Fertility services are on the rise: Artificial intelligence and its role in standardizing assisted reproductive technologies

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Abstract

Assisted reproductive technologies and medically assisted reproduction (ART/MAR) techniques are widely accepted methods of treatment for infertility. ART/MAR techniques are traditionally performed manually by embryologists, but recent innovations in artificial intelligence/machine learning (AI/ML) have the potential to automate or standardize some of these conventional methods. The purpose of this literature review is to investigate, divulge, and evaluate the latest emergence of AI/ML technologies that are being developed for use in conjunction with ART/MAR techniques. This literature review examines only a handful of the numerous ART/MAR techniques available; the intention is to narrow the scope of research down to ART/MAR techniques with considerable evidence supporting successful integration with AI/ML technology. Peer-reviewed journal articles from the years 2018 through 2023 were read, evaluated, and categorized based on the ART/MAR technique of interest. Findings of this literature review suggest that many deep-learning algorithms show promising results for future implementation in fertility clinics. Despite the difference in performance goals and the variety of target ART/MAR techniques, the proposed AI/ML algorithms were able to collectively demonstrate the benefits of utilizing this technology: improved standardization, predictions, and successful outcomes (i.e., birth of a single baby). In order to better understand the potential implications of AI/ML technology use in fertility clinics, additional research needs to be conducted in the future, with a specific focus on the ramifications of bias.

Introduction

Reproductive health strives to ensure that patients are equipped to participate in a safe and satisfying sex life, whilst also maintaining their physical ability to reproduce, as well as their freedom to decide how often and when they will do so (World Health Organization, n.d.). Infertility treatment is a subspeciality of reproductive medicine; their metric of success is supporting a patient through their full gestation period until the birth of a single baby (Gardner, 2022). This goal is achieved via the implementation of assisted reproductive technologies and medically assisted reproduction (ART/MAR) techniques, including but not limited to, *in vitro* fertilization (IVF), intrauterine insemination (IUI), intracytoplasmic sperm injection (ICSI), intracytoplasmic morphologically selected sperm injection (IMSI), and laser-assisted hatching (AH). These medical procedures aim to treat common causes of infertility, which can be observed in either biological sex, and sometimes, can even occur idiopathically. In recent decades, the use of ART/MAR has been widely accepted as a means to combat the dramatic drop in human fertility rates (Aitken, 2022, pp. 3). Whether infertility is caused by an environmental or genetic condition, various ART/MAR techniques have been innovated and are readily available to patients seeking infertility treatment. This literature review demonstrates the importance of developing a robust understanding of how a multitude of factors can drive infertility incidence in patients; moreover, having a grasp on the fundamental concepts of reproductive medicine is critical to the constant improvement of the ART/MAR techniques that are currently employed by embryologists.

Given the sensitive nature of the specimens used in ART/MAR, fertility clinic policies and procedures are designed to be incredibly specific, reliable, and objective. That being said, these procedures are oftentimes performed manually, in real-time, and at the discretion of the embryologist; thus, subjectivity will be present. While it is expected that important medical decisions are made by a highly-trained and experienced professional, human fallibility will play a role in the outcome of the patient undergoing infertility treatment. Thus, this subjectivity is an unavoidable factor, but it can potentially be minimized by the use of artificial intelligence and machine learning (AI/ML). While there are nuances between AI/ML, for the purposes of this project, they will be synonymous and used interchangeably. AI/ML is essentially a program or model that is able to learn from a set of data and write functions that yields a diagnostic output (McDermott *et al.*, 2023). It differs from biostatistics and computer engineering, such that it is a program that writes its own rules, builds its own criteria, and sets its own boundaries (Lungren & Yeung, n.d.). In the field of ART/MAR, there are several AI/ML approaches that are being developed and deployed to enhance the techniques that address infertility problems. What must be stated is the role of AI/ML in this context: it is not to replace the evaluation by and performance of the embryologist; it is merely a tool that strives to create standardization within and across ART/MAR techniques. The purpose of this literature review is to contextualize, unearth, and present contemporary research on the presence and utilization of ML/AI technologies to supplement ART/MAR techniques in a clinical setting.

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Methodology

The primary focus of this literature review is the intersection between ART/MAR techniques and AI/ML technologies. There are numerous ART/MAR techniques that are currently utilized in tandem with AI/ML technologies to enhance infertility treatment; however, for the sake of brevity, only a handful are the focus of this review. The ART/MAR techniques that will be discussed are as follows:

1) Assessment of Spermatozoa Morphology. Spermatozoa undergo what is termed the *acrosome reaction*, wherein proteolytic enzymes are released from the head of the sperm and penetrate the outer membrane of the oocyte in order to initiate the fertilization process (Sadler, 2015). If the majority of a patient's spermatozoa present with morphological abnormalities of the acrosome, this may be an integral diagnostic tool for male patients experiencing problems with infertility.

2) Prediction of Blastocyst Development. A blastocyst is a cluster of dividing cells that eventually develops into an embryo. Blastocysts undergo a process called *compaction*, which occurs when the membranes of blastomeres do not adequately adhere to one another (Byrd, 1993). Abnormalities during the compaction phase may result in a malformed blastocyst that is not viable for uterine transfer.

3) Optimal Location for Laser-assisted Hatching. Laser-assisted hatching is performed during the cleavage stage of an embryo prior to transfer, allowing the embryo to escape from the zona pellucida. The optimal location for laser-assisted hatching is often a segment of zona pellucida membrane that is a safe distance from healthy blastomeres, which is totally reliant on operator experience and skill in order to successfully free the embryo without rupturing or damaging its inner cells.

4) Prediction of Ploidy Status of Embryo. Aneuploid embryos, or those with an abnormal number of chromosomes, result in serious health conditions, such as infertility, miscarriage, and even birth defects.

5) Selection of Embryos for Transfer. There are multiple factors that determine embryo viability and, ultimately, the selection of embryos for transfer. Whether it is blastocyst development or ploidy status, the parameters for this selection typically depend on morphokinetic and morphological data.

These ART/MAR techniques were selected over others for the primary reason that a substantial amount of research exists and, by extension, there is considerable evidence that supports successful integration of these techniques with AI/ML technology. Peer-reviewed journal articles from the years 2018 through 2023 were read, evaluated, and categorized based on the ART/MAR technique of interest.

Results

TABLE 1 | *Overview of the reviewed experimental studies.* Experimental studies included in this literature review were published in 2022. CNN = convolutional neural network

Authors	Purpose	Research Design	Cohort Size	Model Proposed	Summary Points
Lv *et al.* (2022)	To build a deep-learning algorithm for the accurate detection and segmentation of sperm heads	Experimental study	> 10,000 sperm cells	Deep convolutional neural network combined with U-Net-like architecture	Strict morphological assessment on sperm cells is a diagnostic tool for male infertility. An algorithm was developed that could accurately segment the head of sperm cells, even under unstained conditions, images with noisy backgrounds, or in the presence of multiple sperm cells.
Spencer *et al.* (2022)	To evaluate and classify sperm heads by morphology via an ensembled deep-learning model	Experimental study	HuSHeM dataset: 216 images SCIAN dataset: 1,132 images SCIAN total-agreement dataset: 384 images	Stacked ensemble of CNNs	A meta-classifier was developed for sperm head morphology. Standardized classification tool will enhance future automation applications.
Mushtaq *et al.* (2022)	To build a deep-learning algorithm that can automatically detect and measure blastocyst components	Experimental study	Images from publicly available microscopic human blastocyst dataset (years 2012-2016)	ECS-Net	The developed model utilized measured blastocyst components in predicting blastocyst viability. Implications of model utilization could be its role as a recommendation system for embryologists when selecting embryos for transfer.

TABLE 2 | *Overview of the reviewed restrospective studies.* Retrospective studies included in this literature review were published within the years 2021 and 2023. CNN = convolutional neural network, TLM = time-lapse monitoring, ICSI = intracytoplasmic sperm injection, AH = laser-assisted hatching, PGT-A = preimplantation genetic testing for aneuploidy

Authors	Purpose	Research Design	Cohort Size	Model Proposed	Summary Points
Liao *et al.* (2021)	To propose a model that accurately predicts blastocyst formation, quality, and viability	Retrospective study	26,113 embryos	Tandem use of TLM videos and deep-learning algorithms	The proposed model successfully predicted blastocyst formation and viability via the conversion of morphokinetic parameters. The model's performance of of predictiong blastocyst formation and viability was higher than the performance of the participating embyrologists.
Jiang *et al.* (2023)	To develop a model that accurately identifies the optimal location of an oocyte's zona pellucida for micromanipulation	Retrospective study	19,812 oocytes	2 independent CNNs	The developed model classified oocytes and cleavage-stage embryos into 12 different groups via both CNNs in order to identify key landmarks and locations for micromanipulation. This model has the potential to enhance micromanipulation techniques by assisting an embryologist in the decision-making process for ICSI and AH.
Barnes *et al.* (2023)	To develop a model that predicts embryo ploidy status	Retrospective study	10,378 embryos	STORK-A (CNN architecture-based model)	The developed model was an excellent screening tool prior to non-invasive ploidy status prediction testing (e.g., PGT-A), whether the embryo is destined for biopsy or implantation.
Fruchter-Goldmeier *et al.* (2023)	To develop an algorithm that retrospectively analyzes blastocysts for several morphometric parameters	Retrospective study	608 blastocysts	Semantic segmentation neural network model	The developed model retrospectively defined a series of morphometric parameters that can be used to enhance the selection of embryos for transfer. Of these parameters, a larger blastocyst size had a significant positive correlation with higher implantation potential.
Liu *et al.* (2023)	To develop a model that can integrate multimodal inputs to achieve high live birth prediction	Retrospective study	17,580 blastocysts	CNN developed by multimodal inputs	The proposed model successfully incorporated blastocyst images and patient couple's clinical features in order to enhance prediction rates for live birth.

Discussion

Fertility clinics offer ART/MAR techniques in order to improve a patient's chance of getting pregnant and giving birth to a healthy baby. In recent years, however, infertility rates have been rising, and accessibility to fertility services is becoming increasingly more difficult for a multitude of reasons. While treatment cost, clinic location, and patient demographics may predominantly impact this accessibility, the increasing demand for fertility services poses a different challenge, one that cannot be met due to a scarcity of embryologists in the United States.

In the field of medical laboratory science (MLS), an already small community of healthcare professionals, there is an exasperated shortage of MLS that enter niche specialties, such as embryology. While the field of embryology requires additional higher-level education, job experience as an MLS provides technical skills, familiarity with laboratory operations, and hands-on application that lends itself to professional development as an embryologist. While there is an opportunity for growth in the field of embryology, especially with interest generated from other established healthcare professionals, there are simply not enough embryologists to meet the current, overwhelming demand for fertility services. According to Carson and Kallen (2021), approximately 12.7% of women between the ages of 15 and 49 years old seek infertility treatment every year in the United States, while embryologists, classified as "biological scientists, all other" by the United States Bureau of Labor Statistics, are estimated to penetrate less than 0.19% of the industry job market (2022). There is a gross disproportion between the demand for fertility services, such as ART/MAR techniques, to the supply of trained embryologists that are readily available to provide these services. Thus, as of right now, the demand for fertility services cannot be met. This problem needs to be addressed and, fortunately, two potential avenues by which a solution may be found will be evaluated in this discussion.

First, in order to meet demand, supply must be increased. Essentially, professional embryologists do not comprise enough of the workforce; therefore, the profession needs to find a way to gain attention from prospective students interested in being a healthcare worker. Whether this is through incentivising, advertising, or general awareness is beyond the scope of this research project, but it is important to note that this trend is not unique to just embryology—this pattern mimics other lesser-known healthcare professions, as well.

The direction that is the primary focus of this research project, moreover, is the utilization of AI/ML technology to supplement this shortage of embryologists. Let this be clear: this research project does not suggest that AI/ML technology replace embryologists—whether current or prospective personnel. While the innovation of AI/ML technology is intended to be beneficial, with many scientists supporting its usage, a major limitation to its widespread application is not yet knowing the full array of consequences that this technology may bring. The endless list in which AI/ML technology may be implemented, in combination with skepticism borne from the issue of bias, expense, safety, etc. should not give scientists the confidence to voluntarily substitute a human individual with an AI/ML technology. If anything, the uncertainty of AI/ML technology should deter scientists from quick and thoughtless implementation; the reason it likely does not deter, but rather, attracts the idea is because of its potential to make processes, such as ART/MAR techniques, more efficient. While embryologists are critical to providing immediate and ongoing care of patients seeking infertility treatment, the use of AI/ML technology is meant to enhance patient outcomes via optimized standardization. To reiterate, any AI/ML technology programmed for ART/MAR does not possess superior decision-making capabilities; it is merely designed to be an objective tool, an aid to the embryologist in order to improve rates of success in fertility services. AI/ML implementation, in this case, is intended to reduce the strain on embryologists, with the hope of making fertility services more accessible to patients.

Conclusion

The implications of AI/ML technology are numerous, but its application to various ART/MAR techniques holds great promise. The immediate future predicts an expanding convergence between AI/ML and fertility services, with outcomes of enhanced standardization, improved accessibility, and a higher success rate. The current trajectory for the field of embryology relies on the use of AI/ML technology in order to fulfill the needs of its patients; however, additional research needs to be conducted in order to better understand the role and potential consequences of AI/ML bias in patient fertility care.

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