Artificial Intelligence in Reproductive Medicine

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Infertility is a global health issue affecting women and men of reproductive age with increasing incidence worldwide, in part due to greater awareness and better diagnosis. Assisted reproduction technologies (ART) are considered the ultimate step in the treatment of infertility. Artificial intelligence (AI) has been progressively used in the many fields of medicine, integrating knowledge and computer science through machine learning algorithms. AI has the potential to improve infertility diagnosis and ART outcomes estimated as pregnancy and/or live birth rate, especially with recurrent ART failure.

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1. Introduction

Infertility is a global health issue of women and men of reproductive age with increasing incidence worldwide, in part due to improved awareness and better diagnosis. It is defined as the failure to achieve pregnancy after 12 months of regular unprotected sexual intercourse [1]. Besides female and male infertility causes, an unknown cause is present in circa 85% infertile couples, 15% of whom have unexplained infertility [2]. Female infertility causes include: ovarian dysfunction and anovulation, tubal infertility, endometriosis, and diminished ovarian reserve. A male factor is likely to be a primary or contributing cause in approximately 50% of couples and can be related to congenital, acquired, or idiopathic factors that impair spermatogenesis [3]. The best approach to initiate a diagnostic–therapeutic pathway is the simultaneous evaluation and treatment of both female and male infertility factors [4]. Infertility treatment includes ovulation induction and/or stimulation in order to produce multiple mature ovarian follicles. Both clomiphene citrate, a selective estrogen receptor modifier, and letrozole, an aromatase blocker, cause an increase of hypothalamic gonadotropin-releasing hormone (GnRH) pulse frequency and pituitary gonadotropin secretion-inducing ovarian folliculogenesis [2]. The main problem is a multiple pregnancy rate of less than 10%, most of which are twin gestations, and the risk of ovarian hyperstimulation syndrome [5][6].

In women with hypogonadotropic hypogonadism, pulsatile GnRH administration induces follicular maturation and ovulation due to the stimulation of endogenous gonadotropins. Folliculometry and planned intercourse or intrauterine insemination (IUI) may be used to achieve fertilization at the time of ovulation [2]. IUI is a first-line treatment for mild male fertility, and it could be combined with ovarian stimulation in the treatment of couples. If not successful, in vitro fertilization (IVF) is the next step. Undergoing an IVF program consists of a GnRH agonist or antagonist protocol, individually chosen, followed by gonadotropin stimulation. The initial doses of gonadotropin are adjusted according to patient age, estimated ovarian reserve, and response to prior stimulation, and are set during the first three to four days. Transvaginal ultrasonography and measuring of blood estradiol [E2] are used to estimate the ovarian response in order to modify the gonadotropin dose, and final oocyte maturation is induced [7].

In further courses, oocyte retrieval is carried out, and those chosen based on quality undergo IVF or, in the case of male factor infertility, intracytoplasmic sperm injection (ICSI) [8]. ICSI is also recognised as a method of choice for women with thyroid autoimmunity (TAI) undergoing assisted reproduction technologies (ART) [9][10]. Embryos are cultured under optimal conditions [11], and then those of the highest quality are transferred on the second, third, or fifth day after oocyte aspiration into the uterus under ultrasound guidance (US is not mandatory) [2]. Over the next 5–10 years, further increases in birth rates in women with infertility are expected due to greater awareness of lifestyle factors, as well as a possible refinement of current ART and the development of new forms of treatment relying on germ cell manipulation, artificial gametes, genetic screening of embryos, and gene editing of embryos [12]. Donor oocytes or sperm may be options in specific situations.

2. Artificial Intelligence in Reproductive Medicine

Artificial intelligence (AI) as an official term first appeared at the Dartmouth conference in 1956. Ever since, it has been used as a reference to the continual study of artificial intelligence. Such a wide-ranging research endeavour hinges on the use of devices such as computers to reproduce human mental processes, such as cognition, learning, decision making, judging, and language usage [13]. Nowadays, AI is already in use in a lot of different industries, and there is a lot of ongoing research. There are a lot of fascinating applications of AI, such as in the transport and automotive industry (e.g., development of autonomous vehicles [14], transport mapping [15], solving financial problems [16], face and speech recognition [17][18]), and others which raise concerns and are potentially destructive, such as the development of Lethal Autonomous Weapon Systems (LAWS) [19], e.g., missile systems with selective targeting capabilities and learning machines with the cognitive ability to select their enemies with no need for intervention by humans [20]. The developmental foundations for this research area are grounded in a subdiscipline of philosophy called philosophy of mind. Assumptions about the mind such as connectivism, computation theory of mind, and behaviourism are essential for understanding AI [21].

In order to optimally run software needed for AI, adequate hardware is essential. For example, to run some deep learning algorithms, graphics processing units (GPUs) produced by “Nvidia” are used. In modern times, the amount of electronic data created every day is astonishing. Technological advancements have been made for storing this data. This was a necessity to accommodate the 2.5 quintillion bytes saved each day [22][23]. Such an amount of data needs some kind of analytics that are automated; hence, AI is a very powerful tool to fulfil that task. The core element that constitutes AI is algorithms. In general, algorithms are specific steps to solve some problem. For a computer to be able to “read “and process vast amounts of data, a specific type of technology is needed, so-called natural language processing (NLP). NLP uses algorithms that allow computers to “understand“ and process human language, so this part of AI research is tightly connected with linguistics. This technology is used to construct information that is valuable and meaningful from some unstructured data, such as electronic medical records. In that way, a computer is able to further analyse data given to it [24]. The cornerstone of AI is constituted by empirical machine learning algorithms. There are different types of machine learning, and they are classified by how they analyse data and their level of dependence.

In short, machine learning (ML) is classified in three main groups: ML capable of recognizing patterns (unsupervised ML), ML that has algorithms that perform classification and prediction based on previous examples (supervised ML), and ML that uses a system with reward and punishment methods to form a solution strategy to solve some problem (reinforcement learning) [25]. The first big success of AI in medicine started with predictions of protein complexes in molecular medicine that led to some new drug targets discoveries. The big data that electronic medical records (EMRs) and hospital data have within are perfect for AI to analyse and give some useful information. The current status of EMRs is that they are cumbersome and lack inter-record communication. It is of great value to analyse this vast amount of data. An example includes AI that has the ability to detect subjects that are at risk for chronic disease; furthermore, AI could facilitate faster, more efficient health system calculations of cost–benefit ratios and help in decision making. AI is vastly used nowadays to analyse and learn to recognise patterns in image processing, so there is great interest in fields such as radiology, pathology, ophthalmology, and dermatology—so-called “vision- orientated specialties“. It is of great value that AI can reduce common errors in everyday clinical practice and make predictions in real-time [26][27].

In reproductive medicine (RM), AI application started in the late twentieth century. Nowadays, there are a lot of different subtypes of AI technology that have applications in reproductive medicine. Supervised learning methods (decision tree, support vector machines and naive Bayes classifier) are mostly used in non-surgical areas of RM. These algorithms need human assistance and use instances supplied externally to predict the fate of instances given in the future; they are designed to categorise data from given information [28][29]. So, the usage of this type of AI found its application in determining the morphokinetic parameters of the embryos that are most optimal [30], determining cost effectiveness in human oocyte cryopreservation [31], predicting IVF and ICSI outcomes, and classification of sperm cells [32]. Unsupervised learning models are not yet fully used in RM. Such algorithms are effective at so-called class discovery, since they use unlabeled data to “discover” the underlying structure and relationship within and to cluster it [33]. Types of unsupervised ML used are principal component analysis and K means that are mostly used in image processing. They can predict pregnancy based on the quality of oocytes, with a success rate of around 60% [34]. Other subtypes of AI commonly used in medicine include artificial neural networks (ANN). ANNs borrow structures from neuronal connections and consist of layers such as the input layer (where data start to be analysed), inner or hidden layer (where data are analysed), and output layer (where final data are presented), with weight connections and bias nodes between these layers. Deep networks are complex forms of ANN, and these AI technologies are widely used today in speech recognition, visual object recognition, and object detection, as well as in medical fields, such as drug discovery and genomics [35]. In RM, ANN are used in embryo segmentation [36], to describe blastocyst expansion and rank-order blastocysts for transfer [37], and to predict an overall outcome of IVF.

Meanwhile, for robotic aspects of RM, reinforcement AI machine learning is more commonly used [28][38]. Robotic surgery serves as a bridge between conventional open surgery and the minimally invasive laparoscopic surgery, and there are currently several different applications in this field. Examples are robotics-assisted myomectomy, tubal reanastomosis, endometriosis, ovarian tissue cryopreservation, and ovarian transposition. In addition, their applications include male infertility operations such as vasectomy reversal, subinguinal varicocelectomy, targeted spermatic cord denervation, and robotics-assisted microsurgical testicular sperm extraction (microTESE). These procedures, although costly and time consuming, have good results in terms of shorter hospital stay, decreased blood loss, less post-operative pain, and faster convalescence compared to open or laparoscopic surgeries, whereas reproductive outcomes were described as similar to nonrobotic surgical approaches [38][39][40].

Overall, AI has the ability to do work that would require thinking with strict or not-so-strict guidelines given by humans, with AI being able to analyse pixels from pictures and videos and recognise the context of the given image, as well as analysing text information and predicting outcome based on the given inputs.

Most of the research done in AI applied to RM is still lacking randomised controlled trials to prove its value, and it is mostly used for some automatic jobs. Furthermore, the legal aspects and ethics of the usage of this type of technology need to be clarified more in the future. Because of its immense potential and essential need to use large quantities of data to train itself, AI is dependent on more efficient and easier ways of data connection, which is, nowadays, the first step to the inclusion of this type of technology in everyday practice.

References

1. World Health Organization (WHO). International Classification of Diseases; 11th Revision (ICD-11); WHO: Geneva, Switzerland, 2018.
2. Carson, S.A.; Kallen, A.N. Diagnosis and Management of Infertility. JAMA 2021, 326, 65–76.
3. Agarwal, A.; Baskaran, S.; Parekh, N.; Cho, C.-L.; Henkel, R.; Vij, S.; Arafa, M.; Selvam, M.K.P.; Shah, R. Male infertility. Lancet 2020, 397, 319–333.
4. Infertility Workup for the Women’s Health Specialist. Obstet. Gynecol. 2019, 133, 1294–1295.
5. Franik, S.; Le, Q.-K.; Kremer, J.A.; Kiesel, L.; Farquhar, C. Aromatase inhibitors (letrozole) for ovulation induction in infertile women with polycystic ovary syndrome. Cochrane Database Syst. Rev. 2022, 9, CD010287.
6. Gadalla, M.A.; Norman, R.J.; Tay, C.T.; Hiam, D.S.; Melder, A.; Pundir, J.; Thangaratinam, S.; Teede, H.J.; Mol, B.W.J.; Moran, L.J. Medical and Surgical Treatment of Reproductive Outcomes in Polycystic Ovary Syndrome: An Overview of Systematic Reviews. Int. J. Fertil. Steril. 2019, 13, 257–270.
7. Medenica, S.; Garalejic, E.; Arsic, B.; Medjo, B.; Jovic, D.B.; Abazovic, D.; Vukovic, R.; Zarkovic, M. Follicular fluid thyroid autoantibodies, thyrotropin, free thyroxine levels and assisted reproductive technology outcome. PLoS ONE 2018, 13, e0206652.

8. Goudakou, M.; Kalogeraki, A.; Matalliotakis, I.; Panagiotidis, Y.; Gullo, G.; Prapas, Y. Cryptic sperm defects may be the cause for total fertilization failure in oocyte donor cycles. Reprod. Biomed. Online 2012, 24, 148–152.
9. Poppe, K.; Bisschop, P.; Fugazzola, L.; Minziori, G.; Unuane, D.; Weghofer, A. 2021 European Thyroid Association Guideline on Thyroid Disorders prior to and during Assisted Reproduction. Eur. Thyroid. J. 2020, 9, 281–295.
10. Medenica, S.; Abazovic, D.; Ljubić, A.; Vukovic, J.; Begovic, A.; Cucinella, G.; Zaami, S.; Gullo, G. The Role of Cell and Gene Therapies in the Treatment of Infertility in Patients with Thyroid Autoimmunity. Int. J. Endocrinol. 2022, 2022, 4842316.
11. Prapas, Y.; Petousis, S.; Panagiotidis, Y.; Gullo, G.; Kasapi, L.; Papadeothodorou, A.; Prapas, N. Injection of embryo culture supernatant to the endometrial cavity does not affect outcomes in IVF/ICSI or oocyte donation cycles: A randomized clinical trial. Eur. J. Obstet. Gynecol. Reprod. Biol. 2012, 162, 169–173.
12. Farquhar, C.M.; Bhattacharya, S.; Repping, S.; Mastenbroek, S.; Kamath, M.S.; Marjoribanks, J.; Boivin, J. Female subfertility. Nat. Rev. Dis. Prim. 2019, 5, 7.
13. Zhang, C.; Lu, Y. Study on artificial intelligence: The state of the art and future prospects. J. Ind. Inf. Integr. 2021, 23, 100224.
14. Ma, Y.; Wang, Z.; Yang, H.; Yang, L. Artificial intelligence applications in the development of autonomous vehicles: A survey. IEEE/CAA J. Autom. Sin. 2020, 7, 315–329.
15. Abduljabbar, R.; Dia, H.; Liyanage, S.; Bagloee, S.A. Applications of Artificial Intelligence in Transport: An Overview. Sustainability 2019, 11, 189.
16. Bahrammirzaee, A. A comparative survey of artificial intelligence applications in finance: Artificial neural networks, expert system and hybrid intelligent systems. Neural Comput. Appl. 2010, 19, 1165–1195.
17. Abdel-Hamid, O.; Mohamed, A.-R.; Jiang, H.; Deng, L.; Penn, G.; Yu, D.; Abdel-Hamid, O.; Mohamed, A.-R.; Jiang, H.; Deng, L.; et al. Convolutional Neural Networks for Speech Recognition. IEEE/ACM Trans. Audio Speech Lang. Process 2014, 22, 1533–1545.
18. Taigman, Y.; Yang, M.; Ranzato, M.; Wolf, L. DeepFace: Closing the Gap to Human-Level Performance in Face Verification. In Proceedings of the 2014 IEEE Conference on Computer Vision and Pattern Recognition, Columbus, OH, USA, 23–28 June 2014; pp. 1701–1708.
19. Javorsky, E.; Tegmark, M.; Helfand, I. Lethal autonomous weapons. BMJ 2019, 364, l1171.
20. Brenneke, M. Lethal Autonomous Weapon Systems and Their Compatibility with International Humanitarian Law: A Primer on the Debate. In Yearbook of International Humanitarian Law,

Volume 21 (2018); Gill, T.D., Geiß, R., Krieger, H., Paulussen, C., Eds.; T.M.C. Asser Press: The Hague, The Netherlands, 2020; Volume 21, pp. 59–98. ISBN 9789462653429.

21. Ravenscroft, I. Philosophy of Mind: A Beginner's Guide; Oxford University Press: Oxford, UK, 2005.
22. Sagiroglu, D.S.; Sinanc, D. Big data: A review. In Proceedings of the 2013 International Conference on Collaboration Technologies and Systems , San Diego, CA, USA, 20–24 May 2013; pp. 42–47.
23. Marr, B. How Much Data Do We Create Every Day? The Mind-Blowing Stats Everyone Should Read. 2021. Available online: https://bernardmarr.com/how-much-data-do-we-create-every-day-the-mind-blowing-stats-everyone-should-read/ (accessed on 30 September 2022).
24. Nadkarni, P.M.; Ohno-Machado, L.; Chapman, W.W. Natural language processing: An introduction. J. Am. Med. Inform. Assoc. 2011, 18, 544–551.
25. Mahesh, B. Machine Learning Algorithms—A Review. Int. J. Sci. Res. 2018, 9, 381–386.
26. Hamet, P.; Tremblay, J. Artificial intelligence in medicine. Metabolism 2017, 69, S36–S40.
27. Kulkarni, S.; Seneviratne, N.; Baig, M.S.; Khan, A.H.A. Artificial Intelligence in Medicine: Where Are We Now? Acad. Radiol. 2020, 27, 62–70.
28. Wang, R.; Pan, W.; Jin, L.; Li, Y.; Geng, Y.; Gao, C.; Chen, G.; Wang, H.; Ma, D.; Liao, S. Artificial intelligence in reproductive medicine. Reproduction 2019, 158, R139–R154.
29. Singh, A.; Thakur, N.; Sharma, A. A review of supervised machine learning algorithms. In Proceedings of the 2016 3rd International Conference on Computing for Sustainable Global Development , New Delhi, India, 16–18 March 2016; pp. 1310–1315.
30. VerMilyea, M.; Hall, J.M.M.; Diakiw, S.M.; Johnston, A.; Nguyen, T.; Perugini, D.; Miller, A.; Picou, A.; Murphy, A.P.; Perugini, M. Development of an artificial intelligence-based assessment model for prediction of embryo viability using static images captured by optical light microscopy during IVF. Hum. Reprod. 2020, 35, 770–784.
31. Kragh, M.F.; Karstoft, H. Embryo selection with artificial intelligence: How to evaluate and compare methods? J. Assist. Reprod. Genet. 2021, 38, 1675–1689.
32. Chen, F.; Chen, Y.; Mai, Q. Multi-Omics Analysis and Machine Learning Prediction Model for Pregnancy Outcomes After Intracytoplasmic Sperm Injection–in vitro Fertilization. Front. Public Health 2022, 10, 924539.
33. Gentleman, R.; Carey, V.J. Unsupervised Machine Learning. In Bioconductor Case Studies; Springer: New York, NY, USA, 2008; pp. 137–157. ISBN 9780387772394.

34. Milewska, A.; Jankowska, D.; Citko, D.; Wiesak, T.; Acacio, B.; Milewski, R. The Use of Principal Component Analysis and Logistic Regression in Prediction of Infertility Treatment Outcome. Stud. Logic. Gramm. Rhetor. 2014, 39, 7–23.
35. LeCun, Y.; Bengio, Y.; Hinton, G. Deep learning. Nature 2015, 521, 436–444.
36. Zhao, M.; Xu, M.; Li, H.; Alqawasmeh, O.; Chung, J.P.W.; Li, T.C.; Lee, T.; Tang, P.M.; Chan, D.Y.L. Application of convolutional neural network on early human embryo segmentation during in vitro fertilization. J. Cell. Mol. Med. 2021, 25, 2633–2644.
37. Huang, T.T.; Kosasa, T.; Walker, B.; Arnett, C.; Huang, C.T.; Yin, C.; Harun, Y.; Ahn, H.J.; Ohta, A. Deep learning neural network analysis of human blastocyst expansion from time-lapse image files. Reprod. Biomed. Online 2021, 42, 1075–1085.
38. Jayakumaran, J.; Patel, S.D.; Gangrade, B.K.; Narasimhulu, D.M.; Pandian, S.R.; Silva, C. Robotic-assisted laparoscopy in reproductive surgery: A contemporary review. J. Robot. Surg. 2017, 11, 97–109.
39. Moon, A.S.; Garofalo, J.; Koirala, P.; Vu, M.-L.T.; Chuang, L. Robotic Surgery in Gynecology. Surg. Clin. North Am. 2020, 100, 445–460.
40. Parekattil, S.J.; Gudeloglu, A. Robotic assisted andrological surgery. Asian J. Androl. 2012, 15, 67–74.