Artificial intelligence: its applications in reproductive medicine and the assisted reproductive technologies

At its core, artificial intelligence (AI) is “a partnership between man and machine” (Ginni Rometty, IBM CEO). The embodiment of AI is a computer program that can learn to execute tasks involving forms of intelligence normally ascribed to humans. How well a computer will be able to emulate or exceed humans is the essential question driving AI technology.

Already, AI is powering a variety of consumer products, from the Apple voice assistant Siri to product recommendations on Amazon, face recognition on Facebook, and the burgeoning industry of self-driving cars. Perhaps the most useful and promising form of AI is what is called machine learning. In machine learning, hundreds, thousands, or even millions of labeled examples are fed into an algorithm that learns to automatically connect examples with their labels, based on a description of what the examples look like. The labels may be binary, e.g., a human face versus other objects, or include more than two groups. Descriptions may be specific predefined features, such as color histograms, number of eye-like structures, or raw pixels of images. A multitude of machine learning algorithms are available; older algorithms such as support vector machines and random forests tend to work well with predefined features. Newer algorithms such as deep neural networks work on a large variety of data and especially well with raw images. Indeed, deep neural networks have fueled the rebirth of AI, enabling the creation of highly accurate, generalizable predictive models from complex data sets. Three major factors explain the rebirth: the availability of powerful computers capable of training deep neural networks with many tweakable parameters; the existence of exceedingly large digitized data sets that often include hundreds of thousands of accurately labeled examples; and pretrained generic neural networks that are available as open-source libraries (PyTorch, Tensorflow); all of these can be tweaked, adapted, and deployed rapidly to address specific applications. Pretraining is usually performed on very large databases of labeled digital objects, such as millions of images in ImageNet.

Medicine, like other disciplines, has increasingly embraced AI and other digital-age technologies. Examples of AI applications in medicine include: reading electronic medical records and big data management (Watson, IBM), analyzing images (pathology) and scans (magnetic resonance imaging), and creating treatment plans. It has also been used for digital physician consultations (Dr. AI) or virtual nurses, drug monitoring, and precision medicine. These are all aimed at standardizing medical care and increasing medical caregivers' decision-making power. Recently, the AI virtual doctor “Babylon” showed superior results in diagnosing diseases compared to physicians at the Royal College in London. One of the earliest and most prevalent applications of machine learning in medicine is in imaging. AI can be applied to any imaging system, such as X-ray, magnetic resonance imaging, or computed tomography scans. Indeed, it has been shown to be valuable in radiology and pathology. The utilization of AI in medicine is part of a larger trend toward precision medicine, a medical model that proposes to customize medical decisions, treatments, and practice in general. Precision medicine often involves learning how to predict the clinical outcome of specific interventions or procedures, e.g., drug treatment based on specific laboratory tests and images. The resulting predictive models are then applied to individuals, integrating detailed, patient-specific information to diagnose and categorize disease, and guide treatment. The ability to precisely diagnose disease and apply individualized treatment has been shown to improve clinical outcome (1).

AI in Assisted Reproductive Technology

In the past decade, we have witnessed the emergence of several technological advancements in the in vitro fertilization (IVF) laboratory. For example, the development and wide adoption of time-lapse microscopy (TLM) has opened the door to automatization and standardization of embryo culture techniques, as well as optimization of embryo assessment utilizing morphokinetic data. Early attempts at utilizing AI in the IVF laboratory, i.e., the early embryo viability assessment test, applied a simple version of AI to select embryos for transfer. This system failed in demonstrating clinical significance and was never adopted. However, the experience with this early system was used to develop improved software (with an AI algorithm) currently used in some TLM systems. Two companies working in the TLM field, Vitrolife from Sweden and GeneaBiomedix from Australia, have already utilized versions of AI in their embryo selection software. These systems are currently considered experimental and have not yet been prospectively clinically validated. In addition, several healthcare AI start-ups have claimed an ability to select viable embryos and improve pregnancy outcomes using embryo images or TLM videos. Unfortunately, these too have not been validated in multiple clinics or in peer-reviewed journals.

It is our belief that the application of AI in IVF will be significant. Areas where AI may be used to great advantage in IVF include: embryo evaluation and selection, optimizing the assessment of ovarian reserve parameters and sperm selection. It is of interest to note that Niederberger et al. suggested using a neural network to analyze zona-free hamster egg sperm penetration in an animal model as early as 1993 (2). Indeed, AI may be useful in analyzing vast data sets of patient characteristics with diverse infertility treatment outcomes—all with the goal of providing individualized patient-centered treatment. It may also have potential in third-party reproduction, e.g., it may improve our ability to match egg donors with recipients based on a variety of attributes including facial similarity.

In clinical embryology, AI may provide an objective method for evaluating human embryos, enabling the identification of key developmental hallmarks of embryo viability. Current methods of evaluating embryos include static observation of embryo morphology and/or evaluation of morphokinetic TLM data combined with blastocyst morphology. These evaluations are highly dependent on the experience and knowledge of the embryologists, although such analyses can be highly subjective. In a recent study evaluating the same set of embryo images, five experienced embryologists from three different countries showed a great degree of variability in embryo grading with overall low kappa index agreement (3). This is the result of different grading systems between labs and the highly subjective nature of the process. To standardize the embryo evaluation and grading system, we have trained a convolutional neural network on >50,000 TLM embryo images. The AI model called STORK was able to predict blastocyst quality (based on the grade) with an area under the curve of 0.98 in an independent data set. This suggests that AI can learn and successfully identify embryos of high or low quality. The aforementioned study was based on a single image of blastocysts at 110 hours post-intracytoplasmic sperm injection on the morning of day 5. We validated the model using TLM data from other clinics and achieved high accuracy as well, demonstrating the robustness of the model. The achievement of a successful pregnancy is highly dependent on embryo quality (viability) as well as on uterine or other maternal factors. To better improve our predictive abilities for embryo implantation, we developed a decision tree using the AI blastocyst assessment along with maternal age, as it is one of the most significant factors influencing the attainment of pregnancy. With this system, we demonstrated the ability to predict the chance for implantation within each age group. Thus, the system was highly efficient in predicting which embryo would maximize the likelihood of a singleton pregnancy. This AI-driven approach appears to objectively evaluate the embryo, allowing the prediction of implantation potential and laying the groundwork for a future of personalized IVF treatment (3).

AI assessment of embryo images or videos raises additional possibilities and perhaps great potential. Could the analysis of a powerful computer detect patterns of embryo morphology associated with viability that are elusive to the human eye? For example, pioneering work by Rocha et al. (4) on images of mammalian embryos in the bovine model revealed AI's potential in identifying the inner cell mass within the embryo. The interpretation of complex models using deep learning is a nascent field, which may shed new light on the biology of early embryos, possibly revealing imperceptible details that contribute to implantation and successful pregnancies. It would be of interest to analyze whether the addition of morphokinetic data would further improve the ability of AI to predict the likelihood of a live birth. Recognizing that multiple factors, both on the male and female side, may influence the achievement of a successful pregnancy, future deep learning models must not only capture information on embryos, but they must also integrate other relevant patient data.

AI in the Era of Preimplantation Genetic Testing

Preimplantation genetic testing for aneuploidy (PGT-A) to select euploid embryos for transfer is being increasingly utilized throughout the world. Methodologically, the interpretation of results and reporting relies on human analysis, which can be subjective. Recently, AI was applied to PGT-A (Cooper Surgical PGTai; https://www.coopergenomics.com) in the form of a machine learning approach for interpretation and reporting of next-generation sequencing results (images) to eliminate operator subjectivity. We envision that AI applied to big PGT data sets, correlated to clinical outcome, will be increasingly useful in addressing ambiguous results and analyzing the impact of mosaicism. The latter represents a great challenge, as the incidence and significance of mosaicism have been somewhat controversial. It may be possible that AI relying on a computer analysis of yet undescribed features may surpass the ability of humans to select the best embryos. Indeed, AI assessment of embryo morphologic features may lend itself to predicting chromosomal integrity.

While AI is currently being tested in several areas of reproductive medicine—including sperm identification and morphology, automation of follicle counts, automatic embryo cell stage prediction, embryo evaluation, and prediction of live birth, as well as developing improved stimulation protocols (5)—we envision that its use will be broadened and universally applied.

Once adopted, AI's advantages may include lower error rates in performing tasks regardless of the external environment, performing labor-intensive and tedious repetitive tasks, organizing medical records, and logical machine thinking without emotional factors or physical constraints. The challenges of adopting AI include the high initial cost of deployment, the ethics of relying on a machine to replace human decision-making, and the absence of the human connection. It must be emphasized that no supercomputer should replace or substitute human compassion. These challenges are complex and will require careful thought and reflection.

We, however, believe that AI will bring a digital transformation and automatization to the field of reproductive medicine and will ultimately provide great benefits to infertile patients and to society. We envision the role of AI as a tool to serve medical practitioners, which will enhance our diagnostic abilities and increase treatment efficiency. AI will not replace reproductive medicine practitioners and embryologists, but rather will streamline their efforts with the goal of better helping their patients.

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