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

Monday 3rd February 2025

Date	Action	Responsibility	Due date	Progress to date
07/10/2024	The Committee to discuss growing body of evidence against the use of ICSI for non-male and mild-male factor infertility at the February 2025 SCAAC meeting.	Molly Davies, Policy Manager	03/02/2025	A 'watching brief' for this topic has been introduced through development of the SCAAC's horizon scanning function. Publications relevant to the use of ICSI for non-male and mild-male factor infertility will be discussed at the June 2025 SCAAC meeting, following the expected publication of an RCT.
07/10/2024	The Executive to add the two RCTs on time lapse imaging, discussed at the October 2024 SCAAC meeting, to the 'Time lapse imaging and incubation' webpage.	Molly Davies, Policy Manager	03/02/2025	The 'Time lapse imaging and incubation' webpage has been updated to add the additional RCTs to the reference list. A footer has been added to make it clear that these studies were not subject to the independent statistician's review conducted during the July 2023 add-ons review.
07/10/2024	The Executive to review the patient information on the use of steroids (glucocorticoids) to make sure all associated risks are made clear.	Molly Davies, Policy Manager	03/02/2025	The 'Immunological tests and treatments for fertility' webpage has been updated to add that there is evidence of an increased risk of poor outcomes – including pre-term delivery rate and biochemical pregnancy loss.

Health outcomes in children born from ART (including culture media)

Details about this paper

Area(s) of strategy this paper relates to:	The best care
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	5
Paper number:	HFEA (03/02/2025) 005
Meeting date:	03 February 2025
Author:	Mina Mincheva, Policy Manager (HFEA)
Annexes	A - References referring to paragraph 1.6

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • Advise the executive if they are aware of any other recent developments • Review whether any outputs from the HFEA are required • Advise on whether a new related topic of 'Health outcomes for ART patients (including gestational surrogates and egg donors)' should be added as a new prioritised topic.
Resource implications:	N/A
Implementation date:	N/A
Communication(s):	None
Organisational risk:	Low

1. Introduction

1.1. Assisted reproductive technology (ART) includes techniques such as egg freezing, in vitro fertilisation (IVF), intra cytoplasmic sperm injection (ICSI) and pre-implantation genetic testing (PGT). There is a possibility that children born from ART may be at risk of birth defects or developing longer-term health issues, though this could be due to underlying infertility rather than the ART procedure. Culture media used in IVF systems acts as a surrogate for maternal nutrition for the first few days, therefore it is important to optimise the culture environment of embryos during IVF treatment. It is also important to scrutinise embryo culture media components (proprietary to manufacturers) to ensure that risks are minimised, embryo stress is avoided, and embryo health is maintained.

1.2. The regulation of composition, quality and safety of culture media is within the remit of the Medicines and Healthcare products Regulatory Agency (MHRA), with incidents related to that being reported to the MHRA via the Yellow Card system. However, SCAAC monitors the effect of culture media in the context of its safety for the embryo, and the health of any children born following assisted conception.

1.3. The **HFEA's Code of Practice** requires licensed clinics to provide certain information to patients undergoing fertility treatment about the treatment and associated risks. This includes outcomes of proposed treatment, potential immediate and longer-term risks of the treatment and any treatment add-ons used, and the nature and potential risks of using emerging or unproven treatments.

1.4. Since the last literature search on this topic, there has been an increase in publications and reports using national ART datasets linked to other health and population registries to analyse health effects of ART on offspring, for example from the **Committee on Nordic ART and Safety** (CoNARTaS), the **HFEA Register** data, and **European IVF monitoring consortium** (EIM).

1.5. SCAAC last discussed health outcomes following ART in **October 2023**. The Committee highlighted the need for longer-term follow-up linkage studies that look into establishing the cause of potential differences between patient cohorts. It was also noted that outputs from linkage studies using UK Register data could be improved by expanding the data dictionary, particularly to look at performance of different types of culture media. The Committee noted the importance of predefining the clinical questions of interest if submission of specified data is to be required from clinics.

1.6. Since its introduction, this priority topic has focused on health outcomes of children conceived through ART. The committee now is being asked to advise on whether a new related topic of 'Health outcomes for ART patients (including gestational surrogates and egg donors)' should be added as a new prioritised topic. Selected references on this suggested new topic are listed in Annex A. Concerns raised are around higher maternal morbidity among gestational carriers, and for people undergoing fertility treatment – surgical and other complications (such as Ovarian Hyperstimulation Syndrome, OHSS) arising from the fertility treatment itself, as well as the relationship between fertility drugs and cancer incidence later in life. Some recent research on this topic, for example the Velez et al (2024) study that looks at morbidity in gestational carriers, has generated media coverage, and there were parliamentary questions on the health impact of egg donation in late 2024.

1.7. The research highlighted in this paper has been published between 1 September 2023 and 31 December 2024. References in Annex A on the health outcomes of patients undergoing ART, are not part of the literature summary outlined in section 2 as the remit of this topic is health outcomes of children born from ART; it does not currently include the health outcomes of ART patients. This paper provides a summary of the findings described in published literature and is not an assessment of study validity.

2. Research

Narrative / systematic reviews and commentaries

2.1. A narrative review by (Pinborg *et al.*, 2023) overviews the long-term health outcomes in children born after ART and discusses the intrinsic parental factors related to subfertility or ART treatments may affect these outcomes. Authors summarise that ART-conceived children face a higher risk of preterm birth, low birth weight, and birth defects, with frozen embryo transfer (FET) cases more likely to result in large for gestational age (LGA). Furthermore, some concerns about potential cardiometabolic health issues remain, such as high blood pressure in ART children. The risk of cancer is not generally elevated in ART children but may be slightly higher in those born after FET, while neurodevelopmental health and school performance are comparable between ART and spontaneously conceived (SC) singletons.

2.2. A review by (Zhang *et al.*, 2023a) summarises the DNA methylation-dependent and independent mechanisms that control the dynamic epigenetic regulation of imprinted genes throughout the mammalian life cycle. Authors also describe the dysregulation of imprinted genes in embryos conceived through ART and discussed the corresponding underlying mechanisms according to findings in animal models.

2.3. A commentary by (Pinborg *et al.*, 2024) considers milestone achievements in embryo cryopreservation, provides opinion on the benefits of the procedure and the maternal and neonatal risks associated with FET as well as its medical indications based on evidence from large cohort and international register studies. The commentary concludes that cryopreservation should be used for storing surplus embryos, in cases of high risk of Ovarian Hyperstimulation Syndrome (OHSS), or if PGT-A is indicated, and argues that ‘freeze-all’ approach should not be universally applied during ART treatment.

2.4. A narrative review by (Faa *et al.*, 2024) provide an overview of the possible long-term consequences of ART procedures on the health of newborns. Authors argue that risk estimates point to increased liability for major non-chromosomal birth defects, as well as cardiovascular, musculoskeletal, and urogenital (in male newborns) defects.

2.5. A systematic review by (Carneiro *et al.*, 2024) including 45 reports assessed the psychological adjustment of ART-conceived children (3-11 years old) by comparing ART children’s scores on standardised indexes of mental health with normative data. Authors also examined differences across different ART procedures and family formations. All children scored below the clinical range for psychiatric symptoms when compared with normative data for the Strengths and Difficulties Questionnaire (SDQ) or the Achenbach System of Empirically Based Assessment (ASEBA), regardless of type of ART and different family configurations. Authors argue that evidence suggests that surrogacy children with gay fathers present the lowest levels of psychological problems when compared to normative data.

2.6. A descriptive review by (Zeng *et al.*, 2024) overviews the evidence related to the effects of ART on neurodevelopment, specifically focusing on the evidence of the relationship between ART, epigenetic modifications, and neurodevelopmental disorders, including autism spectrum disorder, intellectual disability, attention deficit hyperactivity disorder, and cerebral palsy.

2.7. A review by (Zhang *et al.*, 2023b) provides a descriptive overview of the risks for long-term health in ART offspring, the underlying mechanisms, including underlying parental infertility, epigenetic alterations, non-physiological hormone levels, and placental dysfunction. The authors also propose potential strategies to optimise the management of ART and health care of parents and children to eliminate the associated risks.

2.8. A descriptive review by (Ono *et al.*, 2023) overviewed literature which assessed long-term physical and psychomotor outcomes in children conceived via ART compared to naturally conceived peers. While physical development is largely comparable, some evidence suggests minor growth differences before school age, but these differences are likely influenced by genetic or environmental factors rather than ART itself. Further, ART and naturally conceived children do not vary in academic achievement or attention deficit hyperactivity disorder.

2.9. A study undertaken by (Sundrani *et al.*, 2025) compared gene expression and DNA methylation patterns of angiogenic factors (*VEGF*, *PlGF*, *FLT-1*, *KDR*) in the placentae of Indian women who underwent ART (n = 64) with women who conceived naturally (n = 93), and the association of those factors with maternal one-carbon metabolites and birth outcomes. The study found some differences between the two groups including that gene expression of FLT-1 and KDR was higher ($p < 0.05$) in ART placentae, while DNA methylation levels of VEGF promoter were lower ($p < 0.05$) in ART compared to non-ART women. Gene expression of PlGF was negatively associated with maternal plasma folate ($p < 0.05$) whereas KDR was positively associated with maternal plasma homocysteine ($p < 0.05$), and with chest circumference of the baby ($p < 0.05$). The authors concluded that lower DNA methylation of VEGF and higher expression of FLT-1 and KDR are found in the placentae of Indian women who undergo ART procedures, and that this is likely to influence angiogenesis, placental, and foetal growth.

Maternal, perinatal and neonatal outcomes

2.10. A single-centre study by (Bartsch *et al.*, 2024) analysed 11,920 singleton term births in Vienna (from 2010 to 2020) to examine the association between ART and breech presentation. Results showed that ART-conceived births initially had a higher risk of breech presentation (odds ratio [OR] 1.67, 95% CI 1.71 – 2.38), but after adjusting for maternal age, parity, and other factors, ART was no longer a significant risk factor, with authors suggesting that increased maternal age and lower parity, rather than ART itself, may contribute to the observed risk.

2.11. A national population-based retrospective cohort study by (Raja *et al.*, 2023) compared perinatal outcomes following fresh blastocyst versus fresh cleavage stage embryo transfer (ET) among in singletons, twins, and between singleton siblings using linked Human Fertilisation and Embryology Authority (HFEA) data on 130,516 IVF and ICSI livebirths occurring from 103,062 women. Blastocyst stage ET in singletons was associated with reduced risks of low birthweight (adjusted risk ration [aRR] 0.92, 95% CI 0.86-0.99), being small for gestational age (SGA) (aRR 0.83, 95% CI 0.78-0.89), and congenital anomalies (aRR 0.79, 95% CI 0.71-0.89) without increased risks of preterm birth (aRR1.00, 95% CI 0.94-1.06), high birthweight (aRR 0.99, 95% CI 0.93-1.06), or large for gestational age, LGA (aRR 0.99, 95% CI 0.93-1.05). In twins, blastocyst stage ET was linked to a slightly higher risk of preterm birth (aRR 1.05, 95% CI 1.02-

1.10) Singleton siblings of blastocyst ET had higher odds of being LGA (aRR1.57, 95% CI 1.01-2.46) but lower odds of congenital anomalies (aRR 0.52, 95% CI 0.28, 0.97) compared to their singleton siblings born following cleavage stage ET. There was some evidence of excess risk of preterm birth (aRR 1.42, 95% CI 0.97-2.23) associated with blastocyst stage transfer.

2.12. A population-based record-linkage study by (Purkayastha *et al.*, 2024) evaluated hospital admissions for conditions originating in the perinatal period among children conceived via ART (n=44,618), their naturally conceived siblings (n=8,462) and matched naturally conceived population controls (n=89,072) using UK birth and hospital records (2002–2009). ART singletons and twins showed higher risks of hospitalisation for adverse perinatal events compared with population controls (risk ratio [RR]: 1.30, 95% CI 1.26-1.34, and RR 1.01, 95% CI 0.99-1.03, respectively), but no increased risk was observed in within-sibling comparisons. Similar patterns were seen for diagnoses related to length of gestation and foetal growth, birth trauma, respiratory and cardiovascular disorders and infections, and were also consistent across ART subtypes (IVF vs ICSI), however with greater risks noted for fresh versus frozen embryo transfers.

2.13. A cohort study of mothers with two pregnancies between 2000 and 2018 was undertaken to (Shalev-Ram *et al.*, 2024) to compare perinatal outcomes in siblings conceived using different methods, namely IVF with autologous eggs, IVF with donor eggs and natural conception. Cohort A compared two natural conceptions with one natural conception followed by (autologous) IVF, both groups having 1,080 women. Cohort B compared two natural conceptions with one natural conception followed by oocyte donation IVF with 94 women in each group. The perinatal outcomes measured included small for gestational age (SGA) and preterm birth (PTB), while secondary outcomes of low birth weight (LBW), very low birth weight (VLBW), and large for gestational age (LGA) were also measured. Findings for cohort A included: lower gestational age at delivery in natural conception followed by IVF (38.1 weeks) compared to two natural conceptions (39.1 weeks), higher rates of prematurity <37 weeks (12% vs. 3.5%) and SGA (5.4% vs. 3.4%) in IVF group and adjusted odds ratios (a OR) for PTB: 3.32; for SGA: 1.88. Findings for Cohort B included no significant differences in PTB <37 weeks and SGA between natural conception and donor egg groups, but a higher rate of LGA in the donor egg group (24% vs. 16.5%). The authors concluded that IVF with autologous eggs is associated with higher risks of prematurity and SGA compared to natural conception, whereas donor egg IVF shows no significant differences except for a higher rate of LGA.

Twin pregnancies

2.14. A retrospective cohort study by (Tang *et al.*, 2024) investigated the impact of IVF and gestational weight gain (GWG) on pregnancy outcomes (2,992 twin pregnancies), categorising participants by conception method and GWG levels. Both IVF and inappropriate GWG were independently associated with increased risks of adverse outcomes such as NICU, with a stepwise risk increase for intrahepatic cholestasis of pregnancy, respiratory failure, respiratory distress, pre-eclampsia, maternal intensive care unit admission, and postpartum haemorrhage when these factors were combined. No significant interaction between IVF procedures and disparate GWG levels was identified in relation to adverse outcomes.

2.15. A meta-analysis by (Marleen *et al.*, 2024) included 111 studies (802,462 pregnancies) and quantified the risk of adverse maternal and perinatal outcomes among twin pregnancies conceived following ART compared with non-ART and natural conception. ART- conceived twin

pregnancies were associated with higher risks of preterm birth (both <34 and <37 weeks), hypertensive disorders, gestational diabetes, and caesarean delivery compared to non-ART twins and natural conception. ART twins also showed increased risks for congenital malformations, birthweight discordance, respiratory distress syndrome, and neonatal intensive care unit (NICU) admission. However, ART twins had lower risks for certain perinatal complications, including stillbirth, small for gestational age, and twin–twin transfusion syndrome, compared to non-ART twins and naturally conceived twins.

2.16. A cohort study by (Bone *et al.*, 2024) examined the association between BMI and twin birth and the role of ART as a potential mediator in this association (524,845 deliveries). Underweight women had 16% fewer twins compared with women with normal BMI (adjusted risk ratio [aRR], 0.84; 95%CI 0.74-0.95), while women with overweight, class I obesity, class II obesity, and class III obesity had 14%(aRR, 1.14; 95%CI 1.07-1.21), 16%(aRR, 1.16; 95%CI 1.06-1.27), 17%(aRR, 1.17; 95% CI 1.02-1.34), and 41%higher rates (aRR, 1.41; 95%CI 1.19-1.66), respectively. The proportion of women who conceived by ART increased with increasing BMI, and ART was associated with nearly a 12-fold higher rate of twin delivery (aRR, 11.80; 95%CI 11.10-12.54). In women with a BMI 30 – 40, approximately one-quarter of this association was explained by higher use of ART; with no evidence of such mediation in women with BMI of > 40.

2.17. A meta-analysis by (Chen *et al.*, 2024) analysed 18 cohort studies involving 10,485 women with dichorionic diamniotic twin pregnancies to compare maternal and neonatal outcomes between pregnancies conceived through ART and those spontaneously conceived (SC). ART-conceived pregnancies had higher risks of maternal complications, such as preeclampsia, gestational diabetes, and caesarean delivery, as well as slightly increased risks of neonatal respiratory distress syndrome, congenital malformations, and NICU admissions, though the absolute risks remained relatively low.

2.18. A retrospective study by (Liu *et al.*, 2024a) analysed pregnancy outcomes of monochorionic diamniotic (MCDA) and dichorionic diamniotic (DCDA) twin pregnancies conceived through ART versus natural conception. Results showed that MCDA pregnancies conceived by ART had higher rates of premature delivery, lower neonatal weights, placenta previa, and lower twin survival rates than naturally conceived MCDA pregnancies. Similarly, naturally conceived DCDA pregnancies had better outcomes—including lower preterm birth rates, higher neonatal weights, and twin survival rates—compared to both ART-conceived DCDA pregnancies and DCDA pregnancies reduced from higher-order multiples.

2.19. A study by (Lin *et al.*, 2024a) investigated maternal and perinatal risks associated with monozygotic twin (MZT, n=164) or dizygotic twin (DZT, n=6,101) cases following FET. There was an increased risk of neonatal death among FET-MZT (adjusted OR [aOR] 4.95, 95% CI 1.41–13.2). Females with MZT pregnancies exhibited an elevated risk of preterm premature rupture of the membranes (aOR 2.42, 95% CI 1.54–3.70). MZT were also associated with higher odds of preterm birth (prior to 37 weeks) (aOR 2.31, 95% CI 1.48–3.67), low birth weight (aOR 1.92, 95% CI 1.27–2.93), and small for gestational age (aOR 2.18, 95% CI, 1.21–3.69). The effect of MZT on neonatal death was partially mediated by preterm birth and low birth weight ($P < 0.05$).

2.20. This study by (Lin *et al.*, 2024b) sought to investigate the likelihood of adverse neonatal outcomes of twins following ART compared to non-ART twins. A retrospective population study was undertaken using the Australian National Perinatal Data Collections (NPDC) which included 19,662 twins of ≥20 weeks gestational age or ≥ 400 g birthweight. Maternal outcomes

and neonatal outcomes (preterm birth, low birth weight, resuscitation and neonatal death) were compared. Researchers found pregnancy-induced hypertension and gestational diabetes were significantly higher for ART mothers than non-ART mothers (12.2% vs. 8.4%, $p < 0.01$) and (9.7% vs. 7.5%, $p < 0.01$). They also found that other differences including a higher rate (2.0%) of monozygotic twins for ART than non-ART (1.1%) and higher rates of preterm birth (AOR 1.13, 95% CI: 1.05–1.22), low birth weight (AOR 1.13, 95% CI: 1.05–1.22), and resuscitation (AOR 1.26, 95% CI: 1.17–1.36) for ART versus non-ART twins. Liveborn ART twins had 28% (AOR 1.28, 95% CI 1.09–1.50) increased odds of having any adverse neonatal outcome compared to liveborn non-ART twins, especially for opposite-sex ART twins (AOR 1.42, 95% CI 1.11–1.82). The authors concluded that as ART twins had higher rates of adverse outcome, special prenatal care is recommended, and couples seeking ART should be informed of these risks.

Fresh versus frozen embryo transfer

2.21. A meta-analysis by (Tocariu *et al.*, 2024) looked at 20 studies and 171,481 participants analysed neonatal outcomes following transfer of fresh and frozen embryos (fresh ET vs. FET) in IVF/ICSI cycles. Preterm birth rates were significantly increased with fresh ET compared to FET (odds ratio [OR] 1.26, 95% CI 1.18–1.35), as well as greater odds of a low birth weight (OR 1.37, 95% CI 1.27–1.48) and small-for-gestational-age infants (OR 1.81, 95% CI 1.63–2.00). In contrast, FET can result in macrosomic (OR 0.59, 95% CI 0.54–0.65) or large-for-gestational-age infants (OR 0.64, 95% CI 0.60–0.69). No significant difference was observed regarding congenital malformations or neonatal death rates.

2.22. A study by (Waldaufova *et al.*, 2024) analysed a dataset for all deliveries in the Czech Republic (2013-2018) obtained from the National Registry of Reproduction Health to determine the risk of low birth weight according to ART method (IVF with fresh ET, FET or oocyte donation). Women who underwent IVF with fresh ET and those undergoing oocyte donation cycles had a higher risk (OR, 95% CI) of having a child with a low birth weight than women who received FET (1.30, CI 1.15–1.48 and 1.52, CI 1.17–1.97, respectively).

Embryo biopsy

2.23. A single centre study by (Zhao *et al.*, 2024) investigated the effect of trophectoderm (TE) biopsy on metabolic outcomes of children conceived through preimplantation genetic testing (PGT) compared to those conceived via IVF or ICSI without PGT. Using data from 1,267 children and generalised estimating equations to account for confounders, the results revealed no significant differences in metabolic parameters between PGT children and their IVF or ICSI counterparts aged 1 to 5 years.

Donor versus partner sperm

2.24. No studies were identified in the search period.

Metabolic and reproductive function of ART-conceived men

2.25. No studies were identified in the search period.

Cardio-metabolic outcomes

2.26. A retrospective cohort study by (Zhang *et al.*, 2024a) analysed the association of paternal obesity with alterations in cardiometabolic profile in ART-conceived offspring (2,047 singleton offspring, aged 4-10 years). Compared with offspring of fathers with normal weight, multivariable-adjusted mean differences for offspring BMI z-score were 0.53 (95% CI 0.37-0.68) for obese fathers, 0.17 (95% CI 0.05-0.30) for overweight fathers, and −0.55 (95% CI −0.95–0.15) for underweight fathers; corresponding values for systolic blood pressure z-score were 0.21(95% CI 0.07-0.35), 0.10 (95% CI −0.01-0.21), and −0.24 (95% CI −0.59-0.11), and corresponding values for insulin resistance z-score were 0.31 (95% CI 0.16-0.46), 0.09 (95% CI −0.02-0.21), and −0.11 (95% CI −0.48-0.28), respectively. Between 57.48% to 94.75% of the identified associations among paternal obesity and offspring cardiometabolic alterations might be mediated by offspring BMI.

2.27. A study by (Asserhøj *et al.*, 2024) evaluated blood pressure (BP) and lipid profiles in children aged 7–10 years (n=606) conceived via FET (n=200), fresh embryo transfer (fresh-ET) (n=203), and natural conception (NC) (n=203) as part of the 'Health in Childhood following Assisted Reproductive Technology' (HiCART) cohort. There was a higher birthweight in both boys and girls conceived via FET compared to naturally conceived children (mean difference 0.35 standard deviation scores [SDS] for both genders). FET-conceived girls showed higher systolic BP (0.25 SDS, 95% CI 0.03–0.47) and heart rate (4.53 bpm, 95% CI 0.94–8.13) than fresh-ET-conceived girls. Boys in the FET group showed a slightly more favourable lipid profile compared to boys in the fresh-ET and NC groups. However, no significant differences in BP or heart rate were observed for boys across groups.

2.28. A prospective cohort study by (Zhang *et al.*, 2024b) investigated the association between large for gestational age (LGA) and cardiovascular metabolic health in ART-conceived children aged between 0.4 and 9.9 years. (4,138 born LGA and 9,910 born appropriate for gestational age [AGA]). After adjusting for covariates, LGA children conceived through ART were shown to have higher BMI, blood pressure, fasting blood glucose, fasting insulin, and homeostatic model assessment of insulin resistance values. The odds of overweight and insulin resistance were also higher in LGA subjects. LGA offspring had BMI and BMI z-scores that were 0.48 kg/m2 and 0.34 units greater than those of AGAs, respectively. The effect of LGA on BMI was identified as early as infancy and remained consistently significant throughout pre-puberty.

2.29. A meta-analysis by (Yeung *et al.*, 2024) included 34 reports and compared blood pressure measures of offspring conceived by ART (n=5,229) and non-ART-conceived offspring (n=8,509). Unadjusted analyses showed no significant standardised mean differences (SMD) in systolic (0.06 per SD of mmHg, 95% CI -0.05, 0.18) or diastolic blood pressure (0.11, 95% CI -0.04, 0.25), with high heterogeneity (I^2 = 76% and 87%, respectively). Adjusted analyses from 12 reports (n=2,242 ART; n=37,590 non-ART) similarly found no significant SMD in systolic (-0.03, 95% CI -0.13, 0.08) or diastolic blood pressure (0.02, 95% CI -0.12, 0.16) despite high heterogeneity. Treatment type, birth year, child age, or study location did not modify the results.

2.30. A retrospective cohort study by (Piemonti *et al.*, 2024) relationship between congenital heart diseases and three conception groups: IVF (n=30), ICSI (n=38), and natural conception, NC (n=588) pregnancies. The estimated risk of left ventricular outflow tract, valvular, conotruncal, and atrioventricular septal defects was lower in the IVF group compared to NC. The estimated risk of valvular and atrioventricular septal defects was lower in the ICSI group vs NC. Conversely, the risk for right heart anomalies was higher both in the IVF and ICSI groups compared to NC. Heart rhythm diseases were more frequent in IVF pregnancies. When

comparing ART methods, valvular defects, conotruncal defects, and right heart anomalies were more frequently observed in the ICSI group, while atrioventricular septal defects were more common in the IVF group.

2.31. A prospective cohort study by (Zhou *et al.*, 2024) compared the metabolic profiles of children (aged 2-5 years) born after FET (n = 2,181) versus fresh embryo transfer (ET, n = 2,065) with a mean follow-up of 3.6 years. No significant differences were observed in fasting blood glucose, fasting insulin, Homeostatic Model Assessment of Insulin Resistance Index, total cholesterol, triglycerides, low-density lipoprotein-cholesterol, and high-density lipoprotein-cholesterol levels between offspring conceived by FET and fresh ET in adjusted model (adjusted for parental age, parental body mass index, parental education level, paternal smoking, parity, offspring age and sex). These results remained consistent across subgroup analyses considering offspring age, the stage of embryo transfer, and the mode of fertilisation.

Congenital malformations and birth defects

2.32. A cohort study by (Sargisian *et al.*, 2024) used data from the Committee on Nordic ART and Safety (CoNARTaS) – originating from national ART and medical birth registry data that were cross-linked with data from other health and population registries – to assess the risk of congenital heart defects (CHDs) in children conceived via ART versus spontaneous conception, SC (7,747,637 live births in Denmark, Finland, Norway, and Sweden). Major CHDs were more common in ART children than SC children (1.84% vs 1.15%, adjusted odds ratio [AOR] 1.36, 95% CI 1.31-1.41). Severe CHDs were also more prevalent in ART children (0.35% vs. 0.26%, AOR 1.30, 95% CI 1.20-1.42). Risk was similar across ART methods (IVF vs. ICSI; fresh vs. frozen embryo transfer) and was highest among multiples.

2.33. A retrospective cohort study by (Appiah *et al.*, 2024) used National Vital Statistics System data from 9.6 million singleton live births (2016–2022) to investigate the association between infertility treatments and cyanotic congenital heart defects (CCHD). Results showed that infertility treatments, including both ART and non-ART, were associated with an increased risk of CCHD (OR 2.06; 95% CI 1.82–2.33) compared to natural conception after adjusting for confounders. This association did not differ by the type of infertility treatment (ART versus other infertility treatments) (OR 1.04, 95% CI 0.82-1.33) and remained consistent after adjusting for potential confounders and addressing biases.

2.34. A population-based cohort study by (Venetis *et al.*, 2023) analysed 851,984 infants in the first two years of their life to examine congenital anomaly (CA) risks in relation to fertility treatment and underlying infertility. The authors calculated adjusted risk difference (aRD) in CA of infants conceived through fertility treatment compared with two naturally conceived (NC) control groups—those with and without a parental history of infertility (NC-infertile and NC-fertile). After accounting for infertility, the ART-conceived singleton infants (n = 31,256) had a higher risk of major genitourinary abnormalities compared to NC-fertile singleton (n = 747,018) control infants (aRD 19.0 per 10,000 births, 95% CI 2.3-35.6) or NC-infertile singleton (n = 36,251) control infants (aRD, 22 cases per 10000 births, 95% CI 4.6-39.4), indicating that ART remained an independent risk. An increased major genitourinary abnormalities risk was particularly noted after ICSI in cases without male infertility (aRD, 47.8 cases per 10000 singleton births, 95% CI 12.6 to 83.1), while IUI with ovulation induction treatments showed no significant CA risk elevation.

Risk of cancer

2.35. A cohort study by (Rios *et al.*, 2024) used the French National Mother-Child Register (EPI-MERES), built from data of the French National Health Data System, assessed the risk of cancer among children born after medically assisted reproduction, MAR (n=260,236) representing 3.1% of a larger cohort of 8,526,306 children. Of 9,256 cancer cases identified over a median 6.7-year follow-up, cancer risk (hazard ratio, HR) did not significantly differ between naturally conceived children and those conceived via fresh embryo transfer (ET) (HR 1.12, 95% CI 0.96-1.31), FET (HR 1.02, 95%CI 0.78-1.32), or artificial insemination (HR 1.09, CI 0.86-1.38). However, FET was associated with a higher risk of acute lymphoblastic leukaemia (HR 1.61, risk difference [RD] 23.2 per million person-years). Among children born between 2010 and 2015, fresh ET was associated with an increased leukaemia risk (HR 1.42, RD 19.7 per million person-years).

2.36. A Norwegian registry based study covering all children born between 1984 and 2022 was undertaken by (Oakley *et al.*, 2024) to see if the risk of developing childhood cancer varied by sex for children conceived by ART. The study found sex- and age-specific associations with certain childhood cancers in children conceived using ART, which were not evident in overall combined analyses. The cumulative incidence of cancer was higher in children conceived by ART (IVF/ICSI) than in those not conceived via ART (21.5 vs 17.5 per 100 000 person-years, P = 0.04), and especially higher in boys conceived with ICSI or after cryopreserved embryo transfer. When combining all age groups, both sexes and all cancer types, there was little evidence of increased cancer risk with ART (adjusted hazard ratio (aHR) 1.13, 95% CI 0.94-1.36). However, differences were found when stratifying by age and sex. From age 5-9 years, ART-conceived children had a higher overall risk of cancer (aHR 1.53, 95% CI 1.06-2.20), with a slightly higher estimate in boys (aHR 1.73, 95% CI 1.09-2.74), than in girls (aHR 1.28, 95% CI 0.70-2.33). The risk was not higher up to age 5 years, or after age 10 years. In combined analyses, there was no overall increased risk after ICSI. When stratifying by sex, a higher risk was seen after ICSI for boys (aHR 1.69, 95% CI 1.18-2.42), but not for girls (aHR 0.65, 95% CI 0.37-1.16). The combined risk after cryopreservation (aHR 1.42, 95% CI 0.95-2.13) was driven by a higher risk in boys (aHR 1.79, 95% CI 1.09-2.94), while no evidence of an association was found in girls (aHR 1.01, 95% CI 0.50-2.03). No increased risk was seen with IVF or after fresh transfer for either boys or girls. The authors caution that childhood cancer is a rare outcome (0.25% of children have a cancer diagnosis under 18), and some analyses of cancer subtypes were likely underpowered. However, the results of the study suggest some age and sex-specific differences in childhood cancer diagnoses for children conceived using ART. The authors say that their findings require further study with consideration of possible underlying sex-specific mechanisms related to ART and different childhood cancers.

Neurodevelopment, mental, social and cognitive development

2.37. A study by (Wang *et al.*, 2024) analysed neurodevelopment at 1 year of age in 3,840 children, including 1,906 conceived through ART, from the Jiangsu Birth Cohort. ART-conceived singletons had a lower risk (adjusted risk ratios [RR], 95% CI) of noncompetent development in cognition (0.66, 0.53-0.82), receptive communication (RR 0.76, 0.64-0.91), and expressive communication (RR 0.69, 0.51-0.93) but an increased risk of delayed gross motor development (RR 1.41, 1.11-1.79) compared to non-ART peers. ART twins showed greater delays in several

domains, and ART singletons from "poor" quality embryo transfers had higher risks of noncompetent development in receptive communication (RR 1.50, 1.05-2.14) and gross motor skills (RR 1.55, 1.02-2.36).

2.38. A Danish nationwide registry-based cohort study by (Angel *et al.*, 2024) investigated the risk of children conceived via ART (n=57,964) needing medication for neurodevelopmental or behavioural disorders compared to non-ART conceived children (n= 1,183,070). ART-conceived children had a higher likelihood of being prescribed such medications (adjusted odds ratio [aOR] 1.15; 95% CI 1.09–1.20), with varying associations across treatment types, partially mediated by birth weight. Sibling analysis showed no increased risk based on birth order between ART and non-ART conceptions.

2.39. A meta-analysis by (Hwang *et al.*, 2024) examined the association between ART and attention-deficit/hyperactivity disorder (ADHD) using data from 8 studies comprising 10,176,148 individuals. Results showed a slight increase in ADHD risk in ART-conceived children (pooled hazard ratio [HR] 1.08, 95% CI 1.03–1.13) compared to non-ART group, but the authors argue that the limited effect size and study heterogeneity suggest cautious interpretation of the findings.

2.40. A population-based cross-sequential cohort study by (Islam *et al.*, 2024) the impact of ART (including IVF and other fertility drugs) on mental health outcomes (ie autism, ADHD, anxiety and/or depression) in 1,735 Australian adolescents aged 18–19 years using 'The Longitudinal Study of Australian Children' (LSAC) data. Approximately 5% of mothers (n = 89) used ART to become pregnant, and 22% of adolescents (n = 384) had a mental disorder. Maternal smoking during pregnancy (OR 1.79, 95% CI1.22–2.63), postnatal depression (OR 2.19, 95% CI 1.55–3.11), and maternal unemployment during pregnancy (OR 1.68, 95% CI 1.26–2.24) increased the likelihood of their offspring having mental disorders compared to their respective counterparts. However, there was no relationship between ART and children developing a mental disorder in the LSAC population.

Other health outcomes in ART-conceived children

2.41. A nationwide cohort study by (Ye *et al.*, 2024) assessed the risk of imprinting disorders in children conceived through ART in Sweden from 1997 to 2017, using data from national registers. Among 2,084,127 liveborn singletons, ART-conceived children had a slightly higher risk of imprinting disorders compared with all other children (hazard ratio [HR], 1.84; 95% CI, 1.38–2.45), particularly Beckwith-Wiedemann syndrome (BWS) and Prader-Willi/Silver-Russell syndromes (PWS/SRS), with increased risks observed when ICSI and cryopreserved embryos were used (weighted hazard ratio [wHR], 4.60 for PWS/SRS; 6.69 for BWS). After adjusting for parental background factors, the association was partially attenuated (wHR, 1.50; 95% CI, 0.97–2.32) but remained in the weighted comparison restricted to children of couples with known infertility (wHR, 1.52; 95% CI, 1.05–2.21).

2.42. A meta-analysis by (Cavero-Ibiricu *et al.*, 2024), including 16 studies, examined the risk of cerebral palsy (CP) after ART compared with that in those spontaneously conceived (SC) and this risk in single, multiple, and preterm births. Significantly high risk of CP was found (odds ratio [OR] 1.27; 95% CI 1.12 – 1.43) in children born through ART compared with those SC. This risk increased in singletons (OR 1.48; 95% CI 1.23 – 1.79) but disappeared in multiple (OR 1.05; 95% CI 0.93 – 1.18) and preterm births (OR 1.09; 95% CI 0.87 – 1.37).

2.43. A retrospective single centre cohort study by (Liu *et al.*, 2024b) compared the risk of asthma between 3-6 years old singletons conceived via ART (n=3,227) and naturally conception (NC) (n=1,206). The risks of childhood asthma in ART-conceived singletons were similar to those of NC singletons (adjusted OR [aOR] 0.66, 95% CI 0.44–1.03). The results were similar in multiple sensitivity analyses, and there were no clear differences in asthma risks according to the method of ART. Mediation analysis revealed a significant positive indirect effect of neonatal intensive care unit (NICU) admission (standard path coefficient, b=0.025) and a negative indirect effect of breastfeeding (b=–0.012) on the association between ART and asthma in singleton offspring.

2.44. A study by (Kristjansson *et al.*, 2024) investigated sex-specific epigenetic differences in cord-blood DNA methylation variation by mode of conception (456 ART- conceived versus 507 naturally conceived girls, and 503 ART-conceived and 473 naturally conceived boys). Authors identified 37 differentially methylated CpGs according to ART-conception among girls, and 70 differentially methylated CpGs according to ART-conception among boys, when they used a 1% false discovery rate to account for multiple testing. Ten CpGs were differentially methylated according to conception by ART in both sexes. Among the genes that were associated with these CpGs, BRCA1; NBR2 gene (two CpGs) was hypermethylated in girls while the APC2 (two CpGs) and NECAB3; ACTL10, (four CpGs) related to cellular signalling were hypomethylated in boys.

2.45. A Nordic register-based linking cohort study by (Kyhl *et al.*, 2024) used the CoNARTaS data from the medical birth registries and national patient registries available in the Nordic countries to examine the risk of Type 1 diabetes (DM1) in children born after ART (n= 76,184 singletons) compared to naturally conceived children (n= 4,403,419). The median follow-up was 8.3 and 13.7 years in the ART and non-ART group, respectively. Results showed no significant difference in DM1 risk between ART and non-ART groups overall (adjusted OR 0.98; 95% CI 0.86–1.11), except in the youngest cohort (2011–2015) where ART was associated with a slightly higher risk. There was no significant risk variation by ART method.

2.46. A prospective cohort study by (Nguyen *et al.*, 2024) compared developmental outcomes at 12 months between children conceived through ICSI (n=177) and conventional IVF, cIVF (n=145) in couples with non-male factor infertility, using the Vietnamese version of the Ages & Stages Third Edition Questionnaires (ASQ-3) and Development Red Flags questionnaires. The results showed no significant differences in abnormal ASQ-3 scores (16.9% vs. 13.1%, $P = 0.34$) or Red Flag signs (6.2% vs. 9.2%, $P = 0.36$) between ICSI and cIVF groups.

2.47. A study by (Matsumoto *et al.*, 2024) used data from a nationwide birth cohort (n=2140 children) linked with perinatal database to compare long-term health and development outcomes (up to 9 years of age) between IVF-conceived and non-IVF-conceived children in Japan. After adjusting for confounding factors, no significant differences were observed between IVF-conceived and naturally conceived children for most outcomes, including hospitalisation, obesity, and developmental milestones. IVF-conceived children showed a slightly lower risk of attention problems at 8 years (adjusted Risk Ratio [aRR]: 0.73, 95% CI 0.53–1.00). In subgroup analyses, IVF-conceived term children and singletons demonstrated reduced risk of cognitive delays at 5.5 years (aRR 0.31, 95% CI 0.10–0.96 and aRR 0.37, 95% CI 0.14–0.98, respectively).

2.48. A study by (Williams et al., 2024) investigated the risk of developing Langerhans cell histiocytosis (LCH) in children born after ART using data from the HFEA linked to National

Registry of Childhood Tumours. Calculated person-years at risk were used in conjunction with the incidence of LCH in the general population to determine the expected number of cases if the cohort had the same incidence as the general population with similar age and sex, over the same calendar years. In total, 118,155 children born after ART contributed 796,633 person-years follow-up (average follow-up 6.74 years). Eight cases of LCH were identified, compared with 3.75 cases expected (standardised incidence ratio [SIR] 2.135, 95% CI 0.92-4.21). Significantly more cases were associated with ICSI (SIR 4.02, 95% CI 1.31-9.39) and male factor infertility (SIR 5.41, 95% CI 1.47-13.84). Most cases of LCH had single-system disease (n = 6).

2.49. A study by (Mertens et al., 2024) investigated the effect of mitochondrial DNA (mtDNA) variants as contributors to birthweight differences. The authors deep-sequenced the mtDNA of 451 ART and spontaneously conceived (SC) individuals, 157 mother-child pairs and 113 individual oocytes from either natural menstrual cycles or after ovarian stimulation (OS). Results showed that ART individuals carried a different mtDNA genotype than SC individuals, with more de novo non-synonymous variants. The authors argue that these variants, along with rRNA variants, correlate with lower birthweight percentiles, independent of conception mode. The further discuss that the higher occurrence of these variants in ART individuals stems from de novo mutagenesis associated with maternal aging and OS-induced oocyte cohort size.

2.50. A systematic review by (Talbot *et al.*, 2024) analysed the psychological experiences of donor conceived (DC) people through childhood and adulthood. It included 50 studies with 4,666 DC participants and revealed that most comparative studies (14 out of 19) reported similar or improved outcomes for DC individuals in well-being and relationships, though a minority identified higher rates of worse outcomes (increased autism spectrum disorder and attention deficit hyperactivity disorder, addiction issues, mental illness, disruptive behaviour and identity problems). Qualitative data highlighted themes of identity formation, mistrust and concerns regarding genetic heritage, with early disclosure of DC status associated with better psychological outcomes, though evidence on adulthood outcomes remains limited.

2.51. A case-control study by (Ilmuratova *et al.*, 2024) in Kazakhstan compared the immune profiles of 120 children conceived via ART to 132 naturally conceived (NC) children under five. ART-conceived children showed distinct immunological differences, including lower IgA and IgG levels, absolute lymphocytosis, and altered T-cell activity, with children conceived through FET showing higher T-cytotoxic and active T-lymphocyte levels.

Culture media and ART

2.52. No studies were identified in the search period.

3. Conclusions

3.1. The professional community highlights the need for the continuous surveillance of the short- and long-term consequences of ART treatments to be prioritised by healthcare authorities, which can be achieved by analysis and publication of national ART data linked to other health registries (Pinborg *et al.*, 2024).

3.2. The literature search performed since September 2023 identified studies whose results point to a higher risk for adverse maternal and perinatal outcomes in twin pregnancies. Two large national linkage studies show increased risk for congenital heart defects in ART- conceived

children. Other studies looked at effects of parental obesity, birth weight and fresh vs frozen embryo transfer on cardio-metabolic health of children conceived through ART; while some studies investigated the effects of ART on occurrence of imprinting disorders, cerebral palsy, altered immunology profile, asthma and type 1 diabetes incidence in offspring. Overall, studies highlight the limited effect size of observed outcomes and the heterogeneity of data as limiting factors; they also note that absolute risks associated with different adverse outcomes remain low.

3.3. No studies on health outcomes of children following gamete donation or on the effects of culture media on offspring health were identified for the search period.

4. Recommendations

4.1. Members are asked to:

- Advise the executive if they are aware of any other recent developments.
- Review whether any outputs from the HFEA are required addressing health outcomes of children conceived from ART.
- Advise on whether a new related topic of 'Health outcomes for ART patients (including gestational surrogates and egg donors)' should be added as a new prioritised topic.

5. References

Angel P, Hermansen M, Ramlau-Hansen CH, Gaml-Sørensen A, Kristensen DM, Lindahl-Jacobsen R. Neurodevelopmental or behavioural disorders in children conceived after assisted reproductive technologies: A nationwide cohort study. Fertil Steril [Internet] 2024;Available from: http://www.ncbi.nlm.nih.gov/pubmed/39426700.

Appiah D, Sang J, Olayemi OE, Broni EK, Baykoca-Arslan B, Ebong IA, Kim C. Infertility treatments and cyanotic congenital heart defects among livebirths in the USA: Findings from a contemporary cohort. Human Reproduction 2024;39:2115–2123. Oxford University Press.

Asserhøj LL, Mizrak I, Lebech Kjaer AS, Clausen TD, Hoffmann ER, Greisen G, Main KM, Madsen PL, Pinborg A, Jensen RB. Blood pressure and lipid profiles in children born after ART with frozen embryo transfer. Hum Reprod Open [Internet] 2024;2024:hoae016. Oxford University Press.

Bartsch L, Hämmerle M, Putschögl S, Hartmann B, Kirchengast S. Assisted reproductive technology (ART) is not an independent risk factor for breech presentation among singleton term births in Vienna, Austria. J Biosoc Sci [Internet] 2024;1–5. Cambridge University PressAvailable from: http://www.ncbi.nlm.nih.gov/pubmed/38533532.

Bone JN, Joseph KS, Magee LA, Wang LQ, John S, Bedaiwy MA, Mayer C, Lisonkova S. Obesity, Twin Pregnancy, and the Role of Assisted Reproductive Technology. JAMA Netw Open 2024; American Medical Association.

Carneiro FAT, Leong V, Nóbrega S, Salinas-Quiroz F, Costa PA, Leal I. Are the children alright? A systematic review of psychological adjustment of children conceived by assisted reproductive technologies. Eur Child Adolesc Psychiatry 2024;33:2527–2546. Springer Science and Business Media Deutschland GmbH.

Cavero-Ibiricu A, Canelas-Fernández J, Gómez-Acebo I, Alonso-Molero J, Martínez-Jiménez D, Llorca J, Cabero-Perez MJ, Dierssen-Sotos T. Association Between Assisted Reproductive Technology and Cerebral Palsy: A Meta-Analysis. Pediatr Neurol 2024;152:115–124. Elsevier Inc.

Chen L, Dong Q, Weng R. Maternal and neonatal outcomes of dichorionic twin pregnancies achieved with assisted reproductive technology: meta-analysis of contemporary data. J Assist Reprod Genet 2024;41:581–589. Springer.

Faa G, Manchia M, Fanos V. Assisted Reproductive Technologies: A New Player in the Foetal Programming of Childhood and Adult Diseases? Pediatr Rep [Internet] 2024;16:329–338. Multidisciplinary Digital Publishing Institute (MDPI).

Hwang S, Jung J, Moon H, Ko DS, Kim H-W, Yoon J-P, Kim WK, Seol A, Kim K, Kim YH. The impact of assisted reproductive technologies on ADHD: A systematic review and meta-analysis. Asian J Psychiatr [Internet] 2024;99:104125. Elsevier B.V.

Ilmuratova S, Lokshin V, Prodeus A, Manzhuova L, Nurgaliyeva Z, Kussainova F, Bazarbaeva A, Nekhorosheva V, Abshekenova A. Immune profiling of ART-conceived children in Kazakhstan: a case-control study. Front Pediatr [Internet] 2024;12:1447956.

Islam MI, Chaffey OA, Chadwick V, Martiniuk A. Mental health in children conceived by Assisted Reproductive Technologies (ARTs): Insights from a longitudinal study of Australian children. PLoS One 2024;19:. Public Library of Science.

Kristjansson D, Lee Y, Page CM, Gjessing H, Magnus MC, Jugessur A, Lyle R, Håberg SE. Sex differences in DNA methylation variations according to ART conception-evidence from the Norwegian mother, father, and child cohort study. Sci Rep [Internet] 2024;14:22904. Nature Research.

Kyhl F, Spangmose AL, Gissler M, Rönö K, Westvik-Johari K, Henningsen A-KA, Bergh C, Wennerholm U-B, Opdahl S, Forman J, et al. The risk of Type 1 diabetes in children born after ART: a Nordic cohort study from the CoNARTaS group. Hum Reprod Open [Internet] 2024;2024:hoae021. Oxford University Press.

Lin J, Zhang K, Wu F, Wang B, Chai W, Zhu Q, Huang J, Lin J. Maternal and perinatal risks for monozygotic twins conceived following frozen-thawed embryo transfer: a retrospective cohort study. J Ovarian Res 2024a;17:. BioMed Central Ltd.

Lin L, Yao T, Liao Q, Liu J, Huang L, Zheng L. Neonatal outcomes among twins born through assisted reproduction, compared to those born naturally. Medicine [Internet] 2024b;103:e40630.

Liu S, Xu Q, Qian J, Liu D, Zhang B, Chen X, Zheng M. Pregnancy outcomes of monochorionic diamniotic and dichorionic diamniotic twin pregnancies conceived by assisted reproductive technology and conceived naturally: a study based on chorionic comparison. BMC Pregnancy Childbirth 2024a;24:. BioMed Central Ltd.

Liu S, Zhou X, Wang W, Zhang M, Sun Y, Hu X, You J, Huang X, Yang Y, Feng G, et al. The risk of asthma in singletons conceived by ART: a retrospective cohort study. Hum Reprod Open [Internet] 2024b;2024:hoae041. Oxford University Press.

Marleen S, Kodithuwakku W, Nandasena R, Mohideen S, Allotey J, Fernández-García S, Gaetano-Gil A, Ruiz-Calvo G, Aquilina J, Khalil A, et al. Maternal and perinatal outcomes in twin pregnancies following assisted reproduction: a systematic review and meta-analysis involving 802 462 pregnancies. Hum Reprod Update 2024;30:309–322. Oxford University Press.

Matsumoto N, Mitsui T, Kadowaki T, Mitsuhashi T, Hirota T, Masuyama H, Yorifuji T. In vitro fertilization and long-term child health and development: nationwide birth cohort study in Japan. Eur J Pediatr [Internet] 2024;184:24.

Mertens J, Belva F, Montfoort APA van, Regin M, Zambelli F, Seneca S, Couvreu de Deckersberg E, Bonduelle M, Tournaye H, Stouffs K, et al. Children born after assisted reproduction more commonly carry a mitochondrial genotype associating with low birthweight. Nat Commun 2024;15:. Nature Research.

Nguyen NA, Nguyen NT, Tran VTT, Vo TTM, Uong TS, Nguyen HT, Nguyen NT, Nguyen DL, Pham TD, Nguyen DTN, et al. Developmental outcomes of children born through ICSI versus conventional IVF (cIVF) in couples with non-male factor infertility. Human Reproduction 2024;39:1558–1563. Oxford University Press.

Oakley LL, Kristjansson D, Munthe-Kaas MC, Nguyen HT, Lee Y, Hanevik HI, Romundstad LB, Lyle R, Håberg SE. Sex differences in childhood cancer risk following ART conception: a registry-based study. Human Reproduction [Internet] 2024;Available from: https://pubmed.ncbi.nlm.nih.gov/39724532/.

Ono M, Kuji N, Ueno K, Kojima J, Nishi H. The Long-Term Outcome of Children Conceived Through Assisted Reproductive Technology. Reproductive Sciences 2023; Institute for Ionics.

Piemonti L, Vettor L, Balducci A, Farina A, Contro E. Assisted reproductive technology and the risk of fetal congenital heart disease: insights from a tertiary-care referral center. Arch Gynecol Obstet 2024;310:2073–2080. Springer Science and Business Media Deutschland GmbH.

Pinborg A, Blockeel C, Coticchio G, Garcia-Velasco J, Santulli P, Campbell A. Speaking up for the safety of the children following frozen embryo transfer. Hum Reprod Open [Internet] 2024;2024:. Oxford Academic.

Pinborg A, Wennerholm UB, Bergh C. Long-term outcomes for children conceived by assisted reproductive technology. Fertil Steril 2023;120:449–456. Elsevier Inc.

Purkayastha M, Sutcliffe A, Brison DR, Nelson SM, Lawlor D, Roberts SA. Perinatal health in a cohort of children conceived after assisted reproduction in the UK: a population-based record-linkage study. BMJ Open [Internet] 2024;14:e091910.

Raja EA, Bhattacharya S, Maheshwari A, McLernon DJ. A comparison of perinatal outcomes following fresh blastocyst or cleavage stage embryo transfer in singletons and twins and between singleton siblings. Hum Reprod Open [Internet] 2023;2023:. Oxford Academic.

Rios P, Herlemont P, Fauque P, Lacour B, Jouannet P, Weill A, Zureik M, Clavel J, Dray-Spira R. Medically Assisted Reproduction and Risk of Cancer among Offspring. JAMA Netw Open 2024;7:E249429. American Medical Association.

Sargisian N, Petzold M, Furenäs E, Gissler M, Spangmose AL, Malchau Lauesgaard S, Opdahl S, Pinborg A, Henningsen A-KA, Westvik-Johari K, et al. Congenital heart defects in children born after assisted reproductive technology: a CoNARTaS study. Eur Heart J [Internet] 2024;Available from: http://www.ncbi.nlm.nih.gov/pubmed/39326528.

Shalev-Ram H, Hershko Klement A, Haikin-Herzberger E, Levi M, Rahav-Koren R, Wiser A, Miller N. Perinatal Outcomes in Siblings from Different Conception Methods: In Vitro Fertilization with Autologous Oocyte or Donor Egg vs. Unassisted Medical Conception. Fertil Steril 2024;

Sundrani D, Kapare A, Yadav H, Randhir K, Gupte S, Joshi S. Placental expression and methylation of angiogenic factors in assisted reproductive technology pregnancies from India. Epigenomics [Internet] 2025;17:21–31.

Talbot C, Hodson N, Rose J, Bewley S. Comparing the psychological outcomes of donor and non-donor conceived people: A systematic review. BJOG [Internet] 2024;131:1747–1759. John Wiley and Sons Inc.

Tang W-Z, Cai Q-Y, Wang Y-X, Shao L-Z, Zhang X, Li Z-M, Tian H, Liu T-H, Chen Y, Wang L. Comparative influence of inappropriate gestational weight gain on pregnancy outcomes in IVF-conceived and spontaneously conceived twin pregnancies. Int J Gynaecol Obstet [Internet] 2024; John Wiley and Sons LtdAvailable from: http://www.ncbi.nlm.nih.gov/pubmed/39244721.

Tocariu R, Niculae LE, Niculae A Ștefan, Carp-Velișcu A, Brătilă E. Fresh versus Frozen Embryo Transfer in In Vitro Fertilization/Intracytoplasmic Sperm Injection Cycles: A Systematic Review and Meta-Analysis of Neonatal Outcomes. Medicina (Lithuania) 2024;60:. Multidisciplinary Digital Publishing Institute (MDPI).

Venetis C, Choi SKY, Jorm L, Zhang X, Ledger W, Lui K, Havard A, Chapman M, Norman RJ, Chambers GM. Risk for Congenital Anomalies in Children Conceived With Medically Assisted Fertility Treatment. Ann Intern Med 2023;176:1308–1320. American College of Physicians.

Waldaufova E, Stastna A, Fait T. The low birth weights of newborns conceived using assisted reproduction technology. Bratislava Medical Journal 2024;125:137–143. Comenius University in Bratislava.

Wang W, Meng Q, Hu L, Du J, Xu B, Han X, Liu X, Zhou K, Ke K, Gan M, et al. Assisted reproductive technology and neurodevelopment in children at 1 year of age: a longitudinal birth cohort study. Am J Obstet Gynecol 2024; Elsevier Inc.

Williams DrCL, Bunch MrsKJ, Stiller MrC, Murphy DrMF, Botting DrBJ, Davies ProfessorMC, Luke ProfessorB, Lupo ProfessorPJ, Sutcliffe ProfessorAG. Langerhans cell histiocytosis in children born after assisted reproductive technology. Reprod Biomed Online 2024;49:104379. Elsevier.

Ye M, Reyes Palomares A, Iwarsson E, Oberg AS, Rodriguez-Wallberg KA. Imprinting disorders in children conceived with assisted reproductive technology in Sweden. Fertil Steril 2024; Elsevier Inc.

Yeung EH, Trees IR, Clayton PK, Polinski KJ, Livinski AA, Putnick DL. Infertility treatment and offspring blood pressure-a systematic review and meta-analysis. Hum Reprod Update [Internet] 2024;Available from: http://www.ncbi.nlm.nih.gov/pubmed/39375871.

Zeng Z, Wang Z, Yu P, Wang Y, Pei Y, Dai Y, Liu Y, Yang Y. The Association between Assisted Reproductive Technologies and Neurodevelopmental Disorders in Offspring: An Overview of Current Evidence. J Integr Neurosci 2024;23:. IMR Press Limited.

Zhang B, Ban M, Chen X, Zhang Y, Wang Z, Feng W, Zhao H, Li J, Zhang T, Hu J, et al. Associations between Paternal Obesity and Cardiometabolic Alterations in Offspring via Assisted Reproductive Technology. J Clin Endocrinol Metab [Internet] 2024a;. The Endocrine SocietyAvailable from: http://www.ncbi.nlm.nih.gov/pubmed/38375892.

Zhang G, Mao Y, Zhang Y, Huang H, Pan J. Assisted reproductive technology and imprinting errors: analyzing underlying mechanisms from epigenetic regulation. Hum Fertil 2023a;26:864–878. Taylor and Francis Ltd.

Zhang S, Luo Q, Meng R, Yan J, Wu Y, Huang H. Long-term health risk of offspring born from assisted reproductive technologies. J Assist Reprod Genet 2023b;. Springer.

Zhang Y, Dai K, Chen X, Cui L, Chen ZJ. Association between being large for gestational age and cardiovascular metabolic health in children conceived from assisted reproductive technology: a prospective cohort study. BMC Med 2024b;22:. BioMed Central Ltd.

Zhao J, Li S, Ban M, Gao S, Cui L, Yan J, Yang X, Li J, Zhang Y, Guan S, et al. Metabolic Profiles of Offspring Born From Biopsied Embryos from Toddlerhood to Preschool Age. J Clin Endocrinol Metab [Internet] 2024; The Endocrine SocietyAvailable from: http://www.ncbi.nlm.nih.gov/pubmed/38805186.

Zhou W, Feng W, Chang J, Hu J, Li F, Hu K, Jiao J, Xue X, Lan T, Wan W, et al. Metabolic profiles of children aged 2-5 years born after frozen and fresh embryo transfer: A Chinese cohort study. PLoS Med 2024;21:. Public Library of Science.

Annex A – Selected references referring to 1.6 on health outcomes for patients who underwent ART

FARHUD, D. D., ZOKAEI, S., KEYKHAEI, M., HEDAYATI, M., & ZARIF YEGANEH, M. (2021). In-Vitro Fertilization Impact on the Risk of Breast Cancer: A Review Article. *Iranian Journal of Public Health*. https://doi.org/10.18502/ijph.v50i3.5583

Gennari, A., Costa, M., Puntoni, M., Paleari, L., de Censi, A., Sormani, M. P., Provinciali, N., & Bruzzi, P. (2015). Breast cancer incidence after hormonal treatments for infertility: systematic review and meta-analysis of population-based studies. *Breast Cancer Research and Treatment*, *150*(2), 405–413. https://doi.org/10.1007/s10549-015-3328-0

Hershko Klement, A., Asali, A., Shalev Ram, H., Haikin-Herzberger, E., Shlezinger, R., Wiser, A., & Miller, N. (2024). Cancer-Related Morbidity Among Patients Conceiving Through Oocyte Donation: A Healthcare Registry Cohort Study. *Journal of Women's Health*, *33*(12), 1730–1734. https://doi.org/10.1089/jwh.2024.0248

Kramer, W., Schneider, J., & Schultz, N. (2009). US oocyte donors: a retrospective study of medical and psychosocial issues. *Human Reproduction*, *24*(12), 3144–3149. https://doi.org/10.1093/humrep/dep309

Klement, A. H., Asali, A., Ram, H. S., Haikin-Herzberger, E., Shlezinger, R., Wiser, A., & Miller, N. (2024). Cancer-Related Morbidity Among Patients Conceiving Through Oocyte Donation: A Healthcare Registry Cohort Study. Journal of Women's Health (2002), 33(12). https://doi.org/10.1089/JWH.2024.0248

Lerner-Geva, L., Rabinovici, J., & Lunenfeld, B. (2010). Ovarian Stimulation: Is There a Long-Term Risk for Ovarian, Breast and Endometrial Cancer? *Women's Health*, *6*(6), 831–839. https://doi.org/10.2217/WHE.10.67

Schneider, J., Lahl, J., & Kramer, W. (2017). Long-term breast cancer risk following ovarian stimulation in young egg donors: a call for follow-up, research and informed consent. *Reproductive BioMedicine Online*, *34*(5), 480–485. https://doi.org/10.1016/j.rbmo.2017.02.003

Söderström-Anttila, V., Miettinen, A., Rotkirch, A., Nuojua-Huttunen, S., Poranen, A.-K., Sälevaara, M., & Suikkari, A.-M. (2016). Short- and long-term health consequences and current satisfaction levels for altruistic anonymous, identity-release and known oocyte donors. *Human Reproduction*, *31*(3), 597–606. https://doi.org/10.1093/humrep/dev324

van den Belt-Dusebout, A. W., Spaan, M., Lambalk, C. B., Kortman, M., Laven, J. S. E., van Santbrink, E. J. P., van der Westerlaken, L. A. J., Cohlen, B. J., Braat, D. D. M., Smeenk, J. M. J., Land, J. A., Goddijn,

M., van Golde, R. J. T., van Rumste, M. M., Schats, R., Józwiak, K., Hauptmann, M., Rookus, M. A., Burger, C. W., & van Leeuwen, F. E. (2016). Ovarian Stimulation for In Vitro Fertilization and Long-term Risk of Breast Cancer. *JAMA*, *316*(3), 300. https://doi.org/10.1001/jama.2016.9389

Velez, M. P., Ivanova, M., Shellenberger, J., Pudwell, J., & Ray, J. G. (2024). Severe Maternal and Neonatal Morbidity Among Gestational Carriers. *Annals of Internal Medicine*, *177*(11), 1482–1488. https://doi.org/10.7326/M24-0417

Impact of stress on fertility treatment outcomes

Details about this paper

Area(s) of strategy this paper relates to:	The best care
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	6
Paper number:	HFEA (03/02/2025) 006
Meeting date:	3 February 2025
Author:	Rebecca Taylor, Scientific Policy Manager
Annexes	Annex 1: References

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • Consider the development in research into the impacts of stress on fertility treatment outcomes; • Advise the Executive if they are aware of any other recent developments, and; • Review whether any outputs from the HFEA are required
Resource implications:	TBD based out outputs recommended by the SCAAC
Implementation date:	NA
Communication(s):	TBD based out outputs recommended by the SCAAC
Organisational risk:	Low

1. Introduction

1.1. This paper covers research on the impact of stress in people undergoing fertility treatment on their treatment outcomes. Studies looking at stress levels of people with infertility, links between stress levels and the occurrence of infertility, and interventions to reduce stress in fertility patients that do not look at treatment outcomes, are excluded.

1.2. There is a complex relationship between stress and broader psychological well-being and infertility. Experiencing infertility can cause stress through emotional, social and financial burdens, and mental health disorders such as depression and anxiety can increase stress, which may impact fertility.

1.3. Patients undergoing fertility treatment frequently report high levels of stress and anxiety. There are a number of factors that may contribute to this including:

- The distress of wanting to conceive and experiencing infertility.
- Feelings of anger or injustice that other people are able to conceive apparently effortlessly.
- Feeling alone or isolated in their fertility struggles.
- The disruption fertility treatment can have on working, family and social life.
- Lack of understanding and/or support from friends, family, employers and wider society.
- Worries about the immediate and longer-term financial impact of fertility treatment.

1.4. Patients experiencing fertility problems sometimes report they are told that the high levels of stress they are experiencing may be preventing them from conceiving and "if you relax, it will happen" [1]. This can make patients feel like their infertility is their fault for being stressed, which can add to the distress of struggling to conceive[2].

1.5. A November 2024 study of fertility patients undertaken by Fertility Network UK found that infertility related trauma was more common than thought and highlighted the need to prioritise the emotional and mental health aspects of fertility care.

1.6. The HFEA recognises the importance of psychological support for fertility patients before, during and after any treatment. HFEA's Code of Practice requires clinics to develop a patient support policy to outline how the centre ensures that patients, donors and their partners (where applicable) receive appropriate psychosocial support from all staff they encounter before, during and after treatment. Clinics may offer psychological support to patients including specialist fertility counselling by qualified practitioners, as well as other forms of formal and informal psychological support, such as patient support groups or online forums.

1.7. The impact of stress on fertility treatment outcomes is a medium priority horizon scanning topic that was last discussed by the SCAAC in June 2022. At that meeting the Committee noted that:

- Objective study of this area was difficult due to the impact of confounding factors on stress, many of which may be outside of the control of clinics, making effective stress reduction tools difficult to identify.
- That it may be harmful or at least not helpful to fertility patients to link stress to treatment outcomes, and may even perpetuate stress.

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[1] Stop saying relax to people with infertility, Psychology Today, 26 April 2017
[2] Stop telling women who are trying to get pregnant to "just relax", Today's Parent, 10 May 2019

- Some members felt that, as a clear link between stress and fertility outcomes has not been established, there is no need for individual information for patients, and that specific medical advice may fall outside of the HFEA's regulatory remit.

1.8. This review highlights key developments in our understanding of the impact of stress on fertility treatment outcomes covering the period May 2022 to December 2024. This paper provides a summary of the findings described in published literature and is not an assessment of study validity.

2. Research outcomes

Impact found on fertility treatment outcomes

The impact of psychological factors including stress

2.1. A review by (Zhou et al., 2023) discusses how psychological distress (anxiety, depression, stress) in women undergoing IVF embryo transfer can negatively impact success by affecting immune and endocrine functions. The authors suggest that this distress may create a vicious cycle, worsening psychological pain and reducing IVF success rates. They also suggest that interventions like cognitive behavioural therapy, acupuncture, and yoga may help break this cycle, improving pregnancy and live birth rates. However, the authors note that the precise role of psychological factors in adverse IVF outcomes requires more rigorous research to establish causality, such as the relationship between anxiety, depression, abnormal thyroid function, and immune disorders at the mother-foetus interface.

2.2. A study aiming to examine the connection between certain psychological factors - anxiety, depression, motivation for parenthood, styles of coping with stress - and IVF outcomes was undertaken by (Andrea Ražić Pavičić et al., 2022). 100 women undergoing first time IVF were divided into groups based on positive or negative IVF outcomes and assessed using a general data questionnaire, Parenthood motivation scale, COPE Inventory, and Depression, Anxiety, Stress Scales. Key findings included that motivation for parenthood and coping styles (seeking emotional support, planning, active coping) significantly predict IVF outcomes. Higher scores in seeking emotional support and planning were correlated with negative outcomes, while higher scores in active coping were correlated with positive outcomes. Anxiety and depression were not significant predictors of IVF outcomes. The study underscores the importance of psychological factors in infertility treatment and suggests the need for tailored psychological support and educational programs for those facing infertility.

2.3. In the EARTH study (Mínguez-Alarcón et al., 2024) sought to assess if preconception perceived stress affects live birth, gestational age, and birthweight in women undergoing fertility treatment. This observational study involved women at Massachusetts General Hospital (2004-2019) whose preconception stress was measured using the Perceived Stress Scale 4 (PSS-4). Associations between stress and outcomes were analysed using regression models, considering different conception methods (natural, IUI, IVF) and socioeconomic factors (race, education, income). The authors found higher stress was linked to a lower probability of live birth, especially with IVF. No significant associations were found between stress and gestational age or birthweight, regardless of conception method or socioeconomic factors. The study underscores the importance of considering preconception stress and conception methods when examining stress and live birth outcomes.

2.4. This retrospective cohort study undertaken by (Zhai et al., 2024)aimed to investigate the impact of social psychological stress on the live birth outcomes of assisted reproductive technology (ART) of second marriage (SM) families, where the wife is remarried and older than her first-time married husband. The authors suggested that SM families experience many challenges: psychological, emotional, and societal pressure that could impact ART outcomes. Looking at the live birth rate (LBR) of 561 SM families compared to 5600 first marriage (FM) families undergoing their first ART cycle between January 2012 to December revealed that LBR was significantly lower in the SM group (30.7%) than the FM group (43.6%) even after adjusting and propensity score matching. SM families experience higher levels of social and psychological pressure, leading to lower live birth rates compared to FM families.

2.5. The impact of extreme psychological burdens, specifically the 7th October 2023 Hamas terror attacks in Israel, on IVF outcomes was examined by (Orvieto et al., 2024). The study looked at 23 couples undergoing two consecutive IVF attempts with egg collection taking place before and during the week of October 8th to 12th, 2023. No major differences in treatment protocol were identified and no differences were observed in the number of oocytes and mature oocytes retrieved or fertilization rate, the mean number of top-quality embryos per OPU (1.1 ± 1.7 vs. 2.2 ± 2.9; $p < 0.02$) and ratio of top-quality embryos per number of fertilized oocytes (0.5 ± 0.3 vs. 0.7 ± 0.2; $p < 0.01$) were significantly lower during the spoken week. Semen total motile count was significantly reduced during the spoken week. The authors concluded that acute emotional and psychological trauma could have a negative effect on IVF outcomes through a detrimental effect on sperm and embryo quality.

2.6. A critique of the 2021 Komparu et al study was made by (Komiya et al., 2022), who question the study's reliability due to: unclear registration of the RCT, lack of detailed information on study participants, no discussion of case dropouts, and insufficient detail on IVF protocols used. They conclude that while the study underscores the importance of psychological interventions for women undergoing infertility treatment, the lack of clarity on several aspects weakens its conclusions. Further details are needed to solidify the study's findings and its application in clinical settings.

2.7. A study looking at the impact of stress biomarkers from seminal plasma in the female reproductive tract and their impact on ISCI outcomes was undertaken by (Nikolaeva et al., 2024). The study of 20 couples undergoing ICSI including 5 fertile sperm donors and 10 saliva donors were studies to determine if male stress affects seminal plasma (SP) and ICSI outcomes. Women were exposed to their partner's SP during the ICSI cycle via unprotected sexual intercourse and intravaginal application on the day of egg collection. Biomarkers of activity of the sympathetic adrenomedullary axis (salivary alpha-amylase and adrenaline), sympathetic neural axis (noradrenaline and dopamine), hypothalamic-pituitary-adrenal (HPA) system (cortisol), and immune system (C-reactive protein and interleukin (IL)-18) were estimated in the women to examine their association with SP composition and clinical pregnancy achievement. Findings included that successful ICSI outcomes were associated with higher cortisol levels and unsuccessful ICSI outcomes were linked to lower cortisol and higher noradrenaline, noradrenaline/cortisol ratio, and IL-18 levels. The authors conclude that stress response systems impact SP composition, which in turn influences ICSI success rates.

The impact of interventions to manage stress and other psychological factors

2.8. This study from (Deshpande et al., 2023) examines the effectiveness of Heartfulness-based integrative therapy on infertility outcomes in India. The therapy included a 5-day lifestyle modification workshop and online meditation sessions. The study found that 24/54 couples who had been experiencing infertility conceived following the programme, 18 via natural conception, 5 via ART and one spontaneous abortion. The study suggests that Heartfulness meditation may benefit couples struggling with infertility. The authors suggest further research is needed to investigate the causal relationship of Heartfulness meditation on fertility outcomes ideally through a randomised control study to confirm whether this treatment method should be used independently or as an adjuvant therapy with assisted reproductive technologies.

2.9. This study by (Ha et al., 2023) evaluates the effectiveness of psychosocial interventions on pregnancy rates in women undergoing IVF through a systematic review and meta-analysis of 12 studies. Key findings included that psychosocial interventions significantly improve clinical pregnancy rates (SMD = 1.39). Mind-body interventions and cognitive behavioural therapy (CBT) were found to be particularly effective interventions, with CBT showing a higher effect size (SMD = 2.19). The study concludes that psychosocial interventions, especially mind-body techniques and CBT, can positively impact pregnancy outcomes in IVF treatments.

2.10. A systematic review and analysis of the impact of music therapy on anxiety and pregnancy rates in infertile women undergoing assisted reproductive technologies (ART) was undertaken by (Mahmoud et al., 2022). Using seven RCTs totalling 793 patients, the authors found that music therapy significantly reduces anxiety and pain scores as well as improving overall satisfaction among participants. Although there was an increase in clinical pregnancy rates in the music therapy group compared to the control group, this result was not statistically significant (RR= 1.08, 95% CI [0.94, 1.26], p = 0.28). The study concludes that music therapy has a moderate quality of evidence for improving anxiety, pain, and satisfaction in ART patients, but more research is needed to confirm its effect on pregnancy rates.

2.11. A multicentre RCT aimed to determine the effect of a blended preconception lifestyle programme on reproductive and lifestyle outcomes for couples undergoing their first 12 months of IVF (Boedt et al., 2023). 211 couples were randomised into an attention control group or an intervention group receiving the PreLiFe-programme, a mobile app with advice on diet, physical activity, and mindfulness, plus motivational interviewing. The primary outcome was time to ongoing pregnancy, with secondary outcomes including various reproductive and lifestyle measures. The intervention's hazard ratio for time to ongoing pregnancy was 0.94, indicating little to no effect. The PreLiFe programme was moderately accepted, but many participants did not fully use the app. In addition, study was unfortunately impacted by the Covid-19 pandemic, which resulted in fewer participants than foreseen and stopping the study early. The study's findings are therefore exploratory due to impact of the pandemic and low app usage.

2.12. A randomised controlled trial by (Bian et al., 2023) performed on women undergoing first time IVF and embryo transfer to investigate the effects of heart rate variability (HRV) biofeedback and whether it had an impact on clinical outcomes. HRV biofeedback can be an effective technique to treat anxiety and stress. 60 women were divided into two groups: one received HRV biofeedback, and the other received routine education. Key findings included significantly lower anxiety and depression scores postintervention in the intervention group compared to the control group, four HRV indexes (SDNN, RMSSD, PNN50, and TP) significantly increased in the intervention group, and that the higher clinical pregnancy rate in the intervention group was not statistically significant.

2.13. A systematic review and meta-analysis on the effectiveness of group psychological interventions for women undergoing fertility treatment was conducted by (Warne et al., 2023). The review included 30 studies with a total of 2752 participants. Key findings included significant reductions in depression (Hedges' g = -1.277, 95% CI = [-1.739- -0.815]; *p* = 0.000), anxiety (Hedges' g = -1.136, 95% CI [-1.527- -0.744]; *p* = 0.000) and moderate reduction in fertility stress (Hedges' g = -0.250, 95% CI [-0.388- -0.122]; *p* = 0.000) for the intervention group. The study also found higher odds of pregnancy (OR = 2.422, 5% CI [2.037-2.879]; *p* = 0.000) for the intervention group. Overall, group psychological interventions were effective in improving mental health and pregnancy outcomes for women with infertility.

2.14. A systematic literature search in English and Chinese undertaken by (Bian et al., 2024) in August 2019 across multiple databases to identify randomized controlled trials (RCTs) on the effect of psychological interventions on pregnancy rates in infertile women undergoing ART. Meta analysis of 25 RCTs comprising 4,173 patients (2,098 in experimental group, 2,075 in control group) found a significantly higher pregnancy rate in the experimental group [RR=1.31, 95% CI (1.22, 1.40)]. Subgroup analysis indicated that the positive effect of psychological interventions was consistent across different nationalities, intervention timings, and formats, but the effectiveness varied with different psychological interventions. The authors concluded that psychological interventions may improve pregnancy rates in infertile women undergoing ART. However, they cautioned that the limited quantity and quality of studies means further high-quality research is needed to confirm these findings.

2.15. A literature review on the effects of yoga on infertility, depression caused by infertility, and pregnancy outcomes was undertaken by (Demir Yıldırım and Güngör Satılmış, 2022). A keyword search of Turkish and international databases in July and August 2020 identified 24 suitable studies from 9 countries, the majority from India, which involved practicing different forms of yoga. The review found that yoga positively affects stress, anxiety, and depression, and it should be used as an adjunctive therapy, especially during in vitro fertilization treatment. Yoga also had a positive impact on pregnancy outcomes.

2.16. The study by (Ying Li et al., 2024) investigated the effect of auricular acupressure on alleviating negative psychological states in women during the controlled ovarian hyperstimulation (COH) stage of IVF treatment. Patients were randomly divided into three groups: control (n = 121), auricular acupressure (AA) (n = 126) and sham acupoint (SA) (n = 121). Psychological state was measured using the Symptom Checklist 90 (SCL-90) before and after the intervention, which lasted from COH start to the day before oocyte retrieval. The control and SA groups showed significant increases in symptoms like obsessive-compulsive behaviour, interpersonal sensitivity, depression, and anxiety. The AA group showed decreases in these symptoms and had lower scores compared to other groups. All participants were followed for IVF outcomes from studied COH. The AA group had the highest pregnancy rate at 73% (92/126) with the control group at 58.7% (71/121) and SA group at 61.2% (74/121). Chi-square tests revealed that auricular acupressure significantly improved pregnancy rates (P< 0.05) compared to non-intervention and sham auricular acupressure.

No or conflicting impact found on fertility treatment outcomes

The impact of psychological factors including stress

2.17. The effects of male anxiety and depression on IVF outcomes were examined by (Walker et al., 2023). They undertook a survey-based, retrospective cohort study at a single, large hospital-

affiliated fertility centre with 222 respondents who underwent IVF with or without ICSI. Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS) questionnaire. The study found men with anxiety had lower final total motile sperm counts (fTMSC) during IVF compared to men without anxiety; however, there were no differences in IVF outcomes as measured by live birth rates (LBRs).

2.18. A systematic review and meta analysis on the impact of emotional health and ART outcomes was conducted by (Peaston et al., 2022). The review looked at observational studies reporting the association between pre-treatment anxiety, stress or depression and ART outcomes in men, women or couples. The review found a potential association between decreased sperm motility and increased male state anxiety, but no significant association between women's pre-treatment emotional health and ART outcomes in terms of live birth, clinical pregnancy, chemical pregnancy, oocyte retrieval, embryos transferred or fertilization. Meta-analyses showed no significant standardized mean difference (SMD) for anxiety/stress and clinical or chemical pregnancy, or depression and clinical or chemical pregnancy.

2.19. To examine anxiety around embryo transfer (Yangmei Li et al., 2024) took 604 heterosexual couples from the E-Freeze trial and measured their anxiety using the State-Trait Anxiety Inventory (STAI) at consent (T1) and embryo transfer (T2). The study found that women's anxiety at T1 was linked to ethnicity, infertility duration, and their male partner's anxiety, whereas at T2 it was linked to ethnicity, clinic location, initial anxiety score, and male partner's anxiety. However, the authors found that women's anxiety did not affect trial compliance or pregnancy chances.

2.20. The effect of preoperative anxiety on the depth of anaesthesia and IVF success in 131 who had undergone oocyte retrieval was investigated by (Hekimoğlu Şahin et al., 2023). Patients were divided into two groups based on Beck Anxiety Inventory (BAI) score, low-anxious (Group L, n = 71) and high-anxious (Group H, n = 60). Patient measurements taken included: haemodynamic stability, total propofol and fentanyl consumption, good quality embryo (GQE) rate, and fertilization rate. The authors found that higher anxiety levels led to increased propofol consumption, but did not negatively impact IVF success.

2.21. The study by (Mirzaasgari et al., 2023) explored the role of psychological distress in the relationship between personality dimensions and pregnancy outcomes in women undergoing their first IVF/ICSI treatment. Over 12 months the study assessed 154 women using the Fertility Problem Inventory (FPI) and the Depression, Anxiety, and Stress Scale (DASS-21) to measure psychological distress and the Temperament and Character Inventory-Revised (TCI-R 125) to assess personality dimensions. There were no significant differences in personality traits or psychological distress between pregnant and non-pregnant groups, and path analysis showed no significant direct or indirect effect of harm avoidance on pregnancy outcomes when mediated by psychological distress. The authors conclude that the relationship between psychological factors and IVF outcomes is complex, and further research is needed to understand the interplay between personality traits and infertility treatments.

2.22. In a study of 129 patients who underwent ART due to repeated implantation failure, (Lvy et al., 2024) explored how irrational beliefs about parenthood, fertility stress, and social support are related, and how fertility stress mediates these relationships. Study participants were assessed using Irrational Parenthood Cognitions Questionnaire, Fertility Problem Inventory, and Social Support Rating Scale. Significant differences were found in irrational parenthood beliefs, fertility stress, and social support based on education and income levels. Irrational parenthood beliefs

were positively correlated with fertility stress and negatively correlated with social support. The structural equation model showed that fertility stress effectively mediated the relationship between irrational parenthood beliefs and social support. The study concluded that fertility stress significantly mediates the relationship between irrational parenthood beliefs and social support in patients with repeated implantation failure.

2.23. The aim of the systematic review by (Zanettoullis et al., 2024) was to examine if chronic or acute stress, measured by questionnaires or physiological biomarkers, has a separate impact on each different stage in the IVF process. A systematic keyword literature search was performed, which resulted in 46 articles, 36 of which were included. Most studies concluded that stress has a negative effect on IVF treatment. Findings included that egg retrieval was most affected by chronic and acute stress and there may be an association between chronic stress and the fertilization stage. Only chronic stress was found to impact embryo transfer and further evidence suggested stress decreased during this stage. Follicular cortisol was found to affect three stages. Chronic and acute stress significantly and negatively affected egg retrieval stage. Chronic stress was associated to a lesser extent with fertilization, and no significant relationship was found between acute stress and embryo transfer and pregnancy rate.

The impact of stress hormone cortisol

2.24. A systematic review of the impact of stress measures by cortisol levels undertaken by (Karunyam et al., 2023) used 16 studies to compare cortisol levels in infertile vs. fertile individuals and in infertile individuals who conceived vs. those who did not. Out of 8 studies which looked at IVF outcomes, only 3 reported significantly higher cortisol levels in infertile female subjects that did not conceive after ART. However, the authors caution that variations in study methods prevent a clear conclusion on cortisol levels in infertile patients.

2.25. Examining the relationship between cortisol dysregulation, anxiety and IVF outcomes in infertile women (Chai et al., 2023), found that women undergoing IVF who had high anxiety (as per Self-Rating Anxiety Scale – SAS) or high cortisol levels had lower rates of pregnancy and required more IVF cycles. Comparisons between infertile women and healthy controls found that infertile women especially older women, had higher cortisol levels. A strong correlation was found between cortisol levels and anxiety scores. The authors concluded that while high cortisol levels related to anxiety are common in infertile women, their impact on IVF outcomes is unclear.

The impact of interventions to manage stress and other psychological factors

2.26. The impact of interventions to manage stress and other psychological factors(Nunes et al., 2024) undertook a randomised controlled trial to determine if extremely brief meditation (EBMI) or brief mindfulness interventions (Brief MI) could affect pregnancy rates in women undergoing Assisted Reproductive Technology (ART). 68 women aged 18-50 undergoing ART were divided into three groups: 15 minute daily mindfulness, weekly 40-minute meditation sessions, and a control group who received no intervention. Pregnancy rates were measured two weeks after embryo transfer, but no significant differences in pregnancy rates were found between the intervention and control groups. This led the authors to conclude that neither EBMI nor Brief MI significantly impacted pregnancy rates in women undergoing ART.

Studies on stress and treatment discontinuation

2.27. While not measuring fertility treatment outcomes, (Sousa et al., 2023) undertook a systematic review of studies that evaluated stress as a reason for discontinued assisted reproduction (ART). Twelve eligible studies were found, with 15,264 participants from eight countries, which assessed stress through generic questionnaires or medical records, not by validated stress questionnaires or biomarkers. Stress prevalence ranged from 11–53% and pooled results found stress as a reason for ART discontinuation in 30.9% of participants. Clinical factors associated with worse prognosis, physical discomfort from treatment, family demands, time and economic pressures were identified as sources of 'stress' that contributed to ART discontinuation. The authors note that further studies are necessary to investigate whether stress factor mitigation can reduce ART discontinuation rates.

2.28. In their study (Swift et al., 2024) sought to compare infertility-related stress and quality of life (QoL) between women who discontinued fertility treatments and those who continued, and to explore reasons for discontinuation. A secondary analysis using various statistical methods was conducted on 70 women who discontinued fertility treatments and 166 who continued. Content analysis was used for open-text responses on reasons for discontinuation. No significant differences in infertility-related stress and QoL were found between the two groups. Factors influencing treatment discontinuation included income, QoL dissatisfaction, and infertility duration of three years or more. Three main themes were identified for discontinuation: cost, waiting for a resolution, and re-envisioning family identity. Infertility-related stress and QoL are similar regardless of treatment continuation, indicating a need for emotional support for all women. Discontinuation reasons suggest targeted interventions to support mental health.

2.29. A prospective cohort study involving 16,521 couples trying to conceive for ≤6 months undertaken by (Liao et al., 2024) sought to find out whether preconception depression had an impact on time to pregnancy (TTP) and infertility. Depression was assessed using the Patient Health Questionnaire-9 and reproductive outcomes were tracked at 6 and 12 months. Fertility odds ratios (FORs) and infertility risk ratios (RRs) were analysed using statistical models. 65.6% of couples conceived within 6 months, and 4.5% between 6 and 12 months with a median TTP of 3 months. The infertility rate was 13.01%. Preconception depression in women was linked to reduced fertility odds and increased infertility risk. Couples where both partners had depression showed reduced fertility and higher infertility risk. Study limitations include potential reporting and recall biases, unaddressed confounding factors and that depression was only assessed at baseline. The authors recommend that early detection and intervention for depression should target both partners to improve fertility outcomes.

3. Conclusions

3.1. Research is almost evenly divided between studies that find no impact on outcomes and studies that find an impact. Although even where an impact is found it is generally modest and not statistically significant.

3.2. Measurements of stress are heterogenous for example using different questionnaires, and most depend on self-reporting/self-assessment by patients. Existing studies are limited by stress being conflated with other psychological measures such as psychological distress, anxiety, depression and general emotional health. When an impact between stress and IVF outcomes is found, associations are generally weak. Some studies find an impact on fertility measures e.g.

sperm count, but not on overall outcomes. For the most part studies have a low number of participants.

3.3. Two articles looking specifically at the stress hormone cortisol, found it to be higher in infertile women who were not able to conceive through ART, but the relationship was unclear.

3.4. There is also a growing body of research on interventions to reduce or manage stress and their impact on IVF outcomes. There were a wide variety of interventions including yoga, group therapy ("group psychological interventions"), music therapy, acupressure and multi-faceted lifestyle programmes. Findings are variable, but two systematic reviews concluded that psychological interventions improve ART outcomes.

3.5. All studies on interventions to reduce stress found the interventions had a positive impact on stress/emotional well-being, but this did not always translate to IVF outcomes, or the association was unclear or weak e.g. a higher live birth rate that was not statistically significant. Most studies had a small number of participants.

3.6. A new area of research not found in previous reviews of this topic was stress as a reason for or factor in IVF discontinuation. The impact of discontinuation is clear: if you stop treatment, you will not be successful. Such studies did not provide detailed participant analysis; this could be an area for future research.

4. Recommendations

4.1. Members are asked to:

- Consider the progress in research into the impacts of stress on fertility treatment outcomes;
- Advise the Executive if they are aware of any other recent developments, and;
- Review whether any outputs from the HFEA are required.

5. Annex A – References

Andrea Ražić Pavičić, Nenad Jakšić, Trpimir Jakovina, Milena Skočić Hanžek, Iva Miškulin, & Rudolf Gregurek. (2022). The Role of Psychological Factors in the Outcome of In Vitro Fertilization in Women with Primary Infertility. *Psychiatria Danubina*, *34*, 104–114. https://pubmed.ncbi.nlm.nih.gov/36752249/

Bian, C., Cao, J., Chen, K., Xia, X., & Yu, X. (2024). Effectiveness of psychological interventions on pregnancy rates in infertile women undergoing assisted reproductive technologies: a meta-analysis of randomised controlled trials. *Biotechnology and Genetic Engineering Reviews*, *40*(4), 4512–4531. https://doi.org/10.1080/02648725.2023.2213080

Bian, Y., Liu, F., Wang, Y., Wang, X., & Chen, R. (2023). Effects of Heart Rate Variability (HRV) Biofeedback for Women Undergoing First-time In Vitro Fertilization and Embryo Transfer. *Alternative Therapies in Health and Medicine*, *29*(2), 162–167.

Boedt, T., Dancet, E., de Neubourg, D., Vereeck, S., Jan, S., van der Gucht, K., van Calster, B., Spiessens, C., Lie Fong, S., & Matthys, C. (2023). A blended preconception lifestyle programme for couples undergoing IVF: lessons learned from a multicentre randomized controlled trial. *Human Reproduction Open*, *2023*(4). https://doi.org/10.1093/hropen/hoad036

Chai, Y., Li, Q., Wang, Y., Niu, B., Chen, H., Fan, T., Ke, X., & Zou, H. (2023). Cortisol dysregulation in anxiety infertile women and the influence on IVF treatment outcome. *Frontiers in Endocrinology*, *14*. https://doi.org/10.3389/fendo.2023.1107765

Demir Yıldırım, A., & Güngör Satılmış, İ. (2022). The Effects of Yoga on Pregnancy, Stress, and Anxiety in Infertile Individuals. *Holistic Nursing Practice*, *36*(5), 275–283. https://doi.org/10.1097/HNP.0000000000000543

Deshpande, S., Patel, K. D., Parulkar, T., Mahabalesh, K., Madhusudhan, P., Madhusudhan, D. K., & Thimmapuram, J. (2023). Effect of Heartfulness meditation based integrative therapy on infertility outcomes: A retrospective case series evaluation. *Journal of Ayurveda and Integrative Medicine*, *14*(6), 100793. https://doi.org/10.1016/j.jaim.2023.100793

Ha, J.-Y., Park, H.-J., & Ban, S.-H. (2023). Efficacy of psychosocial interventions for pregnancy rates of infertile women undergoing *in vitro* fertilization: a systematic review and meta-analysis. *Journal of Psychosomatic Obstetrics & Gynecology*, *44*(1). https://doi.org/10.1080/0167482X.2022.2142777

Hekimoğlu Şahin, S., Çopuroğlu, E., Yamak Altınpulluk, E., Süt, N., Karamanlıoğlu, B., Elter, K., & Yaman, Ö. (2023). Effect of Preoperative Anxiety on Depth of Anaesthesia and In Vitro Fertilization Success. *Turkish Journal of Anaesthesiology and Reanimation*, *51*(5), 414–419. https://doi.org/10.4274/TJAR.2023.22829

Karunyam, B. V., Abdul Karim, A. K., Naina Mohamed, I., Ugusman, A., Mohamed, W. M. Y., Faizal, A. M., Abu, M. A., & Kumar, J. (2023). Infertility and cortisol: a systematic review. *Frontiers in Endocrinology*, *14*. https://doi.org/10.3389/fendo.2023.1147306

Komiya, S., Banno, M., & Itagaki, Y. (2022). Regarding “Stress management and In Vitro Fertilization (IVF): A pilot randomized controlled trial.” *Psychiatriki*, 247–248. https://doi.org/10.22365/jpsych.2022.076

Li, Y., McLeish, J., Hardy, P., Cole, C., Carson, C., Alderdice, F., & Maheshwari, A. (2024). Anxiety in couples undergoing IVF: evidence from E-Freeze randomised controlled trial. *Human Reproduction Open*, *2024*(3). https://doi.org/10.1093/hropen/hoae037

Li, Y., Shen, W., Mo, F., Ma, Q., & Xing, L. (2024). The Effect of Auricular Acupressure on Women Psychological Distress during Controlled Ovarian Hyperstimulation for in vitro Fertilization: A Single-Blind, Randomized, and Sham-Controlled Study. *The Tohoku Journal of Experimental Medicine*, 2024.J076. https://doi.org/10.1620/tjem.2024.J076

Liao, T., Gao, Y., Yang, X., Tang, Y., Wang, B., Yang, Q., Gao, X., Tang, Y., He, K., Shen, J., Bao, S., Pan, G., Zhu, P., Tao, F., & Shao, S. (2024). Preconception depression reduces fertility: a couple-based prospective preconception cohort. *Human Reproduction Open*, *2024*(3). https://doi.org/10.1093/hropen/hoae032

Lvy, Y., Zhang, F., Cai, Z., Zhong, D., & Xing, L. (2024). Correlation among irrational parenthood cognitions, fertility stress, and social support in patients with repeated implantation failure and the mediating effect of fertility stress: a cross-sectional survey. *Journal of Assisted Reproduction and Genetics*, *41*(1), 205–212. https://doi.org/10.1007/s10815-023-02953-2

Mahmoud, M. Y., Labib, K., Sileem, S. A., Mustafa, F. A., Hamed, W. M., Abd Elhamid, A., Saleh, D. M., Alanwar, A., Riad, A. A. M., Abdelhakim, A. M., Abbas, A. M., & Mohammed, H. M. (2022). The impact of music therapy on anxiety and pregnancy rate among infertile women undergoing assisted reproductive technologies: a systematic review and meta-analysis. *Journal of Psychosomatic Obstetrics & Gynecology*, *43*(2), 205–213. https://doi.org/10.1080/0167482X.2021.1977277

Malekpour, P., hasanzadeh, R., Javedani Masroor, M., Chaman, R., & Motaghi, Z. (2023). Effectiveness of a mixed lifestyle program in couples undergoing assisted reproductive technology: a study protocol. *Reproductive Health*, *20*(1), 112. https://doi.org/10.1186/s12978-023-01652-6

Mínguez-Alarcón, L., Williams, P. L., Souter, I., Ford, J. B., Hauser, R., & Chavarro, J. E. (2024). Women's preconception psychological stress and birth outcomes in a fertility clinic: the EARTH study. *Frontiers in Global Women's Health*, *5*. https://doi.org/10.3389/fgwh.2024.1293255

Mirzaasgari, H., Momeni, F., Pourshahbaz, A., Keshavarzi, F., & Hatami, M. (2023). The Role of Psychological Distress in the Relationship between Personality Dimensions and Pregnancy Outcome of Women Undergoing Assisted Reproductive Treatment (IVF/ICSI). *Iranian Journal of Psychiatry*. https://doi.org/10.18502/ijps.v18i2.12366

Nunes, G. M., Paiva, S. de P. C., Geber, S., Serra, A. S. V. de A., Sampaio, M. A. C., & Tavares, R. L. C. (2024). The impact of extremely brief meditation and brief mindfulness interventions on assisted reproductive technologies success rates: A randomised controlled trial. *EXPLORE*, *20*(6), 103067. https://doi.org/10.1016/j.explore.2024.103067

Orvieto, R., Shamir, C., & Aizer, A. (2024). Does extreme psychological burden (Hamas terrorist attack on October 7th, 2023) affect in vitro fertilization outcome? *Journal of Assisted Reproduction and Genetics*, *41*(6), 1585–1588. https://doi.org/10.1007/s10815-024-03099-5

Peaston, G., Subramanian, V., Brunckhorst, O., Sarris, I., & Ahmed, K. (2022). The impact of emotional health on assisted reproductive technology outcomes: a systematic review and meta-analysis. *Human Fertility*, *25*(3), 410–421. https://doi.org/10.1080/14647273.2020.1832262

Reschini, M., Buoli, M., Facchin, F., Limena, A., Dallagiovanna, C., Bollati, V., & Somigliana, E. (2022). Women's quality of sleep and in vitro fertilization success. *Scientific Reports*, *12*(1), 17477. https://doi.org/10.1038/s41598-022-22534-0

Sousa, E., Nery, S. F., Casalechi, M., Thimóteo, L. C., Paiva, S. P., Silva-Filho, A. L., & Reis, F. M. (2023). Characteristics, prevalence and sources of stress in individuals who discontinue assisted reproductive technology treatments: a systematic review. *Reproductive BioMedicine Online*, *46*(5), 819–825. https://doi.org/10.1016/j.rbmo.2023.01.020

Swift, A., Thomas, E., Larson, K., Swanson, M., & Fernandez-Pineda, M. (2024). Infertility-related stress, quality of life, and reasons for fertility treatment discontinuation among US women: A secondary analysis of a cross-sectional study. *Sexual & Reproductive Healthcare*, *39*, 100955. https://doi.org/10.1016/j.srhc.2024.100955

Walker, Z., Ernandez, J., Lanes, A., Srouji, S. S., Ginsburg, E., & Kathrins, M. (2023). The effects of male anxiety and depression on IVF outcomes. *Human Reproduction*, *38*(11), 2119–2127. https://doi.org/10.1093/humrep/dead179

Warne, E., Oxlad, M., & Best, T. (2023). Evaluating group psychological interventions for mental health in women with infertility undertaking fertility treatment: A systematic review and meta-Analysis. *Health Psychology Review*, *17*(3), 377–401. https://doi.org/10.1080/17437199.2022.2058582

Zanettoullis, A. T., Mastorakos, G., Vakas, P., Vlahos, N., & Valsamakis, G. (2024). Effect of Stress on Each of the Stages of the IVF Procedure: A Systematic Review. *International Journal of Molecular Sciences*, *25*(2), 726. https://doi.org/10.3390/ijms25020726

Zhai, J., Zhao, S., & Hao, G. (2024). The impact of sociocultural and psychological stress on the outcome of assisted reproductive technology in remarried families. *Journal of Psychosomatic Obstetrics & Gynecology*, *45*(1). https://doi.org/10.1080/0167482X.2024.2351809

ZHOU, Y., SUN, Z., & SONG, J. (2023). Research progress on the impact of anxiety and depression on embryo transfer outcomes of in vitro fertilization. *Journal of Zhejiang University (Medical Sciences)*, *52*(1), 61–67. https://doi.org/10.3724/zdxbyxb-2022-0473

Mitochondrial donation: Polar body transfer

Details about this paper

Area(s) of strategy this paper relates to:	Shaping the future
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	7
Paper number:	HFEA (03/02/2025) 007
Meeting date:	03 February 2025
Author:	Molly Davies, Policy Manager (HFEA)
Annexes	Annex A – 2014 Review of safety and efficacy of polar body transfer to avoid mitochondrial disease: Recommendations and further research Annex B - The process' referred to in the mitochondrial donation regulation

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • Consider the progress of research into PBT techniques for mitochondrial donation; • Advise if they are aware of any other recent developments; and • Advise on any significant implications for licensing and regulation arising out of the scientific developments.
Resource implications:	TBC
Implementation date:	TBC
Communication(s):	TBC
Organisational risk:	Low

1. Introduction

1.1. Polar bodies are byproducts extruded from oocytes and zygotes during the first and second meiotic divisions. The first polar body (PB1) is diploid and extruded from the oocyte on completion of the first meiotic division. The second polar body (PB2) is haploid and is extruded from the zygote following the second meiotic division. Both structures are utilised in techniques of polar body transfer (PBT) which involves either: (1) removal of PB1 from the MII oocyte followed by transfer to an enucleated MII oocyte and fertilisation (PB1T), or (2) removal of the PB2 from a fertilised PN stage zygote and transfer to a recipient zygote with a removed pronucleus (PB2T).

1.2. Whilst introducing healthy mitochondria from a donated source is a successful treatment for preventing the transmission of the majority of mutated mitochondria, small amounts of residual mitochondria may be transferred. If these residual mitochondria contain defective mutations and subsequently replicate, they could lead to unpredictable effects with the persistence/resurgence of mitochondrial disease in the child. As mitochondrial diseases typically manifest when the proportion of mutated mitochondria reach a certain threshold, ongoing monitoring of outcomes in patients is critical to ensure the safety and long-term efficacy of mitochondrial donation treatments.

1.3. In July 2014, the HFEA was asked by the Government to seek views of members of the mitochondrial donation expert panel on the safety and efficacy of polar body transfer (PBT) as a novel method of mitochondrial donation. In their October 2014 report, the panel recommended that “additional studies be undertaken both in the basic research field to improve understanding of the biology of human mitochondria especially during development, and on translational research aimed specifically at providing further safety and efficacy information on PBT”. Extended recommendations on PBT from the 2014 report are given in Annex A.

1.4. In February 2015, Parliament approved the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations to permit the use of maternal spindle transfer (MST) and pronuclear transfer (PNT) to avoid serious mitochondrial disease. The Regulations, which came into force on 29 October 2015, enable licensed fertility clinics in the UK to apply to the HFEA for a licence to perform the MST or PNT, however they explicitly prohibit the transfer of polar body nuclear DNA (Annex B).

1.5. Upon the fourth review in 2016, the expert panel reviewed developments in PBT, acknowledging that, whilst these techniques are currently unlawful in the UK, the panel continued to support the investigation of polar body transfer methodologies as an alternative method of performing mitochondrial donation:
“The very low numbers of mitochondria found particularly in in the 1st, but also the 2nd polar bodies make them ideal, ready-made karyoplasts for transfer to a donor egg or zygote. In conjunction with the carry-over elimination approaches discussed above and below, they offer great potential for near elimination of karyoplast-derived mtDNA. Following a detailed study in mice (Wang et al., 2014), a recent publication described the successful generation of human blastocysts following polar body transfer and showed that the levels of aneuploidy were similar between PBT and control blastocysts (Ma et al., 2017), underlining the promise of this approach for treatment of women at risk of passing on mitochondrial disorders.”

1.6. With the introduction of the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, the HFEA was asked to monitor the development of new donation

techniques through its horizon scanning mechanism (Explanatory Memorandum, HFE (Mitochondrial Donation) Regulations 2015).

1.7. The SCAAC considered the progress of research into mitochondrial donation in February 2017 (briefing), February 2018 (briefing), and February 2021 (briefing), with the last discussion on this topic being held in October 2024 (paper). To monitor the progress of the clinical and research programmes at Newcastle Fertility Centre at Life, the only UK centre licenced for mitochondrial donation in the UK, additional updates were given at the January 2022, July 2023, and October 2024 SCAAC meetings. Alongside research using established techniques of MST and PNT, alternative methods for performing mitochondrial donation have been considered, including pre-pronuclear transfer, germinal vesicle nuclear transfer, mitochondrial DNA gene editors, MitoCeption and PBT.

1.8. During the October meeting, the invited expert highlighted that all evidence from published studies on PBT indicates that it could be a very useful technique. As such the SCAAC is being asked to review the research summarised below against the 2014 recommendations, and to consider developments in the safety and efficacy of PBT.

1.9. Should the SCAAC consider that it is necessary to re-establish the expert panel on mitochondrial donation to review the safety and efficacy of polar body transfer, the committee can make a recommendation to the Authority. The Authority would then decide whether to re-establish the expert panel.

1.10. Any final decisions relating to mitochondrial donation rest with the Authority. In addition, clinical application of any further methods of mitochondrial donation would require revision to the HFE Act, through amendments to the Regulations (annex B).

2. Research developments

2.1. The following research on PBT techniques has been published since the 2016 review. In addition to the research summarised below, PBT is also being explored as a technique to improve oocyte quality, but such research is outside the scope of this paper.

2.2. In 2017, Ma et al., 2017 described the generation of normal diploid zygotes following the transfer of genomes from PB1 into an enucleated donor MII oocyte (PB1T) and fertilisation of reconstructed oocytes. Whilst PB1T generated zygotes developed to blastocysts less frequently (42%) than controls (75%), genome-wide genetic, epigenetic, and transcriptional analyses of PB1T generated zygotes and control ESCs indicated comparable numbers of structural variations and markedly similar DNA methylation and transcriptome profiles. Authors concluded that rescue of PB1 genetic material via introduction into donor cytoplasm may offer a source of oocytes for infertility treatment or mitochondrial replacement therapy for mtDNA disease.

2.3. To investigate whether the second polar body could also be used as a nuclear donor, Wu et al., (2017) established a protocol for the reconstruction of human oocytes or zygotes using first or second polar bodies as donors. A total of 19 good-quality blastocysts from 75 PB1T embryos were obtained and cryopreserved. Of the 17 thawed blastocyst, 10 were euploid and displayed an average mitochondrial DNA carryover of 0.26%. Using PB2T techniques, researchers generated 14 high quality blastocysts from 51 embryos at a comparable efficiency to PB1T methods. Nine blastocysts were euploid with an average mitochondrial DNA carryover of 0.37%. Mitochondrial DNA carryover was maintained at low levels during long-term in vitro

proliferation and differentiation of embryonic stem cells, suggesting that PBT can be a promising approach to treat mitochondrial-related diseases.

2.4. Researchers Wu et al. (2017) hypothesised that, as the human female pre-pronucleus forms at 3.5-4 hours post fertilisation and will not separate completely from the second polar body within 6 hours before being enclosed by the pronuclear envelope, if removed early the pre-pronucleus could be easily isolated with the extruding second polar body to avoid the use of cytoskeleton disruptors in PNT. Applying this strategy, researchers generated 6 good-quality euploid blastocysts with an average mitochondrial DNA carryover of 0.36%. By generating embryonic stem cell lines, researchers showed that the ratio of mitochondrial DNA carryover remained low and relatively stable in all tested samples.

2.5. The comparative study by Tang et al. (2019) investigated the efficiency of four different nuclear transfer techniques to overcome mitochondrial disease in NZB/OlaHsd and B6D2F1 mouse models. In addition to looking at MST and PNT techniques, researchers looked at two novel protocols for optimisation of the second polar body transfer technique using mouse and human oocytes. Comparable blastocyst rates among PB1T, PB2T-b, ST and PNT embryos were recorded, with lower mitochondrial carryover levels being reported in PB1T and PB2T embryos than those generated from MST and PNT.

2.6. Subsequent research by Li et al. (2023) established a spindle-protrusion-retained second polar body separation technique to allow for earlier second polar body transfer for the avoidance of DNA damage accumulation. The optimised method allowed for further elimination of mitochondrial carryover in reconstructed oocytes through a physically based residue removal method. Researchers obtained a close to normal proportion of normal-karyotype blastocyst in both mice and humans. Mouse embryonic stem cells and live-born pups contained almost undetectable mitochondrial DNA carryover.

2.7. Despite the panel considering that demonstration of PBT in a non-human primate model was neither critical or mandatory, Wang et al. (2021) utilised PB1T to generate a healthy macaque monkey (*Macaca fascicularis*), highlighting a useful non-human primate model for evaluating safety and efficacy of PB1T as a method of mitochondrial replacement. Researchers found stable low-level mitochondrial DNA heteroplasmy (<5%) in ear and blood samples of the offspring over a 1.5-year period with no evidence of upward mitochondrial DNA drift.

2.8. Recently, Ji et al. (2025) reported on the feasibility of PB1T to prevent the transmission of the pathogenic mitochondrial DNA 8993T>G mutation (Leigh syndrome) in human embryos. Five well-formed polar bodies from 14 eggs were selected for PB1 transfer, followed by ICSI and culture. Two reconstituted embryos formed blastocysts with no detected mutation when biopsied.

3. Conclusions

3.1. Research into alternative techniques of mitochondrial donation, such as PBT, are still in experimental stages. However, such techniques may be able to address concerns with mitochondrial heteroplasmy seen across established methods. The HFE Act would need to be updated to allow for clinical application of some of these techniques.

4. Recommendations

4.1. Members are asked to:

- Consider the progress of research into PBT techniques for mitochondrial donation;
- Advise if they are aware of any other recent developments; and
- Advise on whether significant progress has been made in addressing the Safety and efficacy issues with PBT techniques outlined in the 2014 scientific review.

5. References

Ji D, Zhang Z, Zou W, Zhang N, Zong K, Du Y, Su X, Wang X, Chen D, Liang C, Zhang Z, Cao Y. [Study of the feasibility of polar body transfer combined with preimplantation genetic testing for blocking the intergenerational transmission of mitochondrial genetic diseases]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2025 Jan 10;42(1):18-25. Chinese. doi: 10.3760/cma.j.cn511374-20240702-00366. PMID: 39779332.

Li W, Liao X, Lin K, Cai R, Guo H, Ma M, Wang Y, Xie Y, Zhang S, Yan Z, et al. Earlier second polar body transfer and further mitochondrial carryover removal for potential mitochondrial replacement therapy. MedComm (Beijing) [Internet] 2023;4:. MedComm (2020).

Ma H, O'Neil RC, Marti Gutierrez N, Hariharan M, Zhang ZZ, He Y, Cinnioglu C, Kayali R, Kang E, Lee Y, et al. Functional Human Oocytes Generated by Transfer of Polar Body Genomes. Cell Stem Cell [Internet] 2017;20:112–119. Cell Stem Cell

Tang M, Guggilla RR, Gansemans Y, Jeught M Van Der, Boel A, Popovic M, Stamatiadis P, Ferrer.

Wang T, Sha H, Ji D, Zhang HL, Chen D, Cao Y, Zhu J. Polar body genome transfer for preventing the transmission of inherited mitochondrial diseases. Cell. 2014 Jun 19;157(7):1591-604. doi: 10.1016/j.cell.2014.04.042. PMID: 24949971.

Wang Z, Li Y, Yang X, Wang Y, Nie Y, Xu Y, Zhang X, Lu Y, Zhang T, Liu Q, Jing N, Liu Z, Sun Q. Mitochondrial replacement in macaque monkey offspring by first polar body transfer. Cell Res. 2021 Feb;31(2):233-236. doi: 10.1038/s41422-020-0381-y. Epub 2020 Jul 28. PMID: 32724085; PMCID: PMC8027822.

Wu K, Chen T, Huang S, Zhong C, Yan J, Zhang X, Li J, Gao Y, Zhao H, Chen ZJ. Mitochondrial replacement by pre-pronuclear transfer in human embryos. Cell Research 2017 27:6 [Internet] 2017a;27:834–837. Nature Publishing Group.

Wu K, Zhong C, Chen T, Zhang X, Tao W, Zhang J, Li H, Zhao H, Li J, Chen ZJ. Polar bodies are efficient donors for reconstruction of human embryos for potential mitochondrial replacement therapy. Cell Research 2017 27:8 [Internet] 2017b;27:1069–1072. Nature Publishing Group.

6. Annex B – 2014 Review of the safety and efficacy of polar body transfer to avoid mitochondrial disease: Recommendations and further research

6.1. The 2014 Review of the safety and efficacy of polar body transfer (PBT) to avoid mitochondrial disease concluded with the recommendation that, at minimum, the following set of experiments should be undertaken and the results considered before PBT techniques can be considered safe for clinical use :

- Polar body 1 transfer (PB1T) using human oocytes that are then fertilised (not activated), and comparative follow up of development in vitro. This could include a molecular karyotype analysis of PB2T.
- Polar body 2 transfer (PB2T) using normally fertilised human oocytes, from which the maternal pronucleus has been removed, and development compared to normal ICSI-fertilised human oocytes. The panel highlighted the importance of demonstrating a robust method for distinguishing the maternal and paternal pronuclei such that the maternal pronucleus can be reliably selected for removal.

6.2. In addition to this, the panel considered that:

- PBT in a non-human primate model, with the demonstration that the offspring derived are normal, is neither critical nor mandatory.

and that studies should be caried out on:

- Mosaicism in human morulae (comparing individual blastomeres) and on human ES cells (and their differentiated derivatives) derived from blastocysts, where the embryos have (i) originated from oocytes heteroplasmic for mtDNA and (ii) been created through the use of any mitochondrial replacement technique using oocytes or zygotes with two different variants of mtDNA.

6.3. The following additional research was also recommended to provide useful information on mitochondrial disease and PBT techniques:

- Karyotype analysis and comparative genomic hybridisation/copy number variation arrays of embryos derived from PBT (taking into consideration variation of karyotypes in polar bodies). In addition, it would be useful to conduct analysis on PB2 following PB1T.
- Detailed analysis of epigenetic modifications and gene expression, with a range of markers for blastocyst cell types in embryos derived from PBT. Comparative examination for epigenetic variation between PB1/ PB2 and oocyte and any embryos created through PBT.
- PBT on unfertilised human oocytes that have abnormal mtDNA. However, the panel recognises that these studies may be difficult (practically) to conduct, and as stated previously considers that the scientific justification for this does not outweigh the ethical concerns about performing such experiments. Comparative studies exploring carryover between the various techniques (MST, PNT, PB1T and PB2T) would be practically impossible and even more ethically contentious. This would also be unnecessary. Only one method should be sufficient to explore whether abnormal mtDNA has any (replicative) advantage after mitochondrial replacement.
- As an alternative method for analysing the behaviour of mutant mtDNA, the use of induced pluripotent stem (iPS) cells derived from patients carrying different mtDNA mutations. Any information gained would apply to all methods of mitochondrial replacement and is not specifically relevant to PBT.
- As with other forms of mitochondria replacement techniques, studies on the mtDNA carryover in a non-human primate model into the possible heteroplasmy of tissues in the fetus would be advantageous. The possibility of carryover of even a small percentage of abnormal mtDNA 32 means that any females born from PBT should be considered at risk of transmitting the disease to their offspring. This recommendation applies to all methods of mitochondrial replacement and is not specifically relevant to PBT.

- Further studies on vitrifying oocytes, polar bodies and zygotes in order to allow synchronisation when carrying out PBT, as well as clinical management of patients.
- Tests for heteroplasmy should be carried out on primordial germ cells obtained from human ES cells derived from blastocysts created through PBT where the oocytes had variant or abnormal mtDNA. If primordial germ cell derivation is not possible or limitations in the model undermine its utility, clonal analysis of single cell-derived human ES cells could be used. Comparisons beginning with blastocysts known to be heteroplasmic for variant or abnormal mtDNA would be informative. This applies to all methods of mitochondrial replacement and is not specifically relevant to PBT.

6.4. When concluding the 2014 report, the panel noted that "progress in this [PBT research] is rapid' and concluded that PBT 'does not introduce different principles to those of MST or PNT and the resulting embryos will be equivalent to those derived by MST and PNT'.

7. Annex B – The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015

7.1. Regulations 4 and 7 of the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 prescribe the process that such an egg or embryo (egg or embryo "P") must have undergone which involves the removal of nuclear DNA from an egg or embryo which has abnormal mitochondrial (egg or embryo "B") and the insertion of this material into an enucleated egg or embryo which has healthy mitochondria (egg or embryo "A").

7.2.

PART 2

Permitted eggs and permitted embryos

[…]

Permitted egg: process

4.—(1) The process referred to in regulation 3(a) consists of the following two steps.

(2) In step 1—

(a) either—

(i) all the nuclear DNA of an egg ("egg A") is removed, or

(ii) all the nuclear DNA of egg A other than polar body nuclear DNA is removed; and

(b) either—

(i) all the nuclear DNA of another egg ("egg B") is removed, or

(ii) all the nuclear DNA of egg B other than polar body nuclear DNA is removed.

(3) In step 2 all the nuclear DNA of egg B which is not polar body nuclear DNA is inserted into egg A.

[…]

Permitted embryo: process

7.—(1) The process referred to in regulation 6(a) consists of the following two steps.

(2) In step 1—

(a) either—

(i) all the nuclear DNA of an embryo ("embryo A") is removed, or

(ii) all the nuclear DNA of embryo A other than polar body nuclear DNA is removed; and

(b) either—

(i) all the nuclear DNA of another embryo ("embryo B") is removed, or

(ii) all the nuclear DNA of embryo B other than polar body nuclear DNA is removed.

(3) In step 2 all the nuclear DNA of embryo B which is not polar body nuclear DNA is inserted into embryo A.

Prioritisation of horizon scanning topics and committee workplan 2025/26

Details about this paper

Area(s) of strategy this paper relates to:	Shaping the future
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	8
Paper number:	HFEA (03/02/2025) 008
Meeting date:	03 February 2025
Author:	Molly Davies, Policy Manager
Annexes	Annex A: Briefings on key issues identified during this horizon scanning Annex B: Horizon scanning reference lists and topic scope (circulated separately) Annex C: Topic priority categorisation table Annex D: Committee workplan 2025-2026 Annex E: Committee purpose and function as per standing orders

Output from this paper

For information or recommendation?	For recommendation

Recommendation:	Members are asked to:
	• consider the scope and priority of topics identified through the horizon scanning process:
	  ○ review the scope of the prioritised topics (given in Annex B)
	  ○ consider the proposal that 'Reproductive organoids' and 'Health outcomes for ART patients (including gestational surrogates and egg donors)' are added as new topics, and
	  ○ agree the prioritisation
	• consider the topics to be added under the 'watching brief' horizon scanning function;
	• consider the recommended committee workplan for 2025/2026; and
	• consider whether advice from additional external advisors or invited speakers would help in achieving the work recommendations.

Resource implications:	Subject to committee recommendations
Implementation date:	As per committee workplan for 2025-2026 (Annex D)
Communication(s):	Publication of committee papers, minutes and associated Clinic Focus article; if required, public-facing information can be developed and updated
Organisational risk:	Low

1. Background

1.1. The Authority established a horizon scanning function in 2004 to identify and monitor emerging and ongoing priority topics that could impact upon the field of assisted reproduction or embryo research. By identifying these topics, the Authority can consider the potential legal, ethical and scientific implications as they arise. We are then prepared to take a policy position on how these areas should be regulated and have guidance in place to ensure practice is carried out in a safe and appropriate manner. We can also make sure the public has access to reliable information about the new techniques and treatments.

1.2. The horizon scanning process is an annual cycle that feeds into the Scientific and Clinical Advances Advisory Committee (SCAAC) workplan and the Authority's consideration of scientific and ethical issues and standards. As part of the horizon scanning process, the HFEA convenes our annual Horizon Scanning Meeting during the **European Society of Human Reproduction and Embryology (ESHRE)** conference, bringing together international experts and regulatory bodies to discuss the latest issues and breakthroughs in fertility treatment and human embryo research. Learnings from such meetings are used to identify and monitor developments in the prioritised topics and guide the comprehensive literature searches conducted throughout the year.

1.3. Horizon topics were last prioritised in **February 2024**, when the committee agreed to rename four of the horizon scanning topics and introduce 'Testicular tissue transplantation to restore fertility in males' as a high priority topic.

2. Prioritisation process

2.1. The process for identifying literature uses the PubMed database to retrieve literature published since the topic was last discussed or prioritised. Where a new topic has been introduced, a literature search for publications across the past ten years is performed and a short summary of the main findings is given. Should significant developments in an existing topic be identified, a briefing may also be provided to highlight any key advances to the SCAAC.

2.2. The scope of each topic is based on the progression of research and its relevance to the remit and function of the HFEA. To account for developments in research, the search strings used are refined annually. Over the coming year, the Executive will continue to standardise the horizon scanning process and migrate the search function to Ovid to align with the updated literature search process for treatment add-ons.

2.3. Briefings on horizon scanning topics are only written if a new topic is suggested for introduction or the Executive wish to highlight a significant development in a topic ahead of the next scheduled discussion. Briefings relevant to the 2024/25 horizon scanning process can be found in Annex A of this paper. A comprehensive list of the publications identified during the literature search is provided in Annex B (circulated separately). The scope of each topic is defined under the relevant subheading.

2.4. Due to an increase in the number of topics considered during the horizon scanning function, it is not possible for the committee to discuss each horizon scanning topic on a regular basis. Although we continue to keep an eye on developments across all topics during this annual literature search, the frequency at which topics are discussed by the SCAAC is determined by

their priority, date of last discussion, and relevance to the remit and ongoing work of the HFEA. Between discussions, the committee continue to actively monitor publications relevant to prioritised topics and other relevant developments, under the standing item 'Relevant public health developments and research findings'. Such discussions are scheduled as required.

2.5. The following criteria can be used as a guide to categorise topics as **high**, **medium**, or **low priority**:

- Within the HFEA's remit
- Timescale for likely introduction (now or within 3 years)
- High patient demand/clinical use if it were to be introduced
- Technically feasible
- Ethical issues raised or public interest

2.6. Topics are **high priority** if they are within the HFEA's remit and meet at least two other criteria. High priority categorisation is also given to established techniques or issues that fall within the HFEA's remit and require ongoing monitoring or provision of patient information.

2.7. Topics are **medium priority** if they are within the HFEA's remit and meet one other criterion, or are outside the HFEA's remit but meet at least two other criteria.

2.8. Topics are **low priority** if they meet one criterion but are outside the HFEA's remit and unlikely to impact on research or treatment in the near future.

2.9. In some cases, it may be appropriate to categorise topics according to their relevance to the work of the HFEA rather than according to the criteria above eg stem cell-based embryo models are not with the HFEA's remit but are relevant to our work on law reform, therefore has been a high priority topic.

2.10. As agreed at the SCAAC's February 2024 meeting, the topic of 'Treatment add-ons' has been separated from the horizon scanning process and is to be performed independently every five years. The most recent review of the treatment add-ons ratings was conducted in July 2023. Between reviews, the committee continue to actively monitor publications that could change the rating of an existing add-on, or introduce a new add-on, under the standing item 'Relevant public health developments and research findings'.

2.11. The following sections of this paper lay out the recommended priority for each horizon scanning topic and an associated schedule for their discussion. A table detailing the priority categorisation is provided in Annex C, with the recommended workplan detailed in Annex D.

3. High priority issues

3.1. Listed in alphabetical order, the Executive considers the following topics to be high priority for 2025:

- Alternative methods to derive embryonic and embryonic-like stem cells
- Artificial intelligence (AI), robotics and automation in fertility treatment
- Emerging technologies in gamete and embryo testing
- Germline/heritable genome editing
- In vitro derived gametes (IVGs)
- Mitochondrial donation
- Scientific considerations relevant to the '14-day rule'
- Stem cell-based embryo models (SCBEM)

- Testicular tissue transplantation to restore fertility in males

4. Medium priority issues

4.1. Listed in alphabetical order, the Executive considers the following topics to be medium priority for 2025:

- Health outcomes in children born from ART (including the impact of culture media)
- Health outcomes for ART patients (including gestational surrogates and egg donors) – suggested addition, to be determined.
- Impact of long-term cryopreservation of gametes and embryo
- Impact of the microbiome on fertility and fertility treatment outcomes
- Reproductive organoids – suggested addition, to be determined.

4.2. As part of the 'Health outcomes in children conceived by ART (including the impact of culture media)' item to be discussed at this committee meeting, the committee will be considering if 'Health outcomes for ART patients (including gestational surrogates and egg donors)' should be added as a new prioritised topic. If the introduction of a new topic is recommended, the Executive suggests that this should be considered as a medium priority and scheduled for discussion in June 2025.

4.3. Following discussions at the HFEA's 2024 Horizon Scanning Meeting, the Executive have additionally recommended that 'Reproductive organoids' is separated from the topic of SCBEM for independent consideration. A briefing on this topic is given in Annex A of this paper.

5. Low priority issues

5.1. The Executive considers the following topic to be a low priority:

- Impact of stress on fertility treatment outcomes

5.2. The current paper on the 'Impact of stress on fertility treatment outcomes' (paper HFEA (03/02/2025) 006) presents inconclusive findings on whether increased stress levels during treatment have a negative impact on outcomes. It is also considered to fall out of the remit of the HFEA, meeting only the criteria of raising public interest. Following discussions at this meeting, the committee may wish to move monitoring developments in this topic to the 'watching brief'.

6. Watching Brief

6.1. As part of our horizon scanning process, we are introducing a list of 'watching brief' topics. This will allow us to monitor issues that, while not currently meeting the prioritisation criteria, present concerns or opportunities that warrant continued oversight by the committee.

6.2. The Executive propose that a full literature search on the watching brief topics is conducted every two to three years and presented to the SCAAC within the horizon scanning paper. As topics will not be scheduled for discussion with a paper, significant research developments relevant to the 'watching brief' topics (i.e. large studies of good quality) will be highlighted to the

committee ad hoc under the standing item 'Relevant public health developments and research findings'.

6.3. Should developments be deemed significant members will have the opportunity to consider watching brief topics for prioritisation. This expanded approach will enable the committee to remain informed and responsive to developments in these areas as they evolve.

6.4. Topics proposed for inclusion include:

- Artificial wombs for early or whole gestation (ectogenesis)
- Impact of environmental toxins on fertility treatment outcomes
- Understanding the genetic basis of infertility
- Use of ICSI for non-male and mild-male factor infertility
- Impact of stress on fertility treatment outcomes – suggested deprioritisation, to be determined.

6.5. With the introduction of 'Reproductive organoids' as a prioritised topic, and the monitoring of advances in embryo culture systems though topics of 'Scientific developments relevant to the 14-day rule', the Executive propose that the topic of 'Artificial wombs for early or whole gestation (ectogenesis)' is removed from the prioritised list of horizon scanning topics. Although artificial womb and placenta technologies for late gestation support fall outside the remit of the HFEA, the Executive will continue to monitor advances through the watching brief process due to their potential impact on the boundary of viability.

6.6. In light of adding 'understanding the genetic basis of infertility' to the Watching Brief list of topics, genetic testing for male infertility will be removed from the scope of the 'emerging technologies in gamete and embryo testing' topic.

7. Recommendations

7.1. Members are asked to:

- consider the scope and priority of topics identified through the horizon scanning process:
  - review the scope of the prioritised topics (given in Annex B),
  - consider the proposal that 'Reproductive organoids' and 'Health outcomes for patients undergoing fertility treatment (including gestational carriers and egg donors)' are added as new topics, and
  - agree the prioritisation.
- consider the addition of the 'watching brief' to the horizon scanning function;
- consider the recommended committee workplan for 2024/2025; and
- consider whether advice from additional external advisors would help in achieving the work recommendations.

8. Annex A: Briefings on key issues identified during horizon scanning

8.1. Following discussions at the HFEA's 2024 Horizon Scanning Meeting, the Executive suggest that 'Reproductive organoids' is separated from the topic of SCBEM for independent consideration. The below briefing has been written to highlight research in organoid models and

systems which can be used to study reproductive tract and the process of implantation. The scope of this topic does not extend to all organoid research, such as neural organoids which fall outside the regulatory remit of the HFEA.

8.2. The Executive considers this topic to fall outside the HFEA's regulatory remit, recommending that the topic is considered as medium priority due to increasing technical feasibility and ethical/public interest.

8.3. As mentioned in paragraph 4.2, the Committee is additionally being asked to consider whether 'Health outcomes for ART patients (including gestational surrogates and egg donors)' should be added as a new prioritised topic.

Reproductive organoids

Background

8.4. The SCAAC's interest in the use of organoids to recreate the reproductive system in vitro stems from their potential application to study and support in vitro gametogenesis (IVG), the early development of embryos and stem cell-based embryo models (SCBEM) ex utero, as well as to inform clinical practice and ultimately, to improve IVF success rates.

8.5. For example, testis and ovarian organoids provides a foundation for IVG, offering a novel platform for studying gamete development and addressing infertility. Similarly, fallopian tube organoids can facilitate the study of fertilisation. Cervical organoids can be instrumental in exploring sexually transmitted infections (STIs). Endometrial organoids enable investigation of endometrial disorders such as endometriosis and polycystic ovary syndrome (PCOS), as well as investigations into endometrial receptivity and the microbiome. These systems also hold potential for screening compounds for treating infertility and could provide a platform to study ovarian ageing.

8.6. The topic of reproductive organoids encompasses research on methods to create the organoids and their applications to study reproductive tract biology in health and disease. The literature search for this new topic covers a ten-year period between 1 January 2015 and 31 December 2024.

Summary of developments

8.7. Traditionally, modelling of the development or disease of tissues and organs (including male and female reproductive tract biology) have been attempted with various approaches, including two-dimensional (2D) primary cell cultures, immortalised or transformed cell lines, spheroids, organotypic tissue piece or organ explant cultures, and animal models (Schutgens and Clevers, 2020).

8.8. Although such conventional approaches have contributed significantly to the understanding of the reproductive tract biology in health and disease, they present with many challenges and limitations. For example, with 2D culture systems, cell lines present with karyotypic abnormalities, lack genetic diversity and polarised orientation, while primary cell cultures are difficult to isolate and establish and lack all cell types that reside in the original tissue. All these drawbacks limit the ability of these approaches to fully recapitulate the spatial complexity cellular interactions and cellular heterogeneity of the human reproductive tract (Haider and Beristain, 2023).

8.9. Recently, organoid cultures have been developed that circumvent many of the disadvantages associated with cell lines. An organoid is defined as a 3D structure grown from stem cells that consists of organ-specific cell types that self-organise through cell sorting and spatially restricted lineage commitment (Clevers, 2016). Organoid cultures can be established from embryonic stem cells (ESC) or induced pluripotent stem cells (iPSC) - together referred to as pluripotent stem cells or PSCs - and from adult stem cells (ASCs) (Clevers, 2016; Schutgens and Clevers, 2020).

8.10. The development of 3D organoid models which recapitulate some of the cell diversity, architecture and functional features of an organ system have been utilised for studying development, function and disease in reproductive biology (Alzamil *et al.*, 2021; Chumduri and Turco, 2021; Francés-Herrero *et al.*, 2022; Haider and Beristain, 2023). With few exceptions, the conditions to isolate, expand, and establish stem cell lines from human reproductive tissues are scarcely known or not yet developed. Consequently, establishment of reproductive organoids is reliant on isolating complex stem/progenitor cell populations enriched from primary tissue sources, or the use of primary cells isolated from digested tissue or the use of primary cells isolated from digested tissue (Haider and Beristain, 2023). Additionally, research into assembloids has gained traction in the past few years. Assembloids are defined as self-organising 3D culture systems, which are more complex than organoids and combine different organoids, or organoids with specialised cell types or primary tissue explants within one functional framework (Kanton and Paş Ca, 2022; Kleinová et al., 2024)

8.11. Organoid systems to study the human reproductive tract include organoids of the ovaries, fallopian tubes, endometrial or uterine lining, cervix and testis. In the reproductive tract modelling research, assembloids are specifically utilised to model cell interactions or molecular signalling pathways at the foetal-maternal interface, such as those involved in embryo implantation and placentation, endometrial growth, differentiation and disease cell interactions.

Level of work recommendation

8.12. The Committee will be asked to monitor any further developments in the scientific and clinical literature relating to reproductive organoids as part of the committee's workplan. The Executive will continue to monitor any developments as part of the annual horizon scanning.

References

8.13. A full reference list detailing all published literature on the topic of 'Reproductive organoids' between 1st January 2014 and 31st December 2024 is given in Annex B (circulated separately). References for this briefing are as below:

Alzamil, L., Nikolakopoulou, K., & Turco, M. Y. (2021). Organoid systems to study the human female reproductive tract and pregnancy. Cell Death and Differentiation, 28(1), 35–51. https://doi.org/10.1038/s41418-020-0565-5

Chumduri, C., & Turco, M. Y. (2021). Organoids of the female reproductive tract. Journal of Molecular Medicine, 99(4), 531–553. https://doi.org/10.1007/s00109-020-02028-0

Clevers, H. (2016). Modeling Development and Disease with Organoids. Cell, 165(7), 1586–1597. https://doi.org/10.1016/J.CELL.2016.05.082

Francés-Herrero, E., Lopez, R., Hellström, M., De Miguel-Gómez, L., Herraiz, S., Brännström, M., Pellicer, A., & Cervelló, I. (2022). Bioengineering trends in female reproduction: a

systematic review. Human Reproduction Update, 28(6), 798–837. https://doi.org/10.1093/HUMUPD/DMAC025

Haider, S., & Beristain, A. G. (2023). Human organoid systems in modeling reproductive tissue development, function, and disease. Human Reproduction, 38(8), 1449–1463. https://doi.org/10.1093/humrep/dead085

Kanton, S., & Paş Ca, S. P. (2022). Human assembloids. https://doi.org/10.1242/dev.201120

Kleinová, M., Varga, I., Čeháková, M., Valent, M., & Klein, M. (2024). Exploring the black box of human reproduction: endometrial organoids and assembloids - generation, implantation modeling, and future clinical perspectives. Frontiers in Cell and Developmental Biology, 12, 1482054. https://doi.org/10.3389/fcell.2024.1482054

Schutgens, F., & Clevers, H. (2020). Human Organoids: Tools for Understanding Biology and Treating Diseases. Annual Review of Pathology: Mechanisms of Disease, 15(Volume 15, 2020), 211–234. https://doi.org/10.1146.

Health outcomes for ART patients (including gestational surrogates and egg donors)

8.14. The paper on 'Health outcomes in children born from ART' being presented at this meeting, contains studies identified on the topic and briefly outlines the scope of this proposed topics, which includes:

- maternal morbidity among those undergoing fertility treatment including gestational carriers
- surgical and other complications (such as Ovarian Hyperstimulation Syndrome, OHSS) arising from the fertility treatment
- the relationship between fertility drugs and adverse health outcomes later in life (eg cancer incidence).

Level of work recommendation

8.15. The Committee will be asked to monitor any further developments in the scientific and clinical literature relating to health outcomes in ART patients as part of the committee's workplan. The Executive will continue to monitor any developments as part of the annual horizon scanning.

References

FARHUD, D. D., ZOKAEI, S., KEYKHAEI, M., HEDAYATI, M., & ZARIF YEGANEH, M. (2021). In-Vitro Fertilization Impact on the Risk of Breast Cancer: A Review Article. Iranian Journal of Public Health. https://doi.org/10.18502/ijph.v50i3.5583

Gennari, A., Costa, M., Puntoni, M., Paleari, L., De Censi, A., Sormani, M. P., Provinciali, N., & Bruzzi, P. (2015). Breast cancer incidence after hormonal treatments for infertility: systematic review and meta-analysis of population-based studies. Breast Cancer Research and Treatment, 150(2), 405–413. https://doi.org/10.1007/s10549-015-3328-0

Hershko Klement, A., Asali, A., Shalev Ram, H., Haikin-Herzberger, E., Shlezinger, R., Wiser, A., & Miller, N. (2024). Cancer-Related Morbidity Among Patients Conceiving Through Oocyte Donation: A Healthcare Registry Cohort Study. Journal of Women's Health, 33(12), 1730–1734. https://doi.org/10.1089/jwh.2024.0248

Klement, A. H., Asali, A., Ram, H. S., Haikin-Herzberger, E., Shlezinger, R., Wiser, A., & Miller, N. (2024). Cancer-Related Morbidity Among Patients Conceiving Through Oocyte Donation: A

Healthcare Registry Cohort Study. Journal of Women's Health (2002), 33(12). https://doi.org/10.1089/JWH.2024.0248

Kramer, W., Schneider, J., & Schultz, N. (2009). US oocyte donors: a retrospective study of medical and psychosocial issues. Human Reproduction, 24(12), 3144–3149. https://doi.org/10.1093/humrep/dep309

Lerner-Geva, L., Rabinovici, J., & Lunenfeld, B. (2010). Ovarian Stimulation: Is There a Long-Term Risk for Ovarian, Breast and Endometrial Cancer? Women's Health, 6(6), 831–839. https://doi.org/10.2217/WHE.10.67

Schneider, J., Lahl, J., & Kramer, W. (2017). Long-term breast cancer risk following ovarian stimulation in young egg donors: a call for follow-up, research and informed consent. Reproductive BioMedicine Online, 34(5), 480–485. https://doi.org/10.1016/j.rbmo.2017.02.003

Söderström-Anttila, V., Miettinen, A., Rotkirch, A., Nuojua-Huttunen, S., Poranen, A.-K., Sälevaara, M., & Suikkari, A.-M. (2016). Short- and long-term health consequences and current satisfaction levels for altruistic anonymous, identity-release and known oocyte donors. Human Reproduction, 31(3), 597–606. https://doi.org/10.1093/humrep/dev324

van den Belt-Dusebout, A. W., Spaan, M., Lambalk, C. B., Kortman, M., Laven, J. S. E., van Santbrink, E. J. P., van der Westerlaken, L. A. J., Cohlen, B. J., Braat, D. D. M., Smeenk, J. M. J., Land, J. A., Goddijn, M., van Golde, R. J. T., van Rumste, M. M., Schats, R., Józwiak, K., Hauptmann, M., Rookus, M. A., Burger, C. W., & van Leeuwen, F. E. (2016). Ovarian Stimulation for In Vitro Fertilization and Long-term Risk of Breast Cancer. JAMA, 316(3), 300. https://doi.org/10.1001/jama.2016.9389

Velez, M. P., Ivanova, M., Shellenberger, J., Pudwell, J., & Ray, J. G. (2024). Severe Maternal and Neonatal Morbidity Among Gestational Carriers. Annals of Internal Medicine, 177(11), 1482–1488. **https://doi.org/10.7326/M24-0417**

9. Annex B: Horizon scanning reference lists and topic scope

9.1. Due to the volume of publications identified during the 2024 horizon scanning literature search, Annex B has been circulated to the committee as a separate document.

9.2. Unlike in previous years, the Executive has provided a high-level summary of the topic scope within this Annex.

9.3. Annex B will be made available on the **SCAAC webpage**.

10. Annex D: Topic priority categorisation table

10.1. The table below details the categorisation of each topic and the recommended priority rating.

Topic	Is it within HFEA remit?	Is timescale for likely clinical introduction now or within 3 years?	Would there be high patient demand/clinical use if it were introduced?	Is it technically feasible?	Are there ethical issues or public interest raised?	Recommended rating
Alternative methods to derive embryonic and embryonic-like stem cells	Yes	N/A	N/A	Yes	Yes	High
Artificial intelligence (AI), robotics and automation in fertility treatment	Yes	Yes	Yes	Yes	Yes	High
Emerging technologies in gamete and embryo testing	Yes	Yes	Yes	Yes	Yes	High
Germline/heritable genome editing	Yes	No	Possibly	Yes	Yes	High
Impact of long-term cryopreservation of gametes and embryo	Yes	Yes	Yes	Yes	Yes	High
In vitro derived gametes (IVGs)	Yes	No	Yes	Yes	Yes	High
Mitochondrial donation	Yes	Yes	No	Yes	Yes	High
Scientific considerations relevant to the ‘14-day rule'	Yes	N/A	N/A	Yes	Yes	High
Stem-cell based embryo models (SCBEM)	No	No	No	Yes	Yes	High
Testicular tissue transplantation to restore fertility in males	Yes	Yes	No	Yes	No	High

Health outcomes in children born from ART (including the impact of culture media)	No	Yes	N/A	N/A	Yes	Medium
Health outcomes for ART patients (including gestational surrogates and egg donors)	No	Yes	N/A	N/A	Yes	Medium
Impact of the microbiome on fertility and fertility treatment outcomes	No	Yes	Yes	Yes	Yes	Medium
Reproductive organoids	No	N/A	N/A	Yes	Yes	Medium
Impact of stress on fertility treatment outcomes	No	N/A	N/A	N/A	Possibly	Low or Watching Brief
Artificial wombs for early or whole gestation (ectogenesis)	No	No	No	No	Yes	Watching Brief

11. Annex D: Committee workplan 2025-2026

11.1. The below table presents the anticipated workplan of the SCAAC for 2025/26. Should the priorities of the Authority change, alterations to the workplan may be agreed with the SCAAC Chair.

Priority topic	Item	Possible speaker(s)	Last discussed	Meeting
Impact of the microbiome on fertility treatment outcomes	Literature review	Internal	October 2023	June 2025
Health outcomes for ART patients (including gestational surrogates and egg donors)	Literature review	Internal	N/A – new topic	June 2025
Germline/heritable genome editing	Literature review	Academic	February 2024	October 2025
Reproductive organoids	Literature review	Academic	N/A – new topic	October 2025
Testicular transplantation to restore fertility in males	Literature review	Academic	N/A – new topic	October 2025
Horizon scanning and agreeing workplan for 2026/27	Workplan review	Internal	February 2025	February 2026
Impact of long-term cryopreservation	Literature review	Internal	February 2024	February 2026
Emerging technologies in embryo and gamete testing	Literature review	Internal	June 2024	February 2026
Artificial intelligence, robotics and automation in fertility treatment	Literature review	Internal	February 2024	June 2026
Alternative methods to derive embryonic and embryonic-like stem cells	Literature review	Internal	June 2024	June 2026

11.2. Discussions on further horizon scanning topics, including ‘Scientific developments relevant to the 14-day rule’, ‘Stem-cell based embryo models’, ‘In vitro derived gametes’ and ‘Mitochondrial donation’ will be incorporated into the 2026/27 SCAAC workplan.

Annex E: Committee purpose and function as per standing orders

11.3. To support the committee’s discussion about their planned activity for 2025/26 the Executive would like to remind members of the purpose and function of the Committee, as detailed in section 5 of the HFEA standing orders.

11.4. Section 5.1 of Annex A states that the purpose of the Committee "is to advise the Authority on scientific and clinical developments (including research) in assisted conception, embryo research and related areas and to make decisions relating to authorised processes."

11.5. Section 5.3 of Annex A states the function of the Committee shall be to:

- make recommendations to the Authority on the safety and efficacy of scientific and clinical developments (including research) in assisted conception, embryo research and related areas;
- make recommendations to the Authority on patient information relating to those scientific and clinical developments;
- advise the Authority on significant implications for licensing and regulation arising out of such developments, and;
- where required, work with the Authority members to consider the social, ethical and legal implications arising out of such developments.

Rating review for treatment add-on - Androgen supplementation

Details about this paper

Area(s) of strategy:	The right information
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	9
Paper number:	HFEA (03/02/2025) 009
Meeting date:	03 February 2025
Author:	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/ recommendation?	For recommendation
Recommendation:	Members are asked to: • consider the quality of evidence for androgen supplementation 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 that may be offered in fertility clinics in addition to routine treatment with the claim that they can improve treatment outcomes. As with all new treatments or technologies being introduced into reproductive medicine, we 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.

1.2. Medical professionals, academics or patient organisations can propose that we review the evidence base for a treatment add-on if they are concerned that it is being offered to patients in a UK licensed clinic:

- with the claim that it will increase 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
- there is evidence that an add-on treatment may reduce treatment effectiveness or there are potential safety concerns.

1.3. SCAAC first recommended that androgen supplementation be considered as a separate treatment add-on from immunological tests and treatments at the **October 2021** meeting. An application was taken to the **June 2022** meeting, where it was agreed that androgen supplementation did not meet the criteria set out by the treatment add-ons decision tree in place at the time.

1.4. However, in **July 2022** the Authority reviewed the process for reviewing and rating treatment add-ons, agreeing:

- the definition of treatment add-ons that the HFEA will provide information for;
- to move to a five-category rating scale;
- to rate additional outcomes, such as miscarriage, and outcomes for specific patient groups, such as male-factor infertility, in addition to live births for specific add-ons; and
- to expand the evidence base in line with SCAAC's recommendation that in the absence of high-quality randomised controlled trials (RCTs) or systematic reviews the evidence base should be expanded to non-randomised studies of intervention (NRSIs).

1.5. Following revisions to the treatment add-ons application form and decision tree, the Committee reconsidered the application to include androgen supplementation as a new add-on to the HFEA's rated list in **June 2024.** At that meeting it was agreed that androgen supplementation is eligible for an HFEA rating.

1.6. As recorded in the **minutes** of the June 2024 meeting, the Committee recommended that only testosterone and not dehydroepiandrosterone (DHEA) was considered as a treatment add-on in relation to androgen supplementation as DHEA is only accessible on the UK market if prescribed by a clinician. However, it is known that patients are able to purchase both testosterone and DHEA (as a health supplement) from overseas via online retailers and it is therefore being used by patients accessing fertility care in the UK.

1.7. Following discussions with the add-ons review panel it was agreed that providing a rating for the use of DHEA as a supplement will help to inform patients about the effectiveness and safety of this intervention. The below paper therefore includes the use of DHEA as a treatment add-on is also included in this paper.

1.8. The review panel identified live birth rate (LBR) or ongoing pregnancy rate[1] (OGPR) and oocyte retrieval as outcomes relevant to the use of androgen supplementation as a treatment add-on. Outcomes for older women and patients with poor ovarian response (POR) or diminished ovarian reserve (DOR) were requested in addition to outcomes for the general population. Inclusion criteria for studies and the definitions used are summarised in Annex D.

2. Literature search – updated process

2.1. The decision tree for determining how evidence will be used by SCAAC when assigning add-ons rating reflects the agreed process and can be found at Annex A.

2.2. 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[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 2014 and 6th December 2024.

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[3]) for each treatment add-on.

3.2. The independent reviewer reassessed the traffic light ratings in light of the new five-category rating system and the literature identified.

3.3. 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.

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[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.

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

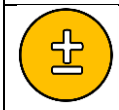
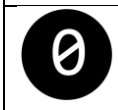
[3] GRADE is an approach for grading the quality of evidence and the strength of recommendations. It was developed by the Grading of Recommendations, Assessment, Development and Evaluation Working Group.

3.4. The assessments made by the independent reviewer are from a methodological perspective without expertise in the clinical or scientific context. The findings of the assessment for each add-on and the independent reviewer's recommended ratings can be found as Annex E.

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 reflects the agreed process and 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. Recommendations

5.1. The Committee is asked to:

- consider the quality of evidence for androgen supplementation as a treatment add-on based on the findings from an independent assessor;
- agree and recommend ratings for each outcome and population.

6. Considerations and recommendations for rating androgen supplementation and DHEA as treatment add-on

6.1. The **ESRHE** good practice recommendations concluded that the current evidence does not support the routine use of adjuncts (such as testosterone and DHEA) before or during ovarian stimulation and that these are not recommended. However, it was noted that use of these adjuncts based on individual patient characteristics or in specific clinical circumstances may warrant further investigation. This recommendation is supported by the **ESHRE guideline: ovarian stimulation for IVF/ICSI**.

6.2. In addition, **Cochrane** have published two systematic reviews on the use of androgens, specifically DHEA and testosterone, for women undergoing assisted reproduction (Nagles et al., 2015; Naik et al., 2024). The most recent review published June 2024 (Naik et al., 2024), concluded that pre-treatment with testosterone likely improves live birth and clinical pregnancy rates in women undergoing IVF identified as poor responders, whereas little or no difference was seen when DHEA was used. It was noted that, further research is needed to identify the optimal duration of treatment with testosterone (Naik et al., 2024).

6.3. A further 15 systematic reviews and meta-analyses addressing the use of testosterone or DHEA in the defined patient groups were identified and are referenced in Annex C.

Dehydroepiandrosterone (DHEA) supplementation

6.4. The Committee is asked to consider the independent reviewers report and the following recommended ratings for DHEA. This review included 16 studies, listed in Annex B.

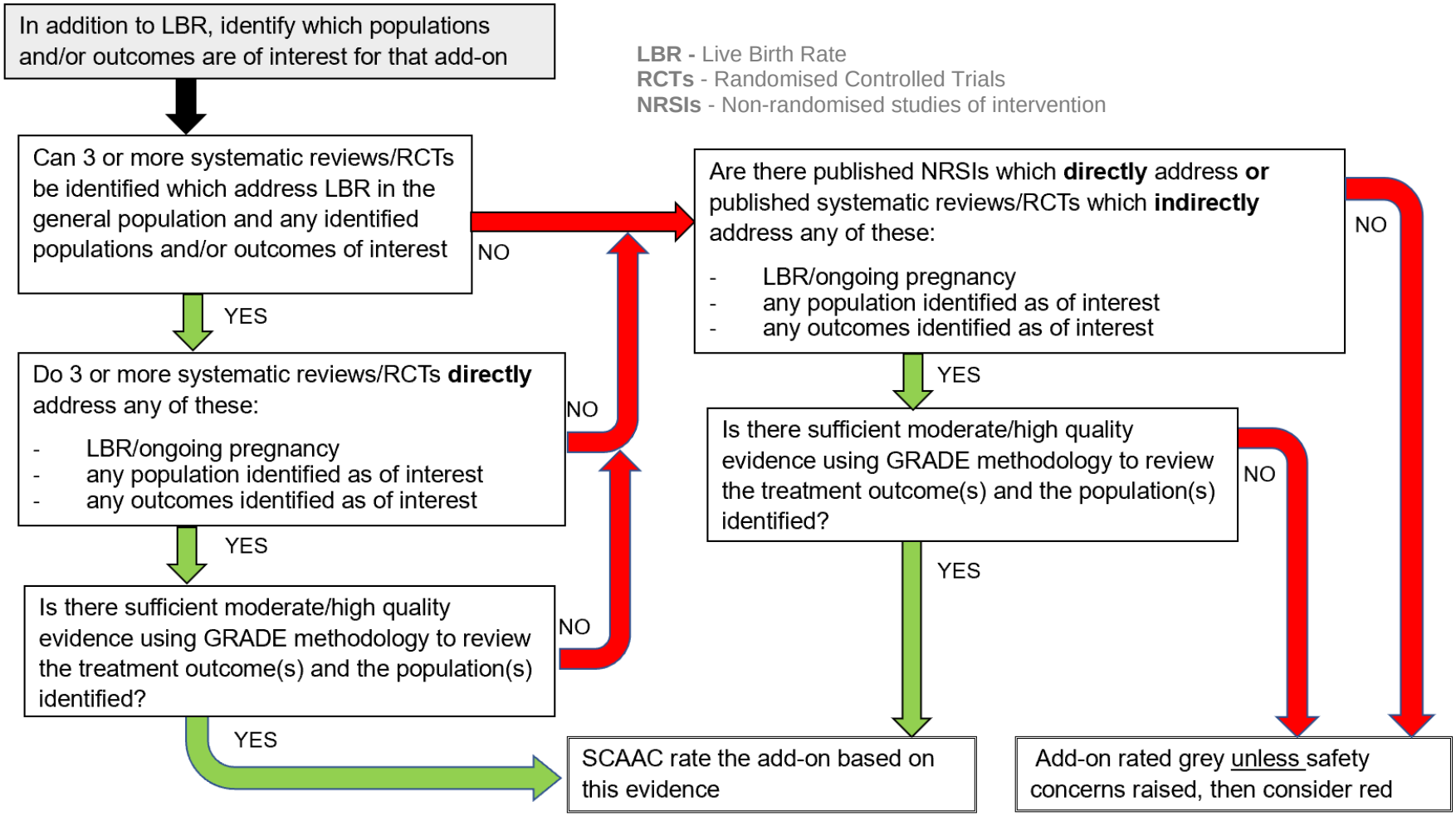
Expert review February 2025 (current)	
	• GREY for live birth rate for most fertility patients • GREY for oocyte retrieval for most fertility patients • GREY for ongoing pregnany rate for most fertility patients • GREY for live birth rate for older women • GREY for oocyte retrieval for older women
 **or** 	• **AMBER/BLACK for** oocyte retrieval in women with poor/diminished ovarian reserve
	• BLACK for live birth rate in women with poor/diminished ovarian reserve

Testosterone supplementation

6.5. The Committee is asked to consider the independent reviewers report and the following recommended ratings for testosterone. This review included 14 studies, listed in Annex B.

Expert review February 2025 (current)	
	• GREY for live birth rate for most fertility patients • GREY for oocyte retrieval for most fertility patients • GREY for live birth rate in women with poor/diminished ovarian reserve • GREY for oocyte retrieval in women with poor/diminished ovarian reserve • GREY for live birth rate in older women • GREY for oocyte retrieval in older women

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



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

8. Annex B: References of reviewed studies

Aflatoonain A, Saeed L, Hosseinisadat R. The effect of androgen administration on in vitro fertilization outcome in poor responders undergoing ovarian stimulation with microdose protocol: A randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol* [Internet] 2022;279:72–76. Eur J Obstet Gynecol Reprod Biol.

Al-Jeborry MM. Efficacy of transdermal testosterone in assisted reproduction outcome of poor responders. *Ann Trop Med Public Health* 2019;22:. Wolters Kluwer Medknow Publications.

Artini PG, Simi G, Ruggiero M, Pinelli S, Berardino OM Di, Papini F, Papini S, Monteleone P, Cela V. DHEA supplementation improves follicular microenviroment in poor responder patients. *Gynecological Endocrinology* [Internet] 2012;28:669–673. Taylor & Francis.

Bosdou JK, Venetis CA, Dafopoulos K, Zepiridis L, Chatzimeletiou K, Anifandis G, Mitsoli A, Makedos A, Messinis IE, Tarlatzis BC, *et al.* Transdermal testosterone pretreatment in poor responders undergoing ICSI: a randomized clinical trial. *Hum Reprod* [Internet] 2016;31:977–985. Hum Reprod.

Fábregues F, Peñarrubia J, Creus M, Manau D, Casals G, Carmona F, Balasch J. Transdermal testosterone may improve ovarian response to gonadotrophins in low-responder IVF patients: a randomized, clinical trial. *Hum Reprod* [Internet] 2009;24:349–359. Hum Reprod.

Fu J, Jiang H, Li L, Xin A, Sun Y, Sun X. Effect of dehydroepiandrosterone supplementation on the embryo quality and follicular fluid markers in patients with diminished ovarian reserve. 2017;

Hoang QH, Ho HS, Do HT, Nguyen TV, Nguyen HP, Le MT. Therapeutic effect of prolonged testosterone pretreatment in women with poor ovarian response: A randomized control trial. *Reprod Med Biol* [Internet] 2021;20:305–312. John Wiley & Sons, Ltd.

Kara M, Aydin T, Aran T, Turktekin N, Ozdemir B. Does dehydroepiandrosterone supplementation really affect IVF-ICSI outcome in women with poor ovarian reserve? *Eur J Obstet Gynecol Reprod Biol* [Internet] 2014;173:63–65. Eur J Obstet Gynecol Reprod Biol.

Kim C-H, Ahn J-W, Moon J-W, Kim S-H, Chae H-D, Kang B-M. Ovarian Features after 2 Weeks, 3 Weeks and 4 Weeks Transdermal Testosterone Gel Treatment and Their Associated Effect on IVF Outcomes in Poor Responders. *Dev Reprod* [Internet] 2014;18:145. Korean Society of Developmental Biology.

Kim CH, Howles CM, Lee HA. The effect of transdermal testosterone gel pretreatment on controlled ovarian stimulation and IVF outcome in low responders. *Fertil Steril* [Internet] 2011;95:679–683. Fertil Steril.

Kotb MMM, Hassan AGMA, AwadAllah AMA. Does dehydroepiandrosterone improve pregnancy rate in women undergoing IVF/ICSI with expected poor ovarian response according to the Bologna criteria? A randomized controlled trial. *Eur J Obstet Gynecol Reprod Biol* [Internet] 2016;200:11–15. Eur J Obstet Gynecol Reprod Biol.

Li CJ, Lin L Te, Tsui KH. Dehydroepiandrosterone Shifts Energy Metabolism to Increase Mitochondrial Biogenesis in Female Fertility with Advancing Age. *Nutrients* [Internet] 2021;13:. Nutrients.

Lin L Te, Cheng JT, Wang PH, Li CJ, Tsui KH. Dehydroepiandrosterone as a potential agent to slow down ovarian aging. *J Obstet Gynaecol Res* [Internet] 2017;43:1855–1862. J Obstet Gynaecol Res.

Marzal Escriva A, Diaz-Garcia C, Monterde M, Rubio JM, Pellicer A. Antral Follicle Priming Before Intracytoplasmic Sperm Injection in Previously Diagnosed Low Responders: A Randomized Controlled Trial (FOLLPRIM). *J Clin Endocrinol Metab* [Internet] 2015;100:2597–2605. J Clin Endocrinol Metab.

Massin N, Cedrin-Durnerin I, Coussieu C, Galey-Fontaine J, Wolf JP, Hugues JN. Effects of transdermal testosterone application on the ovarian response to FSH in poor responders undergoing assisted

reproduction technique--a prospective, randomized, double-blind study. *Hum Reprod* [Internet] 2006;21:1204–1211. Hum Reprod.

Moawad A, Shaeer M. Long-term androgen priming by use of dehydroepiandrosterone (DHEA) improves IVF outcome in poor-responder patients. A randomized controlled study. *Middle East Fertil Soc J* 2012;17:268–274. No longer published by Elsevier.

Mostajeran F, Tehrani H, Ghoreishi E. Effects of Dehydroepiandrosterone on In Vitro Fertilization Among Women Aging Over 35 Years and Normal Ovarian Reserve. *J Family Reprod Health* [Internet] 2018;12:129.

Muhammed EM, Khafajy ZH Al, Rasool HA. The Effect of Testosterone Gel for Patients with Poor Ovarian Response Prior to IVF Cycles: Is It really Effective? *International Journal of Drug Delivery Technology* 2023;13:285–289. Dr. Yashwant Research Labs Pvt. Ltd.

Narkwichean A, Maalouf W, Baumgarten M, Polanski L, Raine-Fenning N, Campbell B, Jayaprakasan K. Efficacy of Dehydroepiandrosterone (DHEA) to overcome the effect of ovarian ageing (DITTO): A proof of principle double blinded randomized placebo controlled trial. *Eur J Obstet Gynecol Reprod Biol* [Internet] 2017;218:39–48. Eur J Obstet Gynecol Reprod Biol.

Saharkhiz N, Zademodares S, Salehpour S, Hosseini S, Nazari L, Tehrani H. The effect of testosterone gel on fertility outcomes in women with a poor response in in vitro fertilization cycles: A pilot randomized clinical trial. *Journal of Research in Medical Sciences* 2018;23:. Wolters Kluwer Medknow Publications.

Sharma N, Nayar KD. The Effect of Transdermal Testosterone Gel Pretreatment on IVF Outcomes in Patients with Poor Ovarian Reserve. *Journal of South Asian Federation of Obstetrics and Gynaecology* [Internet] 2023;Available from: https://creativecommons.

Singh N, Parimalam P, Kumar S, Vanamail P. Role of transdermal testosterone gel pre-treatment on IVF outcome: a prospective randomized controlled trial with active control. *Int J Reprod Contracept Obstet Gynecol* 2021;10:3509. Medip Academy.

Subirá J, Algaba A, Vázquez S, Taroncher Dasí R, Mollá Robles G, Monzó Fabuel S, Baydal V, Ruiz Herreros A, García Camuñas N, Rubio Rubio JM. Testosterone does not improve ovarian response in Bologna poor responders: a randomized controlled trial (TESTOPRIM). *Reprod Biomed Online* [Internet] 2021;43:466–474. Reprod Biomed Online.

Tartagni M, Cicinelli M V., Baldini D, Tartagni M V., Alrasheed H, DeSalvia MA, Loverro G, Montagnani M. Dehydroepiandrosterone decreases the age-related decline of the in vitro fertilization outcome in women younger than 40 years old. *Reproductive Biology and Endocrinology* [Internet] 2015;13:1–6. BioMed Central Ltd.

Tartagni M, Pergola G De, Damiani GR, Pellegrino A, Baldini D, Tartagni M V., Alrasheed H, Salvia MA De, Loverro G. Potential benefit of dehydroepiandrosterone supplementation for infertile but not poor responder patients in a IVF program. *Minerva Ginecol* [Internet] 2014;67:7–12. Edizioni Minerva Medica.

Wang Z, Yang A, Bao H, Wang A, Deng X, Xue D, Tan H, Zhou Y, Wu C, Chen ZJ, *et al.* Effect of dehydroepiandrosterone administration before in vitro fertilization on the live birth rate in poor ovarian responders according to the Bologna criteria: A randomised controlled trial. *BJOG* [Internet] 2022;129:1030–1038. BJOG.

Wiser A, Gonen O, Ghetler Y, Shavit T, Berkovitz A, Shulman A. Addition of dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: a randomized prospective study. *Hum Reprod* [Internet] 2010;25:2496–2500. Hum Reprod.

Yeung TWY, Chai J, Li RHW, Lee VCY, Ho PC, Ng EHY. A randomized, controlled, pilot trial on the effect of dehydroepiandrosterone on ovarian response markers, ovarian response, and in vitro fertilization outcomes in poor responders. *Fertil Steril* [Internet] 2014;102:. Fertil Steril.

Yeung TWY, Chai J, Li RHW, Lee VCY, Ho PC, Ng EHY. A double-blind randomised controlled trial on the effect of dehydroepiandrosterone on ovarian reserve markers, ovarian response and number of oocytes in anticipated normal ovarian responders. *BJOG* [Internet] 2016;123:1097–1105. BJOG.

Zhang HH, Xu PY, Wu J, Zou WW, Xu XM, Cao XY, Wei LZ. Dehydroepiandrosterone improves follicular fluid bone morphogenetic protein-15 and accumulated embryo score of infertility patients with diminished ovarian reserve undergoing in vitro fertilization: a randomized controlled trial. *J Ovarian Res* [Internet] 2014;7:. J Ovarian Res.

9. Annex C: References of systematic reviews and meta-analyses

Conforti A, Carbone L, Girolamo R Di, Gabriele Iorio G, Guida M, Rosaria Campitiello M, Maria Ubaldi F, Rienzi L, Vaiarelli A, Cimadomo D, et al. Therapeutic management in women with a diminished ovarian reserve: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril [Internet] 2024;0: Elsevier.

Katsika ET, Bosdou JK, Goulis DG, Grimbizis GF, Kolibianakis EM. Higher live birth rate following transdermal testosterone pretreatment in poor responders: a systematic review and meta-analysis. Reprod Biomed Online [Internet] 2023;46:81–91. Elsevier Ltd.

Li J, Yuan H, Chen Y, Wu H, Wu H, Li L. A meta-analysis of dehydroepiandrosterone supplementation among women with diminished ovarian reserve undergoing in vitro fertilization or intracytoplasmic sperm injection. International Journal of Gynecology & Obstetrics [Internet] 2015;131:240–245. John Wiley & Sons, Ltd.

Liu Y, Hu L, Fan L, Wang F. Efficacy of dehydroepiandrosterone (DHEA) supplementation for in vitro fertilization and embryo transfer cycles: a systematic review and meta-analysis. Gynecological Endocrinology [Internet] 2018;34:178–183. Taylor & Francis.

Nagels HE, Rishworth JR, Siristatidis CS, Kroon B. Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. Cochrane Database Syst Rev [Internet] 2015;2015:. Cochrane Database Syst Rev.

Naik S, Lepine S, Nagels HE, Siristatidis CS, Kroon B, McDowell S. Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. Cochrane Database of Systematic Reviews [Internet] 2024;2024:. John Wiley and Sons Ltd.

Neves AR, Montoya-Botero P, Polyzos NP. Androgens and diminished ovarian reserve: the long road from basic science to clinical implementation. A comprehensive and systematic review with meta-analysis. Am J Obstet Gynecol [Internet] 2022;227:401-413.e18. Elsevier Inc.

Noventa M, Vitagliano A, Andrisani A, Blaganje M, Viganò P, Papaelo E, Scioscia M, Cavallin F, Ambrosini G, Cozzolino M. Testosterone therapy for women with poor ovarian response undergoing IVF: a meta-analysis of randomized controlled trials. J Assist Reprod Genet [Internet] 2019;36:673–683. J Assist Reprod Genet.

Perelló MA, Moreno JA, Crespo M, Espinós JJ, Checa MÁ. Does Dehydroepiandrosterone supplementation improve reproductive outcomes in patients with normal ovarian reserve undergoing in vitro fertilization? A systematic review and meta-analysis. Medicina Reproductiva y Embriología Clínica 2022;9:100120. No longer published by Elsevier.

Richardson A, Jayaprakasan K. The Use of Androgen Priming in Women with Reduced Ovarian Reserve Undergoing Assisted Reproductive Technology. Semin Reprod Med [Internet] 2021;39:207–219. Semin Reprod Med.

Wang J, Liu B, Wen J, Qu B. The Role of Dehydroepiandrosterone in Improving in vitro Fertilization Outcome in Patients with DOR/POR: A Systematic Review and Meta- Analysis. Comb Chem High Throughput Screen [Internet] 2023;26:916–927. Comb Chem High Throughput Screen.

Xu L, Hu C, Liu Q, Li Y. The Effect of Dehydroepiandrosterone (DHEA) Supplementation on IVF or ICSI: A Meta-Analysis of Randomized Controlled Trials. Geburtshilfe Frauenheilkd [Internet] 2019;79:705–712. Georg Thieme Verlag.

Yuan WS, Abu MA, Ahmad MF, Elias MH, Abdul Karim AK. Effects of Dehydroepiandrosterone (DHEA) Supplementation on Ovarian Cumulus Cells following In Vitro Fertilization (IVF)/Intra-Cytoplasmic Sperm Injection (ICSI) Treatment—A Systematic Review. Life 2023, Vol 13, Page 1237 [Internet] 2023;13:1237. Multidisciplinary Digital Publishing Institute.

Zhang J, Jia H, Diao F, Ma X, Liu J, Cui Y. Efficacy of dehydroepiandrosterone priming in women with poor ovarian response undergoing IVF/ICSI: a meta-analysis. Front Endocrinol (Lausanne) [Internet] 2023;14:1156280. Frontiers Media S.A.

Zhang M, Niu W, Wang Y, Xu J, Bao X, Wang L, Du L, Sun Y. Dehydroepiandrosterone treatment in women with poor ovarian response undergoing IVF or ICSI: a systematic review and meta-analysis. J Assist Reprod Genet [Internet] 2016;33:981–991. Springer New York LLC.

Zhang Y, Zhang C, Shu J, Guo J, Chang HM, Leung PCK, Sheng JZ, Huang H. Adjuvant treatment strategies in ovarian stimulation for poor responders undergoing IVF: a systematic review and network meta-analysis. Hum Reprod Update [Internet] 2020;26:247–263. Oxford Academic.

Zhu F, Yin S, Yang B, Li S, Feng X, Wang T, Che D. TEAS, DHEA, CoQ10, and GH for poor ovarian response undergoing IVF-ET: a systematic review and network meta-analysis. Reproductive Biology and Endocrinology [Internet] 2023;21:1–12. BioMed Central Ltd.

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’.

10.4. The category of ‘older women’ has not been previously defined with relation to treatment add-ons. For clarity, relevant studies have been grouped for inclusion in this category if the study has defined their cohort as containing ‘older women’ without POR.

11. Annex E: Expert statistician independent report

Traffic Light System for Treatment Add-ons: Androgens

Andy Vail, January 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 pre-treatment with the androgens dehydroepiandrosterone (DHEA) and testosterone.

The aim of the work reported below is to critically appraise, interpret and summarise, for consideration by the HFEA, 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 the Cochrane systematic review (link provided by Rebecca) to ensure no missed trials and checked 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.

Several included studies adopted what I have referred to as an 'immediate' design. Under this design, participants in the active arm(s) were allocated to receive a period of treatment prior to IVF whereas those in the control arm proceeded to immediate IVF. This design differs from the placebo-controlled approach in that it pragmatically conflates the biological effect of pre-treatment with the necessity to delay IVF treatment for the period of pre-treatment. The effect of delay could be hypothesised as beneficial or detrimental. What is clear is that it allows for pregnancies to occur in the active arm prior to IVF intervention. These should be included in analyses following the intention to treat principle. Exclusion of spontaneous clinical pregnancies removes the more fertile participants and creates an unfair ('biased') comparison in favour of the control arm. If, conversely, follow-up of controls ceases after their first IVF cycle rather than continuing for a comparable period (including, potentially, subsequent IVF cycles) the comparison will be biased in favour of the active intervention.

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. 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, particularly those relating to the number of retrieved oocytes, are reported where requested by HFEA.

RESULTS

1. DHEA

The current search identified a total of 13 primary research studies. Searching of reviews identified three further randomised studies for consideration. These studies were ineligible for review based on the years elapsed since publication. The study by Tartagni 2015a was not accessible. From the available abstract it appeared likely that this was an earlier report of the study by Tagtagni 2015. Treatment was 75mg/day prior to an IVF/ICSI treatment cycle unless otherwise stated.

1 (i) *General population*

Three placebo-controlled, randomised trials assessed DHEA treatment for participants with normal ovarian reserve.

Tartagni 2015 randomised 109 women aged 36 to 40 years having a first cycle of IVF/ICSI after three or more previous IUI failures. Treatment was for 8 weeks before ovulation induction. The study was small but the only clear risk of bias was from absent reporting of allocation concealment. They found similar oocyte retrieval in each group: mean (sd) 8.9 (1.8) versus 8.2 (2.2) in active and control respectively; p=0.07. Reported means for metaphase II oocytes were even more similar. However, they reported a

marked difference in live birth rates: OR (95% CI) = 2.3 (1.0 to 5.4), much of which was due to fewer miscarriages in the active arm.

Yeung 2016 randomised 72 women who were under the age of 40 years. Treatment was for 12 weeks before ovulation stimulation. There were no clear flags for risk of bias. They found similar oocyte retrieval in each group, reporting medians of 6 and 7 (p=0.88) in active and control respectively. Live birth was lower, but not statistically significantly so, in the active arm: OR (95% CI) = 0.74 (0.25 to 2.4).

Mostajeran 2018 randomised 106 women aged 35 years or more with a healthy body mass index. Treatment was for 8 weeks before ovulation induction. Methodological details were poorly reported and clinical outcomes were sparse. There were no data on oocyte retrieval or on live birth. Clinical pregnancy, including five prior to IVF treatment in the active arm, was higher, but not statistically significantly so, in the active arm: OR (95% CI) = 1.9 (0.86 to 4.1).

Recommendation:

GREY for both outcomes (only two RCTs directly address oocyte retrieval and either live birth or ongoing pregnancy, no safety concerns raised).

1 (ii) *Poor/diminished ovarian reserve*

Seven randomised trials assessed DHEA treatment for participants variously defined as having poor or diminished ovarian reserve. Criteria used for this definition included the Bologna criteria and combinations of antral follicle count, follicle stimulating hormone, luteinising hormone and anti-mullerian hormone.

Kara 2014 randomised 208 women with diminished ovarian reserve. Treatment was for 12 weeks in the active arm with unclear timing of IVF in the control arm. The study was unblinded and poorly reported regarding post-randomisation exclusions. They found similar oocyte retrieval in each group, reporting mean (sd) of 5.7 (3.7) versus 5.4 (3.5) (p=0.44) in active and control respectively. There was even less difference in metaphase II oocytes. They did not report ongoing pregnancies or live birth but clinical pregnancy rate was similar between groups: OR (95% CI) = 0.99 (0.53 to 1.7).

Yeung 2014 randomised just 32 women described as poor responders. This was a different stratum of the trial described above as Yeung 2016. It was placebo-controlled and at low risk of bias. They reported similar oocyte retrieval in each arm: median 3 versus 2.5 (p=0.19) in active and control respectively. Live birth rates were identical: OR=1.0 (0.12 to 8.1).

Zhang 2014 randomised 105 women with diminished ovarian reserve. Treatment was for three menstrual cycles prior to IVF with immediate IVF for the control arm. Loss to follow-up prior to IVF treatment in the active arm complicates interpretation. However analysed, oocyte retrieval rates were similar between arms. They did not report ongoing pregnancies or live birth but clinical pregnancy rate was similar between groups: OR (95% CI) = 1.4 (0.47 to 4.0). Note that this includes one pregnancy in the active arm prior to IVF for which women in the control arm had no comparable opportunity to achieve success.

Narkwichean 2017 randomised 60 women with predicted diminished ovarian reserve. Treatment was for at least 12 weeks with those in the control arm receiving matching placebo. The study was at low risk of bias. Oocyte retrieval was similar between groups: median 4 in each group. Live birth was lower, but not statistically significantly so, in the active arm: OR (95% CI) = 0.65 (0.20 to 2.1).

Fu 2017 randomised 118 women with diminished ovarian reserve. Treatment was for 12 weeks with immediate IVF for the control arm. The trial was at risk of bias from unclear allocation concealment and the absence of blinding. They found similar oocyte retrieval in each group, reporting mean (sd) of 3.2

(1.8) versus 2.5 (1.9) (p=0.06) in active and control respectively. Reported means for metaphase II oocytes were more similar. They did not report ongoing pregnancies or live birth. Clinical pregnancy rate was higher, but not statistically significantly so, in the active arm: OR (95% CI) = 2.4 (0.69 to 8.2). Note that this includes one pregnancy in the active arm prior to IVF for which women in the control arm had no comparable opportunity to achieve success.

Kotb 2017 randomised 140 women with poor ovarian reserve. Treatment was for 12 weeks with immediate IVF for the control arm. This trial reported concealed randomisation but was at risk of bias from the lack of blinding. Note that the first author appears on the retraction watch database for **a different trial**, as does the second author for association with the same colleague. Oocyte retrieval was higher in the active arm: mean (sd) 6.9 (3.0) versus 5.8 (3.1); p=0.03. There was a similar difference in metaphase II oocytes. Live birth was not reported. Ongoing pregnancy was markedly higher in the active arm: OR=2.7 (1.1 to 6.5).

Wang 2022 randomised 821 women with poor ovarian reserve. Treatment was for 4 to 12 weeks with those in the control arm receiving matching placebo. The study was well-designed and at low risk of bias. Despite being comfortably the largest trial in this review, the authors note that the trial was under-powered to detect realistic effects on live birth due to the low clinical success rate in this population. They reported similar oocyte retrieval in each arm: median 2 versus 3 (p=0.70) in active and control respectively. Live birth was also very similar: OR (95% CI) = 0.97 (0.60 to 1.6).

Recommendation:

Oocyte retrieval: Amber/black (three trials at low risk of bias in this population: none claims effect but under-powered to rule out small benefit).

Live birth: Black (three trials at low risk of bias: none reports higher live birth in active arm).

1 (iii) Aged women

Two studies by the same authors assessed DHEA treatment for older women. Both included a cohort of younger women (aged 37 years or less) but also assigned women from an older cohort (aged 38 years or more) to either DHEA treatment or not. This report assesses only the comparisons within the older cohorts.

Lin 2017 allocated 58 women without any claim of randomisation. Treatment was for at least 2 months before ovulation stimulation at a dose of 90mg per day. Those in the control arm received immediate IVF treatment. Aside from this it was a poorly reported study at high risk of bias. Those in the active arm had more oocytes retrieved: mean (sd) 3.5 (2.1) versus 2.4 (1.3). Live birth and ongoing pregnancy were not reported. Clinical pregnancy rate was partially reported. This was possibly out of the unreported number of transfers taking place as the percentages reported were not possible using the number of participants as the denominator.

Li 2021 randomised 45 women. Treatment was for at least 8 weeks. The timing of IVF treatment in the control arm was unclear. There was no description of the randomisation process or its concealment and no suggestion of blinding. Women in the active arm had poorer prognosis in terms of more previous IVF failures. Despite this, oocyte retrieval was higher in the active arm: mean (sd) 5.2 (1.4) versus 3.2 (2.1); p<0.05. Live birth was also higher, but not statistically significantly so: OR (95% CI) = 1.8 (0.36 to 9.4).

Recommendation: GREY for both outcomes (only one RCT directly addresses outcomes for this population, no safety concerns raised).

Comparison with 2024 Cochrane Review

This review included earlier studies but did not include the (possibly) randomised elements of Lin 2017 and Li 2021. It considered the outcomes of 'live birth or ongoing pregnancy' and 'clinical pregnancy' but not that of oocyte retrieval. Analyses were stratified by duration of treatment rather than by patient population. It found no evidence of benefit or detriment from use of DHEA.

2. Testosterone

The current search identified a total of 11 primary research studies. Searching of reviews identified three further randomised studies for consideration. These studies were ineligible for review based on the years elapsed since publication. All of these studies considered the population of women with poor or diminished ovarian reserve.

2 (i) *General population*

No studies identified.

Recommendation: GREY for both outcomes

2 (ii) *Poor/diminished ovarian reserve*

Kim 2014 randomised 120 women with previous poor ovarian response. Treatment with 12.5mg/day transdermal gel was for four (n=30), three (n=30) or two (n=30) weeks preceding the stimulation cycle. Controls received no treatment. The randomisation was of unclear concealment and the interventions were not blinded. There was a clear dose response relationship for both oocyte retrieval and live birth, although analyses were presented separately for each group comparison. Mean (sd) oocyte retrieval reduced from 5.8 (1.9) in the four-week arm to 3.9 (1.3) in the control arm. Live birth showed a statistically significant (p=0.01) dose-response relationship using a chi-squared test for linear trend. Combining the intervention groups also showed higher success with active intervention: OR (95% CI) = 3.7 (0.82 to 17).

Escriva 2015 randomised 66 women defined as low responders. Treatment with transdermal patch (20µg/kg/d) was from day 24 of the preceding cycle to day 2 of the stimulation cycle. The first control group received transdermal estradiol from day 20 of the preceding cycle to day 2 of the stimulation cycle. The second control group received combined oestrogens and oral contraceptive pills for two preceding menstrual cycles. It is unclear whether the timing of the stimulation cycle in this second control group was comparable with those of the other study arms. The trial reported concealed randomisation but lacked blinding. Mean (sd) oocyte retrieval was 2.7 (1.9) in the active arm, which was lower than the first control group but higher than the second: 3.6 (2.5) and 2.2 (1.2) respectively. Live birth rate was highest, but not statistically significantly so, in the active arm: OR (95% CI) = 1.9 (0.50 to 7.0).

Bosdou 2016 randomised 50 women defined as poor responders. Treatment with 10mg/day transdermal gel was for 21 days. Control participants were untreated. Randomisation was not clearly concealed. Blinding of clinicians was claimed without further explanation despite the open-label design. They reported similar retrieval of cumulative oocyte complexes: medians 3.5 and 3.0 in active and control arms respectively. Live birth was also very similar: OR (95% CI) = 0.92 (0.12 to 7.1).

Saharkhiz 2018 randomised 50 women defined as poor responders. Treatment with 25mg/day gel was from day 2 of the stimulation cycle until hCG administration. There was no information on randomisation concealment and, despite the control group receiving matching placebo, there was no blinding of

clinicians. They reported higher mean (sd) oocyte retrieval in the active arm: 2.5 (1.6) versus 1.2 (1.3); p=0.004. They reported four clinical pregnancies in one group and none in the other. However, which group the pregnancies were observed in was inconsistent between text and table.

Al-Jeborry 2019 randomised 132 women defined as poor responders. Unusually, this was a single author paper. Treatment with 10mg/day gel was for 21 days from day 5 of the preceding cycle. Control participants received no additional treatment. There was no information on allocation concealment and no attempt at blinding. The article reported higher mean (sd) oocyte retrieval in the active arm: 5.4 (2.7) versus 3.5 (3.3); p=0.0004. Live birth rate was higher, but not statistically significantly so, in the active arm: OR (95% CI) = 2.3 (0.90 to 5.6).

Hoang 2021 randomised 159 women with poor ovarian reserve. Treatment with 12.5mg/day transdermal gel was for six weeks (n=53) or four weeks (n=53) prior to the stimulation cycle. Control participants received no additional treatment. The text was self-contradictory regarding allocation concealment, describing both an adequate and an inadequate approach. Blinding of participants was claimed but clearly not possible given the open-label design. No outcomes were reported for 23% of randomised participants but these were missing equally across groups and unlikely to alter the conclusions of the authors regarding oocyte retrieval. They reported very similar oocyte retrieval across the three study arms: 5.6 (3.4) for 6-week arm, 5.4 (2.8) for 4-week arm and 5.5 (2.4) for the control arm. However, ongoing pregnancy was higher in the active arms: OR (95% CI) = 3.9 (1.1 to 14).

Singh 2021 randomised 70 women with poor ovarian response. Treatment with 12.5mg/day transdermal gel was from day 10 of the preceding cycle to day 1 of the stimulation cycle. Control participants received no additional treatment. There was no information on allocation concealment and no attempt at blinding. They found similar oocyte retrieval in each group, reporting mean (sd) of 4.3 (3.7) versus 4.9 (3.9) (p=0.49) in active and control respectively. Live birth rate was higher, but not statistically significantly so, in the active arm: OR (95% CI) = 5.7 (0.63 to 51).

Subirá 2021 randomised 49 women with poor ovarian reserve. Treatment with 12.5mg/day gel was for two preceding menstrual cycles (n=17) or from day 10 of the preceding cycle (n=16). Control participants received no additional treatment. The design avoided the 'immediate' control issue described above by similar timing of all stimulation cycles following randomisation. There was a description of adequately concealed randomisation and an intention to blind clinicians although participants were aware of their open-label assignment. Unfortunately 22% of randomised participants were excluded from outcome assessment, for reasons including clinical success and failure, without information on their group assignment. They found similar oocyte retrieval in each group, reporting mean (sd) of 3.5 (3.0) versus 4.1 (3.6) versus 3.8 (3.0) in the long active, short active and control arms respectively. Ongoing pregnancy rates were also very similar: OR (95% CI) = 0.7 (0.10 to 4.7) for the active arms combined versus control.

Aflatoonain 2022 randomised 60 women with poor ovarian reserve. Treatment was described as 'microdose', substituting 40.5mg/day transdermal gel for GnRH agonist during the stimulation cycle for a window during the stimulation cycle. Control participants continued with GnRH agonist throughout. Randomisation was not clearly concealed and there was no attempt at blinding. Note that the first author appears on the retraction watch database for a **different trial**. They found similar oocyte retrieval in each group, reporting mean (sd) of 4.1 (2.3) versus 3.6 (2.8) (p=0.46) in active and control arms respectively. There was a similar difference in metaphase II oocytes. Clinical pregnancy rate was also very similar: OR (95% CI) = 1.6 (0.24 to 10).

Muhammed 2023 randomised 60 women defined as poor responders. Treatment with 10mg/day transdermal gel was for 21 days. Control participants received no additional treatment. There was no information on allocation concealment and no attempt at blinding. They found similar oocyte retrieval in each group, reporting mean (sd) of 5.0 (6.6) versus 4.7 (3.3) (p=0.79) in active and control arms

respectively. Metaphase II oocytes were also very similar although the difference was reversed. Clinical pregnancy rate was also very similar: OR (95% CI) = 1.3 (0.34 to 4.6).

Sharma 2023 randomised 90 women with diminished ovarian reserve. Treatment with 12.5mg/day transdermal gel was from day of the preceding cycle to day 2 of the stimulation cycle. Control participants received a lubricant gel. Randomisation was not clearly concealed. There was no attempt to blind clinicians despite the use of placebo gel. They reported higher mean (sd) oocyte retrieval in the active arm: 4.1 (2.6) versus 2.7 (2.0); p=0.01. Ongoing pregnancy rate was higher, but not statistically significantly so, in the active arm: OR (95% CI) = 1.65 (0.64 to 4.2).

Recommendation:

GREY for both outcomes (strictly following flowchart, there are more than three RCTs addressing each outcome in this population but the GRADE rating would have to be reduced to 'low' or 'very low' as all studies are at high risk of bias and small (imprecision). Note that for an individual trial to have 90% power to detect an improvement from 20% to 25% success rate with intervention it would need to recruit sufficient participants to analyse nearly 1500 per arm. The total recruitment of the eleven trials reviewed above is fewer than 1000 participants, so less than one third of the number required.

2 (iii) *Aged women*

No studies identified.

Recommendation: GREY for both outcomes

Comparison with 2024 Cochrane Review

This review included earlier studies but did not include the potentially randomised elements of Lin 2017 and Li 2021. It considered the outcomes of 'live birth or ongoing pregnancy' and 'clinical pregnancy' but not that of oocyte retrieval. Analyses were stratified by duration of treatment rather than by patient population. It deemed the evidence to be of moderate quality (downgraded for risk of bias but not imprecision) in favour of testosterone. It should be noted that inclusion of the earlier studies by Massin, Fábregues and Kim contributed more than 40% of the evidence to their meta-analysis of live birth or ongoing pregnancy rate, with all providing point estimates strongly in favour of intervention. It is not unusual for early studies to provide optimistic estimates of new interventions.

DISCUSSION

Caution is required as the assessments above are made from a methodological perspective without expertise in the clinical or scientific context.

The recommendations for rating are only intended as a starting point for committee discussion.
Some comparisons contain a range of interventions (e.g. androgens taken in varied doses for different duration before or during the stimulation cycle). 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
DHEA		
General	Tartagni 2015	10.1186/s12958-015-0014-3
	Tartagni 2015a	PMID: 24867068
	Yeung 2016	10.1111/1471-0528.13808
	Mostajeran 2018	PMID: 31223318 PMC: 6571446
Poor ovarian reserve	Kara 2014	10.1016/j.ejogrb.2013.11.008
	Yeung 2014	10.1016/j.fertnstert.2014.03.044
	Zhang 2014	10.1186/s13048-014-0093-3
	Narkwichean 2017	10.1016/j.ejogrb.2017.09.006
	Fu 2017	10.4103/2096-2924.210696
	Kotb 2017	10.1016/j.ejogrb.2016.02.009
	Wang 2022	10.1111/1471-0528.17045
Older women	Lin 2017	10.1111/jog.13456
	Li 2021	10.3390/nu13072449
Excluded	Wiser 2010	10.1093/humrep/deq220
	Artini 2012	10.3109/09513590.2012.705386
	Moawad 2012	10.1016/j.mefs.2012.11.002
Testosterone		
Poor ovarian reserve	Kim 2014	10.12717/DR.2014.18.3.145
	Escriva 2015	10.1210/jc.2015-1194
	Bosdou 2016	10.1093/humrep/dew028
	Saharkhiz 2018	10.4103/jrms.JRMS_864_17
	Al-Jeborry 2019	10.36295/ASRO.2019.220925
	Hoang 2021	10.1002/rmb2.12383
	Singh 2021	10.18203/2320-1770.ijrcog20213476
	Subirá 2021	10.1016/j.rbmo.2021.05.021
	Aflatoonain 2022	10.1016/j.ejogrb.2022.09.027
	Muhammed 2023	10.25258/ijddt.13.1.46
	Sharma 2023	10.5005/jp-journals-10006-2278
Excluded	Massin 2006	10.1093/humrep/dei481
	Fábregues 2009	10.1093/humrep/den428
	Kim 2011	10.1016/j.fertnstert.2010.07.1077
Cochrane Review (both)	Naik 2024	10.1002/14651858.CD009749.pub3