 (0.7) – and more "good quality" blastocysts, though numbers were low in both groups: 0.6 (0.8) vs 0.0 (0.2). Miscarriage and live birth were only reported in the control group but clinical pregnancy was higher in the intervention group: OR (95% CI) = 5.5 (0.63 to 256).

Recommendations

Oocyte numbers: Grey

Blastocyst numbers: Grey

Live birth/Ongoing pregnancy: Grey

Justification: Only one moderate/high quality trial and this too small to be conclusive. Other studies all small and of highly variable quality with inconsistent results for all outcomes).

2. Intrauterine Platelet-Rich Plasma (PRP)

The current search identified a total of 25 primary research studies. Searching of reviews identified one further randomised trial for consideration.

1 (i) *General population*

No studies were identified that included a general population of patients undergoing assisted reproduction.

Recommendation: GREY for all outcomes.

2 (ii) *Recurrent Implantation Failure*

Seventeen randomised trials assessed intrauterine PRP for participants variously defined as having recurrent implantation failure.

Obdiniak 2017 studied 90 women with RIF. Intervention consisted of a single 2ml infusion at an unspecified time prior to frozen-thawed embryo transfer, with controls receiving no intervention. The study was unblinded and reported in abstract form only with inadequate detail to assess allocation processes and other potential sources of bias. They reported an extreme benefit for clinical pregnancy rate: OR (95% CI) = 3.5 (1.3 to 9.6). However, the credibility of this report is undermined by several 'red flags'. They report an odds ratio for the continuous outcome of endometrial thickness and conclude 'no effect' on pregnancy loss despite the small sample size and without presenting any data. It is also a cause for concern that this study remains unpublished after so long.

Nazari 2020 studied 97 women with RIF aged under 40 years with BMI<30kg/m2 and awaiting frozen-thawed embryo transfer. Infusion of 0.5ml was given with embryo transfer whilst controls received no intervention. This study was at high risk of bias for allocation concealment and had no blinding. Other anomalies included a trial registration cited that was for a different trial (Nazari 2019 perhaps, see below) and a study flow chart that was for a single arm design. They reported a much higher pregnancy rate in the intervention group: OR (95% CI) = 4.1 (1.5 to 12).

Alhalabi 2019 studied 80 women with RIF. Intervention was an unspecified dose on the day of oocyte puncture, with controls receiving no intervention. The study was unblinded and reported in abstract form only with inadequate detail to assess allocation processes and other potential sources of bias. They reported more clinical pregnancies in the intervention group: OR (95% CI) = 1.9 (0.54 to 7.1). It is a cause for concern that this study remains unpublished after so long.

Rageh 2020 studied 150 women under the age of 40 years and with BMI<30kg/m^2. Infusion of 0.5 to 1ml was given 48 hours before embryo transfer. This study was at high risk of bias with unspecified allocation and no blinding. No follow-up was reported beyond a biochemical pregnancy test. Endometrial thickness was reported as a baseline similarity (prior to group allocation) rather than as an outcome.

Zamaniyan 2020 studied 120 women with RIF under the age of 40 years and with BMI<30kg/m^2 who were to undergo frozen-thawed embryo transfer. Infusion of 0.5ml was given 48 hours before embryo transfer with controls receiving no intervention. This study was at high risk of bias with inadequately specified allocation and incomplete blinding. They reported low miscarriage rate (one intervention versus two controls) and an extreme benefit of intervention for ongoing pregnancy rate: OR (95% CI) = 6.6 (2.4 to

20). This was matched by a similar result for implantation. Endometrial thickness was reported as a baseline characteristic (prior to group allocation) to be higher in the intervention group (12.4 vs 8.4mm).

Allahveisi 2020 studied 50 women with RIF awaiting frozen-thawed embryo transfer. Infusion of 0.5ml was given 48 hours before embryo transfer with controls receiving Ringer serum rather than PRP. This study was at high risk of bias with inadequate specification of both allocation and blinding. They reported similar implantation and clinical pregnancy rates resulting in similar live birth rates: OR (95% CI) = 1.2 (0.29 to 5.4). Endometrial thickness was reported as a baseline similarity (prior to group allocation) rather than as an outcome.

Zargar 2021 studied 80 women with RIF aged up to 40 years. Infusion of 1.5ml was given 48 hours before embryo transfer with controls receiving no intervention. This study was at unclear risk of bias from allocation concealment. They reported higher pregnancy in the intervention group with similar miscarriage and all five live births occurring in the intervention group.

Safdarian 2022 studied 120 women with RIF aged up to 40 years and with no previous transfer cancellation due to thin endometrium. Infusion of 0.5ml was given 48 hours before embryo transfer with controls receiving no intervention. This study was at high risk of bias with unspecified allocation concealment and no blinding. The numbers of women reported as 'positive' for live birth was higher for both groups than the numbers positive at each preceding stage of biochemical, clinical and ongoing pregnancy. They reported much higher rates for all these outcomes in the intervention group: ongoing pregnancy OR (95% CI) = 2.8 (1.2 to 6.6).

Bakhsh 2022 studied 100 women with RIF under the age of 40 years and with BMI<30kg/m^2 who were to undergo frozen-thawed embryo transfer. Injection of 0.5cc was given 48 hours before embryo transfer. Controls underwent catheter transfer without injection. This study was at high risk of bias with inadequately specified allocation and incomplete blinding. There were language issues with the report, figures in tables that were uninterpretable and an inexplicable claim of statistical significance in the primary outcome of clinical pregnancy: OR (95% CI) = 2.1 (0.42 to 14).

Nazari 2022 studied 418 women with RIF under the age of 39 years and with BMI<30kg/m^2 who were to undergo frozen-thawed embryo transfer. Infusion of 0.5ml was given 48 hours before embryo transfer with controls receiving no intervention. This study was at high risk of bias with unspecified allocation concealment and no blinding. As with Nazari 2020 (see above), anomalies included a trial registration cited that was for a different trial (Nazari 2019 perhaps, see below). They reported extreme effects of intervention with double the number of chemical pregnancies and a seven-fold higher number of live births: OR (95% CI) = 11 (5.3,23). They reported endometrial thickness on the day of transfer to be thinner in the intervention group by 0.5 (0.0 to 1.0) mm.

El-Samman 2022 studied 98 women with RIF aged up to 35 years and with high quality embryos for fresh or frozen transfer. Infusion of 0.5ml was given 48 hours before embryo transfer with controls receiving no intervention. This study was at high risk of bias with unspecified allocation and no blinding. The claim of statistical significance in the primary analysis of endometrial thickness appears to have been based on a confusion in the analysis between 'standard deviation' and 'standard error'. A further issue with this analysis is that there is a four-fold difference in variability between the intervention and control groups for all measures of endometrial thickness. Possible explanations (which may invalidate the analysis) would be an extreme outlier or unnoticed 'missing value' code in the dataset. On face value, the mean change in endometrial thickness was similar between groups but clinical pregnancy was higher in the intervention group: OR (95% CI) = 2.8 (1.1 to 7.6).

Ershadi 2022 studied 90 women with RIF under the age of 40 years who were to undergo frozen-thawed embryo transfer. Injection of 0.5ml was given 48 hours before embryo transfer with controls receiving no intervention. This study was at high risk of bias for allocation concealment and had no blinding. Clinical

pregnancy rate was similar between groups: OR (95% CI) = 1.3 (0.44 to 3.6). Endometrial thickness was reported as a baseline similarity (prior to group allocation) rather than as an outcome.

Baybordi 2022 studied 94 women with RIF up to the age of 45 years. Injection of 0.5-1ml was given 48 hours before embryo transfer. Control was inconsistently described but appears to have been preparation for PRP but without sham injection. This study was at high risk of bias from allocation and poor blinding. There were language issues with the report and figures in tables that were uninterpretable. They reported similar live birth rates in the two groups: OR (95% CI) = 1.1 (0.34 to 3.6).

Yahyaei 2024 studied 80 women with RIF under the age of 40 years and with BMI<29kg/m^2. Infusion of 0.8-1cc was given 48 hours before fresh or frozen embryo transfer with controls receiving no intervention. This study was at high risk of bias with unspecified allocation concealment and no blinding. They reported an extreme benefit of intervention for live birth rate: OR (95% CI) = 10 (2.5 to 58). Endometrial thickness was reported as a baseline similarity (prior to group allocation) rather than as an outcome.

Eftekhar 2024 studied 72 women with RIF under the age of 43 years awaiting frozen embryo transfer. Infusion of 0.5-1cc was given two days before embryo transfer with controls receiving no intervention. This study was at high risk of bias with unspecified allocation concealment and no blinding. It is also unclear why it was not published until 2024 despite being registered and recruiting at the same time as Eftekhar 2018 (see below). They reported a higher ongoing pregnancy rate in the intervention group: OR (95% CI) = 1.4 (0.38 to 5.7). Endometrial thickness was reported as a baseline similarity (prior to group allocation) rather than as an outcome.

Strug 2024 studied 39 women with RIF awaiting frozen embryo transfer. Two 1ml infusions were given: first at cycle day 9-12 (or 10-14 days of oestradiol in programmed cycles) and then two to three days prior to embryo transfer. The study was reported in abstract form only with inadequate detail to assess allocation processes and other potential sources of bias. They reported a possible benefit of intervention for live birth rate: OR (95% CI) = 2.6 (0.46 to 15). However, if the post-randomisation exclusions came from the intervention group, which would make the group sizes nearer to equal, then the suggestion of an effect would disappear. Endometrial thickness was reported as a baseline similarity (prior to group allocation) rather than as an outcome.

Fazaeli 2024 undertook a three-arm trial for which just the PRP and control groups are described here. They studied 64 women with RIF under the age of 40 and with BMI<30kg/m^2. Injection of 0.5-1ml was given two days before embryo transfer with controls receiving no intervention. Trustworthiness checks flagged two authors' names: one for a previous study retracted for "duplication" and one for an article retracted for "unreliable results and/or conclusions". This study was at high risk of bias from allocation and poor blinding. They reported a higher clinical pregnancy rate in the intervention group: OR (95% CI) = 3.5 (0.55 to 57). Endometrial thickness was reported as a baseline similarity (prior to group allocation) rather than as an outcome.

Tehraninejad 2020 studied 85 women with RIF and normal endometrial thickness undergoing frozen-thawed embryo transfer. Infusion of 1ml was given two days before embryo transfer with controls receiving no intervention. This study was high risk of bias with allocation by patient choice. They reported similar biochemical and clinical pregnancy rates resulting in similar ongoing pregnancy rates: OR (95% CI) = 1.0 (0.35 to 3.1). Endometrial thickness was reported as a baseline similarity (prior to intervention) rather than as an outcome.

Recommendations

Endometrial thickness: GREY

Implantation rate: GREY

Miscarriage rate: GREY

Live birth/ongoing pregnancy rate: GREY

Justification: Despite large numbers of studies, we have not found a single RCT of moderate/high quality. Reporting of relevant outcomes was sparse. Endometrial thickness, where reported, was usually at a time preceding intervention. Implantation rate was rarely reported with numerators and denominators or in a format allowing valid statistical comparison. Miscarriage was often not defined, with follow-up not beyond the observation of clinical pregnancy.

2 (iii) *Thin Endometrium*

Four randomised trials assessed intrauterine PRP for participants variously defined as having thin endometrium.

Eftekhar 2018 studied 83 women with thin endometrium (<7mm) under the age of 43 years awaiting frozen embryo transfer. Infusion of 0.5-1cc was given on the 13th day of the HRT cycle and repeated after two days if the endometrial thickness remained under 7mm. The study was at high risk of bias with unspecified allocation concealment and no blinding. Ongoing pregnancy was higher in the intervention group: OR (95% CI) = 2.3 (0.69 to 8.6). Endometrial thickness was also greater in the intervention group: mean difference (95% CI) after two days = 0.6 (0.4 to 0.9) mm.

Nazari 2019 studied 60 women with thin endometrium (<7mm) under the age of 39 years and with BMI<30kg/m^2. Infusion of 0.5ml was given on the 11th or 12th day of the HRT cycle and repeated after two days if the endometrial thickness remained under 7mm. The study was at high risk of bias with unspecified allocation concealment. The cited trial registration was also used by Nazari 2020 and Nazari 2022 (see above). The methods described here are more similar to the details offered at registration although there are differences in eligibility criteria, sample size and reported outcomes. They reported an extreme effect of intervention on clinical pregnancy rate: OR (95% CI) = 15 (1.7,650). They also reported endometrial thickness on the day of transfer to be greater in the intervention group by 0.5 (0.1 to 0.9) mm.

Abduljabbar 2022 studied 70 women with RIF and endometrial thickness between 0.4 and 0.7cm. Infusion of 0.5ml was given immediately after oocyte pick-up with controls receiving no intervention. This study was at high risk of bias with a high risk allocation process and no blinding. Follow-up ceased at a positive pregnancy test. Endometrial thickness at the time of embryo transfer was greater in the intervention group: mean difference (95% CI) = 0.11 (0.07 to 0.15) cm.

Pandey 2023 studied 120 women with RIF under the age of 38 years and with endometrial thickness less than 7mm. Instillation of 1ml was given on the day of trigger for up to three cycles. The study was at high risk of bias with unspecified allocation concealment and no blinding. Clinical pregnancy was higher in the intervention group: OR (95% CI) = 2.8 (0.74 to 13). Endometrial thickness was also greater in the intervention group: mean difference (95% CI) after first cycle was 0.62 (0.4 to 0.8) mm with the difference increasing following consecutive cycles.

Zhang 2025 reported as an abstract only. This was not eligible for review here as the comparison was of PRP plus endometrial microstimulation versus PRP alone.

Recommendations

Endometrial thickness: GREY

Implantation rate: GREY

Miscarriage rate: GREY

Live birth/ongoing pregnancy rate: GREY

Justification: no moderate/high quality studies

2 (iv) Asherman Syndrome or Uterine Adhesions

One randomised trial assessed intrauterine PRP for participants defined as having intrauterine adhesions.

Ahmed 2021 studied 160 women with Grade-III intrauterine adhesions undergoing hysteroscopic adhesiolysis. Following surgery, the intervention group received injection of 5ml PRP to the most affected part of the uterine wall and 5ml gel to the lining of the uterine cavity. Controls received both placebo injection and placebo gel. Exact timing of allocation and the role of the assistant nurse who had sealed opaque envelopes containing the code is unclear. However, this appears to be a moderate quality study with a clear attempt to conceal the allocation prior to surgery and to blind outcome assessment. There were more pregnancies (unspecified definition) in the intervention group: OR (95% CI) = 1.9 (0.77 to 5.0). Other outcomes of interest to this review were not included as the trial's primary aim was to reduce recurrence of adhesions.

Peng 2020 retrospectively studied 94 women with moderate or severe intrauterine adhesions who underwent operative hysteroscopy. There were two groups whose procedure included use of an intrauterine balloon either with or without infusion of 0.5-1ml PRP to the uterine cavity. A third group received the infusion but without the balloon, thereby confounding the comparison of interest to this review. Unfortunately, they excluded over 25% of the women from analysis because they had chosen not to undergo a third-look laparoscopy and did not report any of the outcomes specified for this review. Positive pregnancy tests were observed in fewer women receiving PRP (3/20 versus 7/22).

Aghajanova 2021 studied 30 women with moderate to severe Asherman Syndrome undergoing hysteroscopic resection of scar tissue. At the end of the procedure the intervention group received infusion of 1ml PRP to the fundus. The first four controls received saline infusion. After this point recruitment failed and further participants were either selected for the intervention group prospectively through patient choice or retrospectively for the control group. The study was therefore at high risk of bias. There were fewer live births in the intervention group: OR (95% CI) = 0.75 (0.13 to 4.2). Change in endometrial thickness following surgery was similar in the two groups with the median increase just 0.4mm more in the intervention group.

Recommendations:

Endometrial thickness: GREY

Implantation rate: GREY

Miscarriage rate: GREY

Live birth/ongoing pregnancy rate: GREY

Justification: Only one RCT potentially of moderate quality but small and inconclusive.

2 (v) *Recurrent Pregnancy Loss*

One randomised trial assessed intrauterine PRP for participants defined as having recurrent pregnancy loss.

Nazari 2022b studied 50 women with a history of at least two pregnancy losses who were under the age of 40 years and with BMI<30kg/m^2. Infusion of 0.5ml was given 48 hours before embryo transfer with controls receiving no additional intervention. This study was at high risk of bias with unspecified allocation concealment and no blinding. They reported higher clinical pregnancy in the intervention group with similar miscarriage and all three live births occurring in the intervention group.

Recommendation:

Endometrial thickness: GREY

Implantation rate: GREY

Miscarriage rate: GREY

Live birth/ongoing pregnancy rate: GREY

Justification: No moderate/high quality evidence

COMPARISON WITH PREVIOUS REVIEWS

Vaidakis 2024, the Cochrane review covering both these interventions, identified one randomised trial (Herlihy 2022) of intraovarian PRP and 9 randomised trials of intrauterine (Obidniak 2017; Alhalabi 2019; Zamaniyan 2020; Allahveisi 2020; Zargar 2021; Safdarian 2022; Bakhsh 2022; Ershadi 2022; Baybordi 2022). Non-randomised studies were excluded from consideration, Studies by the teams of Nazari and Eftekhar were 'awaiting assessment' of eligibility. The review conclusion was that the evidence certainty was "very low", whether including all eligible studies or restricting to those at low risk of bias (only Baybordi 2022 met their criteria).

Evidence-based IVF, the website recently funded by the Australian Government to review treatment add-ons, covers both interventions. For each it concludes that the evidence is "unclear" for the outcomes of pregnancy, miscarriage and live birth.

DISCUSSION

Caution is required as the assessments above are made from a methodological perspective without expertise in the clinical or scientific context. It is worth noting that it is not uncommon for a trial to be well-designed to answer a question of little clinical value.

The recommendations for rating are intended only as a starting point for committee discussion.
Some comparisons contain a range of interventions (e.g. varied quantity, timing and duration of dose) in populations defined by different eligibility criteria. Alternative post-hoc but biologically plausible rationales could be put forward to 'lump' or further 'split' categories presented above.

REFERENCES: Reviewed studies

Adjunct	Study	DOI/reference
Intraovarian PRP		
Poor ovarian reserve	Herlihy 2022	10.1016/j.fertnstert.2022.09.330
	Barrenetxea 2024	10.1093/humrep/deae038
	Barad 2024	10.1093/humrep/deae108.954
	Peng 2025	10.11817/j.issn.1672-7347.2025.240408
	Stojkovska 2019	10.3889/oamjms.2019.825
	Melo 2020	10.1007/s10815-020-01710-z
	Keikha 2022	10.4314/ejhs.v32i6.10
	Yu 2025	10.1038/s41598-024-82630-1
Intrauterine PRP		
RIF	Obidniak 2017	10.1016/j.fertnstert.2017.07.1080
	Nazari 2020	10.1080/14647273.2019.1569268
	Alhalabi 2019	10.1093/humrep/34.Supplement_1.1
	Rageh 2020	10.21608/ebwhj.2019.17936.1039
	Zamaniyan 2020	10.1080/09513590.2020.1756247
	Allahveisi 2020	10.1016/j.heliyon.2020.e03577
	Tehraninejad 2020	10.1111/jog.14445
	Zargar 2021	10.31083/j.ceog.2021.01.2131
	Safdarian 2022	10.15296/ijwhr.2022.08
	Bakhsh 2022	10.5935/1518-0557.20210046
	Nazari 2022	10.1007/s43032-021-00669-1
	El-Samman 2022	10.21608/aimj.2022.92034.1557
	Ershadi 2022	10.4103/jfmpc.jfmpc_1817_21
	Baybordi 2022	10.18502/ijrm.v20i9.12065
	Yahyaei 2024	10.1038/s41598-024-77578-1
	Eftekhar 2024	10.22074/ijfs.2023.553636.1305
	Strug 2024	10.1016/j.fertnstert.2024.05.121
	Fazaeli 2024	10.18502/ijrm.v22i10.17668
Thin endometrium	Eftekhar 2018	10.1016/j.tjog.2018.10.007
	Nazari 2019	10.18502/ijrm.v17i6.4816
	Abduljabbar 2022	10.7759/cureus.27913
	Pandey 2023	10.1016/j.xagr.2023.100172
	Zhang 2025	PMID: 40340871
Asherman/UA	Ahmed 2021	10.18203/2320-1770.ijrcog20210289
	Peng 2020	10.1002/ijgo.13353
	Aghajanova 2021	10.1007/s10815-021-02328-5
RPL	Nazari 2022b	10.5468/ogs.21261
Other Reviews		
Cochrane	Vaidakis 2024	10.1002/14651858.CD013875.pub2
Evidence-based IVF		https://www.unimelb.edu.au/ivf/treatment