Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	Time-lapse systems for embryo incubation and assessment in assisted production
Topic exploration report number:	TER260

Introduction and aims

Embryo incubation and assessment is an important step in assisted reproductive technology (ART). Previous assessment of embryos involved removing them from the incubator for a quality assessment under a microscope. This method gives a 'snapshot' assessment of the embryos at that particular time-point.

Time-lapse systems (TLSs) take digital images of the embryos within the incubator. This allows professionals to assess the quality of the embryos without needing to remove them from the incubator. Some TLSs use software algorithms to help assess the embryos, using morphokinetic parameters.

Health Technology Wales researchers searched for evidence on the effectiveness of TLSs in embryo culture.

Summary of evidence

We identified six systematic reviews on TLS for embryo incubation and assessment, including one Cochrane Systematic Review (Armstrong et al. 2019) that looked for randomised controlled trials (RCTs) evaluating TLS through the following comparisons:

- TLS with conventional morphological assessment of still TLS images, versus conventional incubation and assessment.
- TLS using embryo selection software versus TLS with conventional morphological assessment of still TLS images
- TLS using embryo selection software versus conventional incubation and assessment.

Nine RCTs were identified in total (n = 2,955), but authors concluded that due to the low/very low quality of included evidence and high risk of bias, clear differences between the comparisons above for live birth or ongoing pregnancy, miscarriage and stillbirth, or clinical pregnancy could not be drawn.

Older systematic reviews (Racowsky et al. 2015, Polanksi et al. 2014, Kaser et al. 2014) had less certainty of outcomes due to the smaller evidence base at that time, concluding that the available evidence did not demonstrate improved outcomes compared to usual practice.

One systematic review and meta-analysis investigated the external reproducibility of qualitative (n = 15 studies) and quantitative (n = 6 studies) time-lapse algorithms for embryo selection. The authors concluded that qualitative parameters are reproducible for embryo deselection, but quantitative parameters are less transferable; authors reported all studies were of moderate quality (Newcastle-Ottawa scale).

We identified one ongoing systematic review evaluating the use of artificial intelligence for time lapse assessments of embryos. The anticipated completion date for this review was May 2021, but updated findings were not available.

Some TLSs can be used with assistive software to help assess the quality of the embryos. Such software would be considered a Tier C digital health technology according to the Evidence Standards Framework for Digital Health Technologies**.** Technologies within this classification include digital interventions that would treat, monitor or calculate with an impact on treatment, diagnosis or care. For technologies of this classification, it is recommended that high-quality randomised controlled study or studies are done in a setting relevant to the UK system is produced to demonstrate effectiveness of the technology.

Areas of uncertainty

- There are different types of TLSs available; some are devices that can be placed in existing conventional incubators, some have an integrated incubator. Furthermore, some TLSs include use of algorithms to help assess the quality of embryos. Were this topic to proceed to fuller appraisal, consideration would be needed as to what types of TLSs (and what types of comparisons) should be included.
- It is unclear at this stage whether the parameters used in conventional assessment, or those TLS assessment, would be the same standardised parameters, or whether the parameters used differ across centres.
- There is uncertainty around the quality of studies identified in this report; a fuller appraisal would be required to ascertain the quality and appropriateness of the evidence.

Conclusions

We identified several systematic reviews evaluating evidence on TLSs for embryo assessment and selection, including systematic reviews of RCTs. However, uncertainty around the quality of the evidence and the availability of different types of TLS devices (with or without assistive algorithms) means that drawing conclusions on the effectiveness of TLS may be difficult.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	We did not identify any relevant evidence from this source.
Health Technology Assessment Group	We did not identify any relevant evidence from this source.
Health Information and Quality Authority	We did not identify any relevant evidence from this source.
EUnetHTA	We did not identify any relevant evidence from this source.
International HTA Database	We did not identify any relevant evidence from this source.
UK guidelines and guidance	
SIGN	We did not identify any relevant evidence from this source.
NICE	Clinical guideline [CG156]. Fertility problems: assessment and treatment (2013, last updated 2017) https://www.nice.org.uk/guidance/cg156 Does not mention embryonic selection / monitoring methods explicitly, but under Section 2 Embryo selection for single embryo transfer, the guideline notes that "Embryo selection is based on the assessment of developmental stage and morphological grading criteria in the laboratory. These features are indicative of implantation potential, though the predictive accuracy is relatively poor. However, if prediction of implantation potential could be improved, this would facilitate embryo selection for single rather than double embryo transfer."
Secondary literature and economic evaluations	
https://www.epistemonikos.org/en/	Armstrong S, Bhide P, Jordan V, et al. (2019). Time-lapse systems for embryo incubation and assessment in assisted reproduction. The Cochrane database of systematic reviews. 5: CD011320. doi: 10.1002/14651858.CD011320.pub4 Freour T, Basile N, Barriere P, et al. (2015). Systematic review on clinical outcomes following selection of human preimplantation embryos with time-lapse monitoring. Human reproduction update. 21(1): 153-4. doi: 10.1093/humupd/dmu054 Kaser DJ, Racowsky C. (2014). Clinical outcomes following selection of human preimplantation embryos with time-lapse monitoring: a systematic review. Human reproduction update. 20(5): 617-31. doi: 10.1093/humupd/dmu023 Liu Y, Qi F, Matson P, et al. (2020). Between-laboratory reproducibility of time-lapse embryo selection using qualitative and quantitative parameters: a systematic review and meta-analysis. Journal of assisted reproduction and genetics. doi: 10.1007/s10815-020-01789-4

	Polanski LT, Coelho Neto MA, Nastri CO, et al. (2014). Time-lapse embryo imaging for improving reproductive outcomes: systematic review and meta-analysis. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 44(4): 394-401. doi: 10.1002/uog.13428 Racowsky C, Kovacs P, Martins WP. (2015). A critical appraisal of time-lapse imaging for embryo selection: where are we and where do we need to go? Journal of assisted reproduction and genetics. 32(7): 1025-30. doi: 10.1007/s10815-015-0510-6 Reignier A, Lammers J, Barriere P, et al. (2018). Can time-lapse parameters predict embryo ploidy? A systematic review. Reproductive biomedicine online. 36(4): 380-7. doi: 10.1016/j.rbmo.2018.01.001
https://www.tripdatabase.com/	Csaba P, Anna-Maria N, Markus M. (2017). Time-lapse culture with morphokinetic embryo selection improves pregnancy and live birth chances and reduces early pregnancy loss: a meta-analysis. Reproductive biomedicine online. 35(5): 511-20. doi: 10.1016/j.rbmo.2017.06.022 This review was excluded from the summary of evidence due to methodological concerns, limiting the reliability of this review's analysis and conclusions (inaccurate reporting, inappropriate study inclusion and unclear reporting on the risk of bias tool used)
Cochrane library	We did not identify any additional secondary evidence from this source.
Ongoing secondary research	
PROSPERO database	Use of artificial intelligence in time-lapse imaging technology for automated embryo classification and selection: a systematic review https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=206267 Anticipated completion date May 2021.

Date of search:	May 2021
Concepts used:	time lapse, embryo culture, IVF