



Artificial intelligence—the future is now

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Abstract

The pros and cons of artificial intelligence in assisted reproductive technology are presented.

Keywords Artificial intelligence · Assisted reproductive technology · Embryology · In vitro fertilization · ART · IVF · Reproductive medicine · Infertility

Introduction (Trolice)

Many industries are researching to determine the best utilization of artificial intelligence (AI) technology and healthcare is no exception, from pathologists and radiologists employing AI with the intent of more accurately diagnosing cancer, to surgeons improving their precision and mapping disease with robotic devices.

The term “artificial” intelligence is, itself, a contradiction. While the primary definition of AI based on the Oxford Language Dictionary is “made or produced by human beings rather occurring naturally,” the secondary definition relates to a person or their behavior as being “insincere.” Therein lies the conundrum of the indiscriminate embrace of AI—while scientists have created this non-human ability to process “big data,” the field of medicine risks a disingenuous loss of the human element—that being the doctor-patient relationship.

The field of AI is the marriage of humans and computers while reproductive medicine combines clinical medicine and the scientific laboratory of embryology. The application of AI has the potential to disconnect healthcare professionals from patients through algorithms, automated communication, and

clinical imaging. However, in the embryology laboratory, AI, with its focus on gametes and embryos, can avoid the same risk of distancing from the patient. Areas of application of AI in the laboratory would be to enhance and automate embryo ranking through analysis of images, the ultimate goal being to predict successful implantation. Might such a trend obviate the need for embryo morphological assessment, time-lapse imaging and preimplantation genetic testing for aneuploidy (PGT-A), including mosaicism? [1]. Additionally, AI could assist with automation through analysis of testicular sperm samples searching for viable gametes, embryo grading uniformity [2].

This leads us to our inaugural section in *JARG* on “Controversies in Reproductive Medicine” which will be dedicated to the purpose of examining, the pros and cons of the areas in our field that have been embraced without consensus. This month, we examine the opposing views of utilizing AI to the embryology laboratory. Curchoe [3] presents arguments in favor of AI by highlighting the success in automation through higher productivity of routine tasks to manage repetitive responsibilities and reduce errors. We also learn the potential to personalize patient care through smart decision-making and offering patients instantaneous communication via online “chatbots.”

The cautionary approach to AI is presented by Quaas [4] who reminds us there are no prospective studies to support a definitive benefit of this technology on patient outcomes, i.e., embryo implantation and live birth rate. While we await true meaningful application, AI’s machine learning of “big data” requires careful calibration to avoid amplification of bias. Ultimately, the concern lies in another potential “add-on” in our ever-growing array of ancillary and expensive procedures in ART whereby the risk for patient exploitation runs high.

The robust and spirited debate over AI will allow the reader to ponder the future changes that may occur in our field as well as already being implemented.

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PRO-AI for the ARTs—nothing lost, nothing created, but everything transformed (Curchoe)

Each century seems to generate a world-changing discovery in science: Newton's laws of motion, Einstein's theory of relativity, Darwin's natural selection, and Watson and Crick's (and Wilkins and Franklin's) discovery of the structure of DNA. McCarthy's artificial intelligence [5] is similarly changing the world as we know it in the twenty-first century.

Could any one of us scarcely imagine living without Alexa, Siri, Facebook, Amazon, or Google? My Apple watch reminds me to drink water and breathe deeply. My email client guesses my intentions and suggests the next words. We will never know the name of most of the AI systems running behind the scenes, but they touch nearly every aspect of our modern lives. As the great chemist Antoine Lavoisier once said, "Nothing is lost, nothing is created, everything is transformed." Everything that AI touches is indeed transformed. Could AI for reproduction (repro-AI) similarly transform our industry?

Some critical, but time-consuming and monotonous, recurring tasks in the IVF lab, for example, quality control, embryo and oocyte vitrification, and biopsy sample loading, demand the highest attention to detail. Repetitive and monotonous tasks that demand the highest level of detail and precision have been demonstrated to reduce the productivity of employees over time—the dreaded embryologist "burn out." One of the most commonly cited benefits of AI is automation. AI Automation has already resulted in higher production rates and increased productivity in a diverse array of business sectors. In the ARTs, automation tantalizingly promises to abolish the maddeningly routine, subjective, manual, and time-consuming tasks that pre-dominate in the embryology lab, embryo grading [6], semen analysis [7], and quality assurance [8], while potentially contributing to superior safety and standardization.

Another benefit of AI automation is the promise to free the "bottleneck" of embryologists' time from the mundane laboratory responsibilities to focus on more important tasks, like ICSI, embryo biopsy, and training junior staff. There is a growing need but dearth of experienced embryologists; unfortunately, vital mentorship is time-consuming. Time management can be improved by AI-driven automation microfluidics and robotics for embryo culture systems to efficiently use the raw materials, e.g., culture media, reagents, and plastics.

IVF clinics cannot accept errors in administrative or laboratory processes. Patient identification, chain of custody, and cryostorage inventory of tissues are often performed by "junior" embryologists as it is the prevailing tenet to assess their preparedness, to be real "bench" embryologists. The training model in embryology is predicated on low-level data entry. I cringe to consider the number of new embryologists, who received expensive educations, but left the field prior to

completing the one- or two-year time period before being "allowed" to learn oocyte retrievals or work with patient samples. I suspect this model is convenient for the clinic and senior embryologists who, of course, do not want to process vast amounts of data.

AI is widely used in business for smart decision-making, such as to coordinate data delivery, analyze trends, develop data consistency, provide forecasts, and quantify uncertainties. The reproduction and infertility problems of poor response to stimulation, recurrent miscarriage, or implantation failure, to name a few, are complex and multifactorial. These are problems that AI is uniquely suited to solve. AI in precision reproductive medicine [9] has the potential to incorporate the genetic uniqueness of individuals and the molecular mechanisms of their infertility, to personalize the best treatment. Already, AI systems have been trained to provide guidance for diagnosing infertility conditions [10] and tailoring controlled ovarian stimulation protocols [11]. Provided human emotions do not introduce bias into the training, AI systems are valuable adjuncts toward decision-making and predictions.

AI-powered solutions are also enhancing the consumer experience by generating highly specific responses to customer queries and grievances through "chatbots" and natural language processing. Repro-AI tools have the potential to reduce the strain on lab and nursing staff by enhancing the patient experience, by fielding routine questions about calendars, medication administration, embryo grading, or answering IVF cycle queries about options. Telehealth combined with AI may one day allow clinicians to conveniently make recommendations without the need for in-person office visits—bringing to life the dream of the "quasi-DIY" (do it yourself) IVF cycle that reduces costs, increases convenience, and democratizes access for everyone.

AI and machine learning (ML) are used to analyze data much more efficiently than humans could ever collate, analyze, and/or understand to solve intricate problems, such as fraud detection and weather forecasting. The advanced computing capabilities of AI are being used pre-conception to develop complex predictive models to select the best embryo for transfer [12–14], and diagnose the ploidy status of embryos [15, 16], as well as allow post-conception disease diagnoses while predicting adverse outcomes during pregnancy [17] (e.g., preterm birth, preeclampsia [18], and miscarriage [19]) that have a complicated and undetermined etiology. In places like the USA, maternal mortality is increasing, despite the contrary trend worldwide. Pregnancy and maternal healthcare generate many different data types (e.g., ultrasound imaging [20], diagnostic screening, fetal monitoring [21], genetics) that can be integrated by repro-AI to address maternal health. There is a significant gap in the research on pre-conception, pregnant, and breastfeeding persons and pharmacological safety and efficacy drugs due to their systemic and deliberate

exclusion from randomized clinical trials, yet up to 80% of pregnant or lactating women will need to take a pharmacological substance at some point [22]. AI techniques have been shown to play an important role in premarket drug safety, especially in the field of toxicity. Repro-AI could help address this gap safely.

AI-driven advances in data entry and processing promise to help make digital systems (EMRs, cryostorage, and sample identification) more efficient and less likely to experience problems due to data processing mistakes. Another massive benefit of better data management that cannot be overstated: most labs do not take a single image of patient embryos. They do not have the digital infrastructure to archive embryo images or integrate them with the rest of the “chart.” Most of the AI systems in development absolutely rely on images (or better yet, video!) being available for analysis.

There is an immense pool of knowledge and experience at hand within the IVF industry, i.e., academia, regulatory bodies, and professional societies. A joint approach that enables both developers and adopters of repro-AI technologies to thrive will allow the industry to bring the benefits of repro-AI quickly and safely [23] to infertility patients whose cycles still fail too often, despite significant advances in the field over the last 40 years.

The real-world consequences of Einstein’s space time continuum would not be felt for nearly 100 years until the first commercial GPS devices corrected for the significant warp of Earth’s mass on the space-time continuum. I predict the benefits of repro-AI will occur in a shorter time. However, the robust use of repro-AI will rely on the continued development and mass adaption of enabling technologies: time-lapse microscopy, single-step embryo culture, integrated clinical and laboratory digital health records, and environmental systems monitoring. We have just started to imagine some of these technologies could be possible, such as “lab on chip” (end to end IVF, ICSI, biopsy, and embryo freezing in a box), and “DIY” IVF cycles.

Nascent repro-AI systems have not yet reached clinical significance and relevance. As I argue in “The Paper Chase and Big Data Arms Race” [24], all current repro-AI systems have not yet had the advantage of training on real BIG data sets. Impressively, we are achieving acceptable levels of accuracy and specificity with merely thousands of data points for embryo grading, ploidy prediction, implantation prediction, and clinical pregnancy prediction. Repro-AI research [25] is ongoing and active, and the complete dataset may be downloaded for analysis from www.repro-ai.org. Of course, more research is needed to promote the application of AI in reproductive medicine. Significant challenges in selection bias from sample collection, ethical, transparent data collection and sharing, and in determining the best ways to implement AI in clinical work have yet to be solved. Gathering repro-AI scientists, whether virtually, like in this month’s special AI

focused issue of JARG, or in person through special interest groups will be critical to the continued advancement and, ultimately, the success of these technologies.

The CON: babies not gadgets (Quaas)

On a recent movie night, we watched “the Mitchells vs the Machines”: a dysfunctional family needs to save the world from destructive robots controlled by a man-made disgruntled AI application which has turned from helpful companion to evil adversary. The movie is an animated comical family-friendly social commentary on the dangers of AI and the increasingly omnipresent screens around us leading to a seemingly more connected, but really more disconnected world. Ironically, while highlighting the dangers of tech consumption, the film can be viewed on a streaming platform that uses AI to “feed us more content” [26].

AI is omnipresent. And the idea of it turning against us is not novel, as a century of cinematic history demonstrates, through movies such as “Metropolis,” “Blade Runner,” “The Terminator,” “The Matrix,” “I, Robot,” “Interstellar,” and “Ex Machina,” to name but a few.

It is only logical that AI with its enormous potential has made its way to the field of reproductive medicine. And while it is unlikely that AI’s application in the field of ART will turn against its creators or against its original intended purpose, it is still worth examining the possible pitfalls of the promised “brave new world.”

What are the potential benefits of AI in ART and what is the current status of its application in our field? Every aspect of our day-to-day practice will undoubtedly be touched by AI and the promise for betterment is huge if implemented wisely. Potential applications include assistance in embryo or gamete selection, the search for spermatozoa in testicular sperm extraction procedures, computerized follicular ultrasound interpretation, automated management of controlled ovarian hyperstimulation, ART outcome prediction, and donor/recipient matching in third party reproduction, and using tools such as facial recognition software.

Unfortunately, the presented concepts are currently much more impressive than the actual benefits of AI in ART. As of today, no prospective studies have demonstrated AI’s clear-cut benefit or cost reductions over current practice [27].

Arguably, there is no other area in our field that is flourishing more with research interest than AI [28], yet we are still waiting for actual major breakthrough accomplishments and improvements in the day-to-day practice of ART.

Numerous technical and ethical concerns also exist.

One of the big advantages of AI is its ability to integrate large amounts of data and synthesize it in ways that allow for pattern recognition and development of predictive models and selection tools [29]. But the science of “Big Data,” using computational analysis of huge data sets to identify patterns and

associations, also means big challenges—in the form of data bias, data security, and questions of data access and ownership. “Machine learning” algorithms involve a training phase and rely on the appropriate input of data. Inaccuracies or systemic errors during the “deep learning” step of AI systems may lead to amplification of bias or the complete disregard of certain types of data [28]. For example, if only embryos selected for transfer are included in the AI training stage, the training dataset is not representative of the data on which it will subsequently be used, leading to bias in the embryology laboratory.

Increasing digitalization and computerization has had massive advantages, but also unintended consequences: every major company, for example in the banking and customer service industry, now also needs a dedicated cybersecurity branch to protect itself from data breaches. Thus, mankind’s efforts to simplify processes of daily life often have the opposite effect as intended, at least temporarily. In this sense, widespread implementation of AI in ART may be analogous to the change from paper medical charts to electronic health records: initially, there is actually an increase in workload, with the hope that it will ultimately lead to a reduction, with added advantages. Therefore, it seems crucial to ensure, prior to implementation, that it will ultimately be of benefit to our patients rather than to the careers and commercial interests of researchers and technology companies.

The explosion of research output in the area of AI in ART [28] is self-serving if it only results in fancy abstracts at scientific meetings but no improvement in live birth rate.

To use an analogy from the field of minimally invasive gynecologic surgery: robotic technology can serve as an excellent marketing tool to attract patients in a competitive market. The use of the robot is often featured on the cover of brochures or billboards to advertise hospitals or clinics, even though well-designed trials have not demonstrated improved outcomes with the use of robotic-assisted surgery; and some even suggest detrimental effects such as longer operative time or increased blood loss [30–32].

Financial incentives exist in ART that can influence practice patterns from a conflict of interest. Examples of premature implementation of proprietary technologies prior to clear-cut demonstration of benefit to patients include time-lapse imaging, the endometrial receptivity assay (ERA), and pre-implantation genetic analysis for aneuploidy (PGT-A). All of these may ultimately be beneficial contributions to our field, but their introduction was undoubtedly accelerated by commercial interests.

The extent of benefit and the cost-benefit ratio is also worth examining with the advent of AI in ART. Assisted reproduction is already prohibitively expensive, as a lack of insurance coverage for treatment of the disease exists in many parts of the world [33]. Every “add-on” (evidence-based or otherwise) to the standard IVF procedure increases cost [34]. From an

ethical standpoint, this begs the question whether we should perhaps prioritize broader access to “bread and butter” infertility treatments for more people, rather than provide more and more sophisticated and expensive treatments to the privileged few.

Aside from cost considerations, every technological add-on may have the effect of widening the access gap between those that have the time and educational background to inform themselves about the increasingly complicated process of ART, and those that are scared, intimidated, and alienated by its complexity.

We have recently witnessed how the individual digital know-how affected access to the COVID-19 vaccine, with marginalization of those with poor computer literacy or limited Internet access resulting in a “digital chasm” [35].

The terms and intricate features of IVF cycles have caused an intellectual divide among patients due to the introduction of esoteric concepts such as embryonic mosaicism and structural rearrangement. Injudicious implementation of AI has the potential of worsening this phenomenon.

Analogous to the application of PGT, there is the potential for inappropriate use of AI for the ethically questionable prediction of nonmedical outcomes. The prediction of medically useful outcomes (laboratory or clinical) by integrating large data is undoubtedly an area of research worth pursuing and the literature on AI in ART abounds with predictive models for prognostic purposes to the point of becoming a “distinct sub-discipline of reproductive medicine” [36].

This is useful when it holds the potential to alter the outcome, such as when a patient decides whether to pursue treatment with her own or donor eggs, or when it guides improved embryo selection. It is less helpful when it only provides prognostic information with no impact on the outcome. For example, does predicting a high likelihood of an unfavorable outcome, such as embryonic developmental arrest a few days before it actually happens, make it easier for a patient to accept thereby being less disappointing?

Ultimately, our patients care about the desired result of ART, i.e., live birth, rather than fancy gadgets utilized throughout a cycle. By and large, they care about being treated using a humanistic rather than robotic approach. Infertility is a highly emotional and sensitive journey [37], and patients often feel like a “number,” funneled through a streamlined conveyor belt-like process.

Maybe in a few years infertility clinics will have self-service “transvaginal ultrasound stations” where patients get automated 3-D follicular scans while having their blood taken by a robot. The data is immediately analyzed and results in an instant gonadotropin dose adjustment of the automated subcutaneous medication administration system. This type of AI “DIY” may lead to a reduction in staff costs for the clinic, but fails to take into account the intangible factor of human interaction. When I only have a couple of items to buy at the

supermarket, I still go to the cashier even if a self-checkout station is available because the latter has no capacity to greet and smile. Unquestionably, the frequent follicular scans during ovarian stimulation could be done just as well by a technician, and maybe by a machine in the future. But most patients appreciate the regular interaction with an empathetic doctor, and it is impossible to prove but not far-fetched that this may impact outcomes beyond just emotional stability during a challenging and stressful treatment journey.

Unsurprisingly, “The Mitchells vs. the Machines” has a happy ending, as the Mitchells come together as a family and defeat the evil machines to save humanity. AI and machine learning are here to stay and offer the potential to significantly enhance the field of reproductive medicine. Appropriate and deliberate appreciation for their potential pitfalls and risks will allow us to use these technological game changers wisely to help more patients reach their ultimate goal: babies.

Conclusion (Trolice)

Physicist Stephen Hawking warned about AI “The development of full artificial intelligence could spell the end of the human race...It would take off on its own, and re-design itself at an ever increasing rate. Humans, who are limited by slow biological evolution, couldn't compete, and would be superseded.”

AI has tremendous potential to improve performance in business and medicine. In the embryology laboratory, AI would be expected to improve clinical workflow, reduce manual evaluations of quality control, and, ultimately, expedite time to pregnancy. Potential applications of AI are assessing gamete quality, sperm selection for ICSI, embryo grading, recommending patient stimulation protocols, the selection of egg donors, and alerting the need for maintenance of IVF equipment to name a few [38]. Most importantly, AI will be of the highest value in ranking of embryos toward the prediction for a live birth. Concurrently, AI would reduce the inefficiency of gametes and embryos through enhanced oocyte identification while optimizing personalized medicine through the analysis of all embryological, clinical, and genetic data [1]. Improving the efficiency of oocytes and sperm contributing to optimal embryos, AI has the promise to reduce the dosage and, thereby, cost of gonadotropins as well as the wastage of supernumerary embryos.

AI algorithms may help practitioners from around the globe to standardize, automate, and improve IVF outcomes for the benefit of patients. Collaboration is required between AI developers and healthcare professionals to make this happen.

To be sure, AI has clear and rate-limiting challenges. As a measure of its assessment of embryo quality, the overall

accuracy in predicting euploidy was only 70% [15]. AI requires calibration and there is currently no agreement on how to compare performances of various AI models for optimal methods. The problem of heterogeneity exists among different AI platforms limiting its ability to cross-sync and link to electronic health records. Adding to the limitation of AI applications are its different techniques and algorithms without a “gold-standard.” Alterations among clinics in data point definitions, patient demographics, and differences in clinical and laboratory procedures may cause data bias, resulting in AI tools that are only applicable to the training in one original clinic [39].

Our readership, and the field of reproductive medicine broadly, should be prepared to judge discriminately whether AI benefits patients or represents yet another slippery slope case of human ARTs having been initiated before all the cards were on the table!

We await with bated breath whether the promise of AI to reduce healthcare costs, workload, and accurately predict live birth comes to fruition. Perhaps less of a threat may be perceived from this new technology by considering the words of former IBM executive chairperson Ginni Rometty, “Some people call this artificial intelligence, but the reality is this technology will enhance us. So instead of artificial intelligence, I think we'll augment our intelligence.”

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