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MEN'S HEALTH (A DABAJA, SECTION EDITOR)

Artificial Intelligence in Reproductive Urology

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Abstract

Purpose of Review The promise of artificial intelligence (AI) in medicine has been widely theorized over the past couple of decades. It has only been with technological advances over the past few years that physicians and computer scientists have started discovering its true clinical potential. Reproductive urology is a sub-discipline that AI could be of great contribution, as current predictive models and subjectivity within the field have several limitations. We review the literature to summarize recent AI applications in reproductive urology.

Recent Findings Early AI applications in reproductive urology focused on predicting semen parameters based on questionnaires that identify potential environmental factors and/or lifestyle habits impacting male fertility. AI has shown success in predicting the patient subpopulation most likely to need a genetic workup for azoospermia. With recent advances in image processing, automated sperm detection is a reality. Semen analyses, once a laboratory-only diagnostic test, have moved into health consumer homes with the advent of AI.

Summary AI's prospects in medicine are considerable and there is strong potential for AI within reproductive urology. Research in identifying the factors that can affect reproductive success either naturally or with assisted reproduction is of paramount importance to move the field forward.

Keywords Artificial intelligence · Machine learning · Reproductive urology · Male-factor infertility · Artificial neural network · Urology

Introduction

There are approximately 7.3 million couples with infertility in the USA, and sole male factor accounts for approximately 50% of cases [1]. Infertility workup is indicated for couples who are unable to achieve a successful pregnancy after regular, unprotected sexual intercourse. The American Society of Reproductive Medicine (ASRM) advocates for workup after 6 months of attempted conception in couples with advanced maternal age [2]. Time is of the essence for these couples, and thus efforts are being made to increase the efficiency of diagnostics, as well as to improve artificial reproductive technology (ART) outcomes.

Artificial intelligence (AI) is an advanced form of predictive computing that is now commonly being utilized in modern consumer technology. For instance, the foundation of voice assistants found on various smartphones is built upon AI architecture. AI has the ability to identify patterns in data and formulate fine-tuned predictions through a training algorithm. With the advent of decreased storage costs, larger data sets, and improving computer technology, AI has become an area of focus for advancing medicine. AI is quickly being integrated into various applications for different medical specialties, most notably radiology, molecular medicine, and oncology. While AI and its involvement in healthcare has been researched as early as the late twentieth century, we are just realizing its true potentials over the past decade.

There is sentiment within the reproductive medicine community that AI is an important application that needs to be prioritized for development and use [3]. During infertility

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workup, there are countless variables, such as age, lifestyle factors, and reproductive hormone levels to consider when predicting conception success. When ART is indicated, sperm and embryo selection are performed manually and graded subjectively. This results in expensive medical costs, time-consuming diagnostics, and potential areas for human bias [4•]. AI could greatly contribute to the field of reproductive medicine by standardizing processes that are subjective with wide operator variability, as well as analyze multiple variables for infertility and conception success. This review presents a brief overview of AI and current investigations into AI applications for reproductive urology.

Primer on Artificial Intelligence

Fundamentally, AI is the automation of data interpretation using algorithmic rules to emulate the logic of human experts [5]. AI has also developed subdisciplines, which include machine learning and deep learning. Machine learning is the process in which a computer performs predefined tasks and learns from experiences and inputs with greater observations [6]. Deep learning takes this a step further with the artificial neural network (ANN). ANN is considered analogous to the human brain, consisting of numerous layers of interconnected data processors with various weights to reflect interdependencies that determine target outputs or trigger actions [7, 8]. Each data processor receives inputs, and the net result of all inputs determines the output. The ANN is manipulated by weighting inputs, and weights can be adapted based on the backpropagation of incoming data until suitable [7]. The development and evolution of ANN systems bring us closer to replicating the way humans learn in machines.

It is important to consider that there are numerous algorithmic approaches that can be utilized to meet the needs of an objective. A single model cannot be globally applied, as results will be subpar and may not meet the needs of the primary user. The foundation of all machine learning algorithms is constructed on three steps for predictive modeling: data preparation, model selection with data fitting, and model validation. The more data the ANN can learn from, the better it can fine-tune the algorithm and expand its predictive potential [9]. The details of AI and its subdisciplines are technically complex, but a broad understanding by all clinicians will allow for an investigation into possible applications for their respective fields.

Current AI Applications in Medicine

AI is actively being researched across a broad spectrum of medical disciplines, and this is reflected in the exponential rise in academic publications over the past few years [10]. In particular, the forefront of AI application has been in radiology. The computer combs through medical imaging and indexes patterns and minutiae not visualized readily. By associating image findings and patterns to final diagnoses, the machine learning algorithm is re-trained and predictive performance improves [11].

The power of AI is not limited to radiology, as AI is classifying novel protein complexes with therapeutic potential through protein-protein interaction algorithms for the advancement of molecular medicine. Moreover, AI has been shown to identify DNA variants that can act as predictors of disease [12]. In oncology, AI is predicting aggressive tumor progression and cancer prognosis. In cardiology, AI is identifying predictors for survival of patients with heart failure with preserved ejection fraction [13]. ANNs have proven powerful analytical tools capable of predicting disease outcomes and discovering novel therapeutic targets. The potential for future applications is noteworthy. As research investigations increases and technology further develops, AI has the potential to transform all medical disciplines in a diverse manner.

Current AI Applications in Urology

Physicians and scientists in Urology have investigated and implemented AI in clinical practice to aid in disease diagnosis and treatment [14, 15]. From a diagnostic perspective, AI has the ability to classify prostate tumor histopathology and lymph node spread through image segmentation [16]. A recent study demonstrated the ability of AI to form automated diagnoses of prostate cancer location using multi-parametric MRI with a sensitivity and specificity of 0.92 and 0.82, respectively [17]. In another use of AI with urologic imaging, De Perrot et al. accurately differentiated between phleboliths and kidney stones on low-dose CT scans for patients presenting with acute flank pain [18].

AI showed similar advantage in diagnostic ability for urinary tract infections [19]. Instead of waiting 24–48 h for a urine culture to result, clinicians rely on clinical symptoms and urinalysis for early treatment. AI, in combination with these variables and other patient factors, was shown to outperform current predictive models for diagnosis of UTI, as well as provider judgment [20]. Since UTI is a common reason for antibiotics use and with current concerns over rising antibiotic resistance, this technology could develop into an important tool for proper antibiotic administration.

As in all oncologic fields, AI as a predictive model for urologic cancer progression is undergoing investigation [21]. In comparison with traditional regression statistics used in the evaluation of urologic cancer databases, AI models appear to be more accurate and comprehensive [22]. Two AI methods, ANN and Neuro-fuzzy modeling (NFM), were compared against traditional statistical methods for predictive accuracy on relapse of bladder cancer in a cohort of 109 patients. Both methods were significantly more accurate than traditional statistical methods (88%, 95%, and 71–77% respectively) [23].

AI is also augmenting efforts to provide patient-centered care for prostate cancer patients The Michigan Urologic Surgery Improvement Collaborative (MUSIC) created a collection of tools for patients based on a registry with data of more than 7500 men diagnosed with prostate cancer. The aim of these tools, termed "askMUSIC," is to help newly diagnosed patients answer the question, "what treatments did patients similar to me choose?" AI has strengthened the patient's role in the shared decision-making process, allowing the patient to feel more informed and in control of their disease [24]. The use of AI within urology is a prime example of the broad applications across different subspecialties within the field.

AI Applications in Reproductive Urology

Prediction in Male Infertility Workup

Early efforts for artificial intelligence in reproductive urology were largely focused on identifying factors for predicting semen quality. This initiative was spurred largely by a noted trend of decreasing fecundity rates over the past couple of decades. Gil et al. looked at utilizing various AI networks to analyze the association between environmental factors and/or lifestyle habits in its possible effects on semen quality [25]. Some of the variables they assessed included cigarette exposure, alcohol consumption, and body mass index (BMI). They obtained data through 100 university students by questionnaire, and through utilization of ANN they were able to show high prediction accuracy (~ 86%) for sperm concentration, and (73–76%) for motility [25]. Candemir et al. proposed an alternative algorithmic model to predict semen quality from a similar questionnaire, with additional variables including season of analysis and genitourinary trauma history [26]. A radial basis function neural network was used in this model, and success rates of up to 90% were reported in estimating semen quality. When compared to previous models on predicting semen quality, this was deemed the most accurate [26]. El-Shafeiy et al. have additionally demonstrated further optimization of an ANN for predicting fertility quality by coupling an additional optimization algorithm, termed the Sperm Whale Optimization algorithm [27]. Predictive models for semen quality could be used as a first step in screening men who may need infertility evaluation. Earlier identification of men who may have sub-fertility by recommending a semen analysis would lead to earlier intervention for couples desiring pregnancy.

Besides predicting semen quality, there have been investigations into applying AI for prediction of seminal plasma zinc and leptin levels, both potential biomarkers for fertility. Studies have shown that seminal zinc is required for normal sperm function and fertilization [28]. In a validation study, Vickram et al. indexed 177 patients with primary inputs as semen parameters and prediction output as seminal zinc level. Their AI model showed high performance in predicting seminal plasma zinc levels [29]. Seminal leptin was investigated as a possible biomarker in another study for sperm retrieval success in non-obstructive azoospermia. The results found that leptin improved prediction of success when utilized alongside classic biomarkers, such as FSH, in an ANN model [30]. These studies show promise for AI in further analyzing semen parameter with seminal element and protein levels to identify potential biomarkers for infertility.

Identifying Chromosomal Abnormalities in Azoospermic Males

Azoospermia is present in 10–15% of men undergoing an infertility evaluation, and it is important to determine if the underlying etiology of azoospermia is genetic [31]. Akinsal et al. utilized an ANN to predict the subset of azoospermic patients that should undergo further genetic testing. They performed a retrospective study investigating multiple male factors and found that total testicular volume and LH have the highest power in identifying those who require additional genetic evaluation. Overall, they found promise in utilizing AI to identify a smaller cohort needing further investigation [32]. Utilizing AI to predict those with potential genetic abnormalities may mitigate the expense and time-lag of formal genetic testing.

Semen Analyses

Semen analysis (SA) is commonly performed for any male undergoing an infertility evaluation. In the laboratory, the majority of sperm parameters are measured manually, with sperm motility and concentration either estimated using a microscope or with a computer-assisted sperm analysis (CASA) system [33]. In particular, the process of classifying sperm morphology to the strict Kruger criteria is manually time-consuming, and as such alternative technologies that expedite the process remain expensive. Thirumalarjaju et al. reported success with AI interpreting sperm morphology using an ANN. After training and validating the network with over 3500 images of sperm, the algorithm was used to analyze 9 semen samples with 100% accuracy in identifying all abnormal and normal samples [34]. Additionally, we now have the ability to create multi-modal SA, in which the media file that houses SA video frames contains the patient's serum levels of sex hormones, lifestyle characteristics, and semen parameters [35]. This provides medical researchers with unparalleled ability to identify patterns across various mediums with the aid of AI.

The commercial availability of home semen analysis kits has expanded over the years, and now emerging technologies are promising better accuracy and validity [36]. Currently, there are both analog and digital home kits. Automated analog home kits utilize monoclonal antibodies or centrifuge system to identify sperm concentration. Digital home kits utilize a smartphone and its digital camera to provide analysis. Each device includes a microscope that interfaces with the camera and records video that can be viewed and/or analyzed by an accompanying smartphone app [37]. The YO home sperm test is a mobile application that utilizes light signal and color changes in pixels to identify moving cells and translates the movement into motile sperm concentration (MSC) via proprietary algorithms. MSC is reported as either "low" or "moderate/normal" based on an established 6 million per ml cut off with a 97.8% accuracy when compared to automated laboratory systems [38].

Digital home semen analysis kits show promise, but there remains the limitation of reporting too few semen parameters. These may be overcome by the addition of AI. Recent reports have demonstrated AI's ability to not only accurately measure sperm motility but morphology as well. Benmar ® has developed a microfluidic microscope that transmits video to a smartphone which uses AI and cloud computing to calculate sperm motility. The AI algorithm results correlated well with a male-fertility expert's interpretation of the videos with coefficients of 0.84 and 0.90 for motile sperm total motility respectively [39].

Sperm Identification and Artificial Reproductive Technologies

Several techniques, such as masturbation, penile vibratory stimulation/electroejaculation, or various operative techniques can be utilized to retrieve sperm for ART. Once the specimen is obtained, the sample are processed at the laboratory level and then must undergo sperm detection and selection. In particular with non-obstructive azoospermia patients, the sperm detection remains time-consuming and selection of candidate sperm for use with intracystoplasmic sperm injection (ICSI) remains an area that requires further study. Currently, a wide variety of laboratory techniques are utilized for selecting the sperm to be utilized for ICSI [40]. Sasaki et al. presented their findings at the 2018 Institute of Electrical and Electronics Engineers International Conference, in which they investigated the ability to utilize adaptive threshold methods to improve true positive rate detection of sperm while controlling the false positive rate. At ASRM 2018, the authors discussed further findings of their research, in which they were able to differentiate 8020 spermatozoa and 25,522 non-spermatozoa cells through AI [41•]. Although further study within the field is needed, the early results are promising for improving ART outcomes in regard to sperm selection.

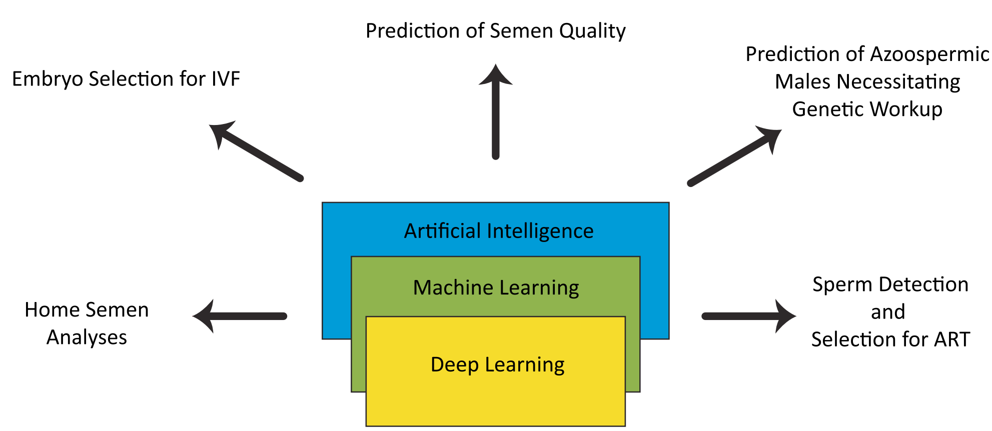
Embryo Selection for In Vitro Fertilization

In vitro fertilization (IVF) is one of the most common treatments for infertility, but it only has an approximately 45% success rate [4•]. The process of IVF consists of ovarian stimulation with retrieval, fertilization with obtained semen specimen, followed by embryo culture. The actual embryo selection process is performed manually by skilled embryologists during the blastocyst phase, dependent on morphology. While there is intent to grade the embryos in a standardized manner, there remains room for subjectivity bias, and as a result, there is variability amongst medical centers. Khosravi et al. analyzed 10,148 embryos and formulated an AI approach termed "STORK," and their algorithm showed high performance in predicting embryo quality, outperforming individual embryologists [4•]. They attempted to take the algorithm a step forward by integrating the prediction of live birth, but the results were unsatisfactory, suggesting that morphology alone was not enough for prediction. Nonetheless, this application shows the potential of AI in improving ART.

Conclusion

In the past few years, AI has evolved enormously in the healthcare sector. Amongst medical professionals, there is much optimism that AI will continue to bring about paradigm shifts in healthcare. Its application in reproductive urology

Fig. 1 Current artificial intelligence applications in reproductive urology



remains in the nascent phase (Fig. 1), but the promise of improving ART and infertility diagnostics is evident. Additionally, research questions regarding the roles of multiple fertility variables may be discovered through AI. These potentials are possible due to a fundamental difference between AI and logical approaches, in that the latter relies on the knowledge of the expert, whereas, within limits, an algorithm derives "its own" conclusions. It is difficult for humans to parse and analyze large data sets, whereas a computer may be able to do it efficiently. AI is critical in mining through the data and identifying underlying patterns. Major technology companies, such as Google, Apple, and Amazon, are earnestly heading into healthcare endeavors based upon data collection and machine learning algorithms. At the end of the day, the physician is the sole responsible professional for a patient's treatment, and clinical training and experience weigh into true clinical applicability. Thus, it is important for both healthcare professionals and computer scientists to work together in creating applications that are clinically important.

Compliance with Ethical Standards

Conflict of Interest Kevin Y. Chu, Daniel E. Nassau, Himanshu Arora, Soum Lokeshwar, Vinayak Madhusoodanan, and Ranjith Ramasamy each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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