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Procedia Computer Science 181 (2021) 442–447

Procedia Computer Science

www.elsevier.com/locate/procedia

CENTERIS - International Conference on ENTERprise Information Systems / ProjMAN - International Conference on Project MANagement / HCist - International Conference on Health and Social Care Information Systems and Technologies 2020

Artificial intelligence at assisted reproductive technology

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Abstract

Introduction: Artificial Intelligence (AI) is a strong technological wave providing the ability for a machine to perform cognitive functions; it is quickly gaining traction in assisted reproductive technology (ART).
Aim and Methods: Discrepancies in results among reproductive centres still exist making the construction of new systems capable to foresee the desired outcome a necessity. We will describe the steps and gains to a possible AI system to predict IVF outcomes. Throughout this manuscript, we intend to review several clinical parameters for the evaluation of the fertilization process and describe their integration in an AI system, without providing details about the computer algorithm that will obviously depend on funding to be developed.
Discussion: The proposed fertility treatment software covers the entire workflow of IVF treatments. An electronic system keeps the verification and matching data software on every step of the treatment (Anti-Müllerian hormone based ovarian stimulation, measurements of follicular diameter with 3D ultrasound, sperm test, oocyte collection, oocyte tracking, embryo selection, preimplantation genetic screening) and matching of sperm and egg samples of patient who is having IVF treatment.
Conclusion: An AI ART software can have many advantages, namely: decrease interobserver variability, adjustment of drug doses in oocyte stimulation, decrease face-to-face medical contacts and thus increase medical and user productivity, better selection of sperm samples and evaluation of oocyte quality and embryo selection.

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10.1016/j.procs.2021.01.189

Keywords: artificial intelligence , assisted reproductive technology, 3D ultrasound, oocyte selection , embryo selection

1. Introduction

Artificial Intelligence (AI) is a strong technological wave providing the ability for a machine to perform cognitive functions, such as perceiving, reasoning, learning and interacting. AI has rapidly entered our lives by solving business problems due to three technological developments that have reached enough maturity and convergence: advancement in algorithms, massive data, and increasing computational power and storage at low cost. [1]

AI is quickly gaining traction in human reproduction and embryology. Advances in AI applications are constantly promoted by the increasing amount of data available in reproductive medicine. Despite some potential pitfalls, making decisions for infertility patients based on the analysis of medical data is the optimal clinical approach. To reduce the gap between research and clinical practice, we need to focus on combining Assisted Reproductive Technology (ART) and AI development.

In 2014 the European number of reproduction clinics has increased (1169 in 2013 to 1279 in 2014, +9.5%), but also the overall number of reported treatments (686 271 in 2013 to 776 556 in 2014, +13.1%). Among the 42 members of European Society of Human Reproduction and Embryology (ESHRE), 39 have sent their data (92.9%), 1279 institutions offering ART services, a total of 776 556 treatment cycles, involving 146 148 with *in vitro* fertilisation (IVF), 362 285 with intracytoplasmic sperm injection (ICSI), 192 027 with frozen embryo replacement (FER), 15 894 with preimplantation genetic testing (PGT), 56 516 with egg donation (ED), 292 with *in vitro* maturation (IVM) and 3404 with frozen oocyte replacement (FOR) were reported. European data on intrauterine insemination (IUI) using husband/partner's semen (IUI-H) and donor semen (IUI-D) were reported from 1364 institutions offering IUI in 26 countries and 21 countries, respectively. A total of 120 789 treatments with IUI-H and 49 163 treatments with IUI-D were included. The European countries with the largest treatment numbers in 2014 were Spain (109 275 treatments), Russia (94 985), France (90 434) and Germany (81 177). [2]

Despite advances in personalized ovarian stimulation, extended embryo culture, pre-implantation genetic testing, and embryo selection, on average, only one-third of all IVF cycles result in a pregnancy. This represents a significant problem that AI can be leveraged against: short time to pregnancy through improved IVF cycle efficiency (reduction of failed retrievals or transfers and miscarriages), from replacement of a single, euploid embryo resulting in a healthy, live-birth. [3]

2. Background

Reproductive experts can determine the best treatment for the individual infertility of patients by incorporating AI: machine learning (ML) and deep learning (DL). [4]

ML is the scientific discipline that focuses on how computers learn from data. It arises at the intersection of statistics, which seeks to learn relationships from data, and computer science, with its emphasis on efficient computing algorithms. This marriage between mathematics and computer science is driven by the unique computational challenges of building statistical models from massive data sets, which can include billions or trillions of data points. The types of learning used by computers are conveniently subclassified into categories such as supervised learning and unsupervised learning. However, in addition, another division can be useful when considering how machine learning might inform the practice of medicine: distinguishing learning those tasks that physicians can already do well and learning those where physicians have had only limited success. With these broad categories in mind, we can visit some areas in medicine that have benefited or might benefit from machine learning approaches. [5]

In contrast to ML, DL is very flexible in how it allows the labels to relate to the input features: labels are functions of intermediate variables (also known as hidden variables, intermediate features, nodes or neurons), which are in turn functions of other intermediate variables, and so on, until some intermediate variables are functions of the input features. A deep neural network (DNN) can be viewed as a mathematical function built by composing simple transformations called layers, so that the outputs of one-layer feed into the inputs of the next. The idea of deep learning is that stacks of transformations are extremely powerful and flexible in the kinds of relationships that they can model while still being trainable. The most commonly used training method is backpropagation, which iteratively adjusts all weights so as to minimize the error between predictions and training labels. Backpropagation is named for the backward (output-to-input) flow of computation when determining how much to adjust each weight, which makes efficient reuse of intermediate values that were computed by the forward pass. The power of deep learning frameworks, such as PyTorch and TensorFlow, is that, given any user-defined model, they automatically derive the correct set of computations needed for backpropagation, no matter how deep or complex the architecture. ART algorithms, sampling methods and other techniques for training DNNs are an important area of current research.[6]

3. Objective and Methods

Optimization the outcome of IVF treatment is an extremely semantic issue in reproductive medicine. Discrepancies in results among reproductive centres still exist making the construction of new systems capable to foresee the desired outcome a necessity. As such, AI represent a combination of a learning, self-adapting, and predicting machine. In this manuscript we describe the steps and gains to a possible AI system to predict IVF outcomes. For the realization of the project will have to be taken into account together with other statistical models, such as the ensemble techniques, Classification and Regression Tree (CART) and regression analysis techniques, discriminant analysis, and case based reasoning systems. The implementation of the project with the development of the software remains dependent on external funding for the development of computer algorithms, statistical analysis and database migration, and will be subject to aspects of confidentiality, which for these reasons will not be described in detail in this manuscript.

4. Assisted reproductive technology software

The proposed fertility treatment software offers a number of advantages and hence could become a critical success factor for the superior performance and growth in fertility centres. It covers the entire workflow of IVF treatments, from the time of first appointment of the patient until the final discharge summary, everything is recorded, reported, analysed and automatized. An electronic system keeps the verification and matching data software on every step of the treatment (Anti-Müllerian hormone (AMH) based ovarian stimulation, measurements of follicular diameter with 3D ultrasound, sperm test, oocyte collection, oocyte tracking, embryo selection, preimplantation genetic screening (PGT-S)) and matching of sperm and egg samples of patient who is having IVF treatment without any error with artificial intelligence system optimized. There is, however, a concern about data protection mechanisms about precious historical data residing in current legacy software products.

- **Anti-Müllerian hormone based ovarian stimulation**

AMH is used to establish patient profiles and predict ovarian response to stimulation; it's role in assisted reproductive technology techniques is crucial. AMH is known for its expression by granulosa cells of developing follicles during sexual differentiation; it is a dimeric glycoprotein that belongs to the transforming growth factor-β (TGF-β) family. Concentrations of AMH reflect the functional ovarian reserve, and it declines significantly with age. [7] Its role in ART is crucial as an indicator of ovarian response to stimulation. Individualized gonadotropin dosing using antral follicle count (AFC) or AMH as ovarian reserve tests (ORT) has been introduced to optimize the ratio between benefits and risks of ovarian stimulation for IVF. [8] The incidence of moderate/severe ovarian hyperstimulation syndrome (OHSS) increases significantly with the number of oocytes, especially when the number of oocytes was retrieved exceeds 18. Ling Cui in 2019 published a systematic review and meta-analysis suggest that AMH-based stimulation has the same results of ongoing pregnancy rate and risk of OHSS, and can reduce the dose of FSH and duration of stimulation. [9]

The AI ART software define the dose of recombination FSH before the ovarian stimulation.

- **Automatic measurements of follicular diameter with 3D ultrasound**

Ultrasound follicular count (antral follicle count, AFC) is a necessary tool for measuring ovarian reserve, whereby the estimated number of follicles responsive to FSH can predict the number of oocytes retrieved in IVF cycles and may be the basis for individualized ovarian stimulation therapy. Advances in the ultrasound technology have recently lead to the improvement in resolution and quality of the image. The automatic measurements of follicular diameter by using some specific 3D software is associated to several advantages: Examination time is reduced because the ultrasound scan data are stored, technique reduces the operator's influence on scan interpretation and objectivity; therefore, interobserver variability is reduced. [10]

Using follicular volume obtained with automatic measurements of follicular as the measure of follicular growth combined with volume-based criteria for the hCG triggering, improve the treatment outcome compared to that achieved with conventional monitoring with follicular diameter. [11]

The AI ART software can analyse in detail all information by automatic measurements of follicular diameter with 3D ultrasound to monitoring the cycle and hCG triggering.

- **Evaluation and selection of oocytes**

The overall success of reproduction, either spontaneously or after ART, is highly dependent upon the quality of oocytes. Currently, the pregnancy rate per retrieved oocyte is estimated at 4.5%. Non-invasive approaches to predict human oocyte developmental potential reported that viscoelastic properties of human zygotes measured non-destructively within hours after fertilization could reliably predict viability and blastocyst formation, with >90% precision, 95% specificity and 75% sensitivity. [12]

Applying AI methods to the evaluation of human oocytes using time-lapse or assesses gene expression through transcriptomics or genomics can optimize the ART.

- **Sperm selection and semen analysis**

Semen analysis is the first step in the evaluation of infertile couples. For sperm analysis, important inter-laboratory variations have been observed in manual analyses especially when dealing with analyses with wide ranges of normal values. A computer-aided sperm analysis (CASA) system was assessed versus manual technique, with equivalents results. Four parameters are studied: concentration, motility, vitality and morphology. CASA systems are no simple 'black boxes', issuing cold, bare results outside any human intervention but rather they are valuable assets providing faster and more precise results for the main parameters in routine sperm analyses. [13]

We propose to synchronize CASA systems with AI ART software to permit to select sperm for ART.

- **Embryo selection**

Precise assessment of embryo viability is a prime factor in maximizing pregnancy rate and optimizing of IVF treatments. The introduction of automatic morphological analyses of embryos or blastocysts in conjugation with AI is an attractive possibility. Time-lapse microscopy (TLM) is a technology for enhancing embryo selection in the embryology laboratory. This non-invasive objective assessment of embryos has provided a new tool for predicting embryo development and implantation potential [14].

Time-lapse imaging of embryos and image data have been used to obtain large datasets. Several studies were presented at the 2018 Annual Congress of the American Society for Reproductive Medicine and the European Society for Human Reproduction and Embryology. More specifically, one of those studies achieved 83% overall accuracy in predicting live birth by looking at 386 time-lapse images of single blastocyst transfers [15]. Another study reviewed 50,392 images from 10,148 embryos and managed to obtain 97.53% accuracy in discriminating between a poor and good blastocyst [16]. Others used pre-treatment characteristics of known cycles to predict first cycle success, which had an accuracy of 81% [17]. It utilized the Retinex algorithm to enhance the quality of the input images, eventually achieving an average shape accuracy of 87.8% to detect trophectoderm (TE) regions, introduced an automatic method for joint segmentation of TE and inner cell mass in blastocyst images. [18]

Embryo morphology remains the current tool for embryo selection for transfer permitting a AI ART software analyse.

- **Preimplantation genetic testing (PGT)**

PGT is now a widely applied procedure in genetic practices and ART, with more than one third of ART Centres in US already utilizing PGT technology. The current selection process of embryos with the highest developmental potential requires a further improvement, as significant proportion of transferred euploid embryos still fail to result in an ongoing clinical pregnancy. [19]

To avoid a potential damage of embryo biopsy procedures, one of the important challenges will be the development of non-invasive approaches to PGT, optimization and automatization in AI ART software.

5. Conclusion

AI as a device that perceives its environment and takes actions that maximize its chance of successfully achieving its goals, has been applied to different areas of medicine, not as a substitute for medical work but as a facilitator and optimizer of capabilities, as an instrument to support clinical decision-making. It is based on the integration of clinical data from large databases and the creation of computer algorithms using multiple variables, ML and DL.

The area of ART has been a topic of significant expansion in recent years, and so could greatly benefit from AI support. An AI ART software can have many advantages, namely: decrease interobserver variability, adjustment of drug doses in oocyte stimulation and thus reduce adverse effects such as hyperstimulation, decrease face-to-face medical contacts and thus increase medical and user productivity as active tools of society, better selection of sperm samples and evaluation of oocyte quality and embryo selection.

There are however some dilemmas to consider when using AI to ART: the protection of personal data and corresponding legislation and the integration of human experience in clinical decision. Overcoming these difficulties, an algorithm containing the variables mentioned throughout this manuscript will certainly have direct clinical applicability and be a tool adopted by the main fertility clinics throughout the world. As previously mentioned, the implementation of the project with the development of the software remains dependent on external funding for the development of computer algorithms, statistical analysis and database migration.

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