Journal of Surgery
Gkrozou F, et al. J Surg 9: 11011
www.doi.org/10.29011/2575-9760.011011
www.gavinpublishers.com

Review Article

AI and Fertility Service: Present and Future Reality?

F. Gkrozou*, C. Skentou, N. Koutalia, D. Lentzaris , A. Katrachouras, A. Vatopoulou

Department of Obstetrics and Gynaecology, University Hospital of Ioannina, Greece

***Corresponding author:** Fani Gkrozou, Department of Obstetrics and Gynaecology, University Hospital of Ioannina, Stavrou Niarchou Street, Ioannina, 45101, Greece

Citation: Gkrozou F, Skentou C, Koutalia N, Lentzaris D, Katrachouras A, et al. (2024) AI and Fertility Service: Present and Future Reality?. J Surg 9: 11011 DOI: 10.29011/2575-9760.11011

Received Date: 06 March 2024; **Accepted Date:** 11 March 2024; **Published Date:** 13 March 2024

Abstract

Artificial Intelligence (AI) has evolved rapidly the last few years and has passed from experiments to implementation period even in medicine. Progress in neural networks and theories, the accessibility of large datasets and advances in computing power have assist to new achievements in present AI applications. With the help of Machine Learning (ML), computers can discover models from large and puzzling dataset automatically and as result can predict outcomes with high accuracy. It looks like AI can play a crucial role in healthcare and improve the performance of Assisted Reproductive Technology (ART). At the current situation, a variety of challenges are creating questions about AI. It is obvious though, that it will direct the different fields of medicine in further development and improvement. This review is presenting the existing use of automation at some aspects of ART and also improvements that can be produced through that approach.

Keywords: Artificial Intelligence, Machine Learning, Computing Science, Assisted Reproductive Technology

Introduction

Women between 20-44 years of age will face Infertility issues between 8-12% worldwide [1,2]. Around nine million babies have been born through Assisted Reproductive Technology (ART). Evidence of its safety and efficiency. However, live birth rates in the UK or US have been only marginally improved over the last decade, thus there is space for improvement in reproductive medicine [3,4]. In our days, everything is going digital and it is estimated that once automation will be widely implemented at ART, efficiency and consistency will be improved. Automation allows tasks that usually are performed by humans to be implemented by a computerised system [5]. It is mainly In robotic systems and microfluidics. Artificial Intelligence (AI) on the other hand can provide support automatically, by incorporating memory through learning and can be trained to perform actions without human interaction. Classification of AI though can be tricky because of vagueness of the term; however, it can be broadly divided into three types based on its capability to perform different things: narrow, general, and strong AI [6]. At the moment we have achieved only narrow AI, the lowest level of AI [7]. By the term AI machine learning (ML) and natural language processing (NLP) are included. The systems can learn from input data or understand human language, without being programmed specifically to do that. At present, there has been a transaction from traditional machine learning approaches (e.g., logistic regression, random forest) to more robust deep learning algorithms, such as artificial neural networks (ANN), convolutional neural networks (CNN), and more recently transformer neural network (TNN) [7]. Deep learning is based on the analysis of larger data sets with an increasingly diminished need for human involvement and interpretation [8]. It is possible that AI will be probable revolutionising ART success rates into different key steps, since we are using larger data set.

In the early 1990s, the web was built using static information, with no way for users to change data. In Assisted Reproductive Technology (ART), data were collected by using paper-based methodologies; or the phone to communicate with patients, letters to patients and also communicates its content with newspapers or TV. In the late 1990s, Web 2.0 involved a switch into a more interactive and dynamic experience through server-side processing forms, data- bases, and social media. Web 2.0 was less about the information and more about the interaction. Fertility clinics started to use electronic medical records and swapping communication to other type of media like LinkedIn, Instagram, Facebook, Twitter and TikTok. The complexity of data gathered increased by using more digitization found in electronic witnessing, digital and continuous quality control, genetic testing, and time-lapse systems. Even we are at the time of big data, it is still difficult to find effective and consistent algorithms, able for to make decisions by themselves. Artificial intelligence (AI) seemed perfectly suited to resolve the challenges brought on by Big Data. The increased number of publications in the past couple of years demonstrates the promising capabilities of AI to bring more consistency and efficacy to ART [9].

Web 3.0 is the next generation of internet technology that relies on the use of AI to process data and create a personalized user experience, improving peer-to-peer technologies, virtual reality, internet of things (IoT). All this data can be opened and decentralized. As result, all users will be the owners of their data. Appointments with experts can take place virtually, the same as many parts of fertility treatment. Based on the fact that larger the information available, more metadata are that are being generated and made publicly available, Web 3.0 technologies (Machine Learning [ML], AI, IoT, natural language processing) will allow a new system to be developed based on the combination of that information. This information retrieval accessibility would represent an important advantage for the development of better personalized healthcare technologies, including matching patients to treatment plans and predicting fertility success rates [9]. This review is presenting the existing use of automation at some aspects of ART and also improvements that can be produced through that approach.

Implentation of AI at Health System

There are significant challenges, when someone is trying to introduce an AI system into a clinical in vitro fertilization (IVF) laboratory workflow. If an ART clinic is still using paper charts, or there is no possibility to capture and store any digital image of patient's embryos, the implementation of AI will take longer. In addition, data management solutions to augment patient demographics, clinical and laboratory key performance indicators (KPIs), and other relevant data streams (ultrasound images and preimplantation genetic testing results, competency assessments) into a single dashboard are lacking. Most studies on predicting pregnancy outcomes after ART techniques, deal with the lack of prospective data. Images of blastocysts before biopsy and cryopreservation are stored the most. The culture conditions of the laboratory, technical competency of the operator [10,11], embryo quality, and/or expansion post-thaw are not analyzed in models that use clinical pregnancy as an end point, despite being dependent on them. An additional issue can be the fact of diversity between parameters used in different clinics. Some clinics can capture blastocysts images at 110 hours, but some others just before freezing, depending on embryos development speed. This is the reason why is necessary to set an exact time for the images to be captured or to create an AI system that doesn't need this variability and is based also on data from other clinics.

Soon, AI will access multiple sources of data to reveal patterns in diagnosis, treatment, and results. Big data will offer the possibility at AI systems to predict patient's risk and develop more personalised treatments. These systems potential will allow the prediction of pregnancy complications. It will also be more suitable at anticipating complications during pregnancy, perhaps identifying patients at high risk better than currently feasible. Artificial intelligence will also reduce ‘‘time to pregnancy’’ and improve efficiency, which is the time it takes to perform certain tasks or reduce embryo waste. The most powerful use of AI is to enhance hu- man capabilities, minimize variability, improve precision, and speed, and not to replace them. The impact of AI will be most visible using natural language processing and ML. AI can cover different areas, like clinicians, patients, administration. Using these systems, patient engagement in their care will be enhanced and streamlined. In every day clinic practice is necessary to discover before implenattion of AI, if it is worthy. What can be the benefits in process of embryos selection for example, rather than the traditional approach. It will also be necessary to purchase a new software system and make a notable investment, which is not sure if it is valuable or not. AI needs training and to do that, realistic datasets are necessary, that reflect the existed diversity and decrease the risk of bias. Taking that into consideration, more embryos should be included and not only these that have been selected for transfer. AI systems apart from training need validation on independent datasets. AI implementation is depending on how fast ART clinics will involve digital transportation and standardization. Once this is practice, AI systems will be self- evolved through learning, revalidation and use of new data. Recently, the US Food and Drug Administration has expedited the approval of medical devices and therapies (39 as of July 2019) that use partially and/or fully independent AI-based systems [12].

AI will improve outcome, by allowing less mistakes, being more efficient and more important without emotional factors. The main disadvantage of AI is the fact that human Is replaced by a machine, and possible some decisions made will be accompanied by lack of empathy. However, evidence show that human won't be replaced, but supported to be more efficient and productive. Personal data associated with digital technologies, is a big concern and need to be addressed appropriately, especially once cloud service is in use.

AI - Quality Control and Assurance in the IVF labarotory

At the environment of IVF laboratories, the majority of the procedures has been made mainly manually. AI systems are aiming to decrease the burden and the subjectivity of in the labaroty. These systems will provide a more standardised model, independent on the technician or environment where it takes place and can interfere with the embryo. The application of IoT (Internet of things), like actuators, gadgets, appliances, or machines, that are programmed for certain applications provides the IVF laboratories the opportunity of better monitoring and operating their facilities [13]. The IoT devices are most of the time of low-cost, low-power electronics connected wirelessly to gather data or act on events in real-time. These environmental sensors, actuators, networks or software can be deployed for real-time monitoring of room temperature, humidity, volatile organic compounds, door open count, and so forth. A more advanced, experimental form of IoT is a something different called smart dust. Smart dust are nodes of multiple microelectromechanical systems, no more than a few millimetres wide, that can detect changes in light, position, acceleration, stress, pressure, humidity, sound, and vibration. These disposable sensors transmit in formation wirelessly with autonomous power to a central computer or a cloud where data are compiled, analyzed through algorithms, and-if required-can instruct other devices to respond.

The IoT devices are frequently connected to cloud-based applications to collect, store, retrieve, and analyse data [14]. At the moment, particular instruments at the laboratories are collecting high quality control data and upload this information at cloud-based infrastructure. These data contribute with having quality control parameters with a more subjective way and may soon offer the opportunity to be integrated with electronic health records and relate measured parameters to clinical outcomes. At a ART laboratory, is important to have a quality management system to assess staff competency. Once data collection is automated, embryologists' performance will be tested, trends will be predicted, such as deterioration of implementation. As far as embryos concern, these systems will help to check the quality of embryos and other markers of developmental stages, and as result changes can be proved and done for optimal results [15]. We anticipate that AI systems will complete automatically these quality assurance processes, provide systemic, early detection of adverse outcomes, and identify clinically relevant patterns in pregnancy outcomes. Two abstracts of 2019 presented at the American Society for Reproductive Medicine were the first to spot the importance of the use of AI to monitor embryologists performing intracytoplasmic sperm injection in a clinical setting. The extremely low coefficient of variation between the manual and AI-based quality assurance assessment methods demonstrate the high accuracy of the automated AI system [14].

Embryo Culture Systems

The implementation of advanced microscopy, robotics, microfluidics, computer science, automation, AI, and digitalization of manual processes open up new horizons at embryo culture systems. Robotic and microfluidic platforms can perform visual tracking of a single sperm, immobilization of sperm, aspiration of sperm with picolitres volume, and insertion of that sperm into an oocyte. Fertilization of mouse embryos and continuous culture on a single platform, as well as automated vitrification systems, hint at the promise of fully integrated robotic and automated work-flows in human IVF laboratory [16-20]. Literature has shown that culture conditions for embryo culture will be improved if AI will be based on factors like temperature, pH, patients' demographics. In the future embryo culture media may include therapeutic strategies, treating each embryo with their own media formulations composed of optimized energy sources, antioxidants, or growth factors [21,22].

Data Management

Once medical records are digitalised, patients' data sets can act as 'big data' within ART. A combination of AI with big data, presents a powerful and promising tool for data analysis that reduces the need for manual processing. Potential new predictive outcomes and markers for fertility will be identified [9]. When storage takes place on a central cloud database improves safety of information stored and also connectivity between medical centres [21]. Electronic witnessing systems and radio frequency identification (RFID) allows the automated patient identification. The widely used RI-witnessTM system (Research Instrument, CooperSurgical, Denmark) favors the passage from manual barcode identification, which involve at least two embryologists to confirm sample labelling, to automated RFID-based labelling. This decreases IVF workflow time, improves accuracy, and reduces risk of manual error including gamete mismatch [23]. However, errors are still possible because of the number of steps necessary when moving gametes/embryos between dishes; a recent advancement promises a unique AI embryo witnessing system utilizing CNN to track and successfully (100%) assign patient specific key to their fresh embryos, thereby allowing traceability at every micro-movement, alongside eliminating mismatch between embryos of different origin [24]. It must be noted, however, that this algorithm was trained with fresh cleavage and blastocyst stage embryos, therefore, not yet applicable for use with frozen embryos. Moreover, the AI algorithm may require further systemic evaluation prior to routine clinical use.

Patient Treatment Pathway

Integration of AI in the very first steps of ART has allowed for a personalised medicine approach, especially in diagnosis and decision-making process of patient stimulation protocol and dosing, as well as predictive modelling for success treatment. For example, an algorithm designed to predict live birth rates from patient Anti-MüLlerian Hormone (AMH) levels saw high predictive ability with low error rates [25,26]. Similarly, the PIVET algorithm, aimed to personalise recombinant follicle-stimulating hormone (rFSH) dosing using input patient data such as BMI, age, and antral-follicle counts (AFC) [27]. Furthermore, an individualised rFSH dosing algorithm based on women's AMH and body weight (Rekovelle®, Ferring Pharmaceuticals Ltd, UK) has been recently shown to reduce risk of Ovarian Hypestimulation Syndrome (OHSS) [28]. Such clinical application of prediction outcomes throughout the entirety of IVF has already been used and made commercially available through digital platforms such as Univfy® (Univfy Inc, USA). Similarly, many fertility units are developing patient-focused mobile applications, as result to produce clinically relevant 'big data' through the integration of intelligent algorithms. Their adaption will take time, as it happens with all innovative techniques. We need to be aware that the large range of data is a result of the training of an AI algorithm.

Oocyte Selection

Oocyte selection is not included at the everyday clinical routine at an IVF centre. It is difficult to get the information about the quality or maturity of oocytes. IN addition, by selecting them only depending on morphological characteristics, potentially could reduce the number of oocytes available for use. Image-trained CNN deep learning algorithms such as AIR-O (Artificial Intelligence Ranking system for Oocytes, IVF 2.0 Ltd., UK) [29], VIOLET (Future Fertility, Canada) promises to outperform skilled embryologists in accurately predicting fertilization and blastocyst development rate [30]. An AI system able to predict oocyte developmental potential will improve cases of social freezing and managing patient expectations or oocyte allocation strategies during egg-donation cycles. Potentially, it will also determine the effect of different stimulation protocols on oocyte quality. Even of it want be immediately a tool of de-selection of oocytes, due to the limited starting number of oocytes, improvement and incorporation of intelligent oocyte selection tools might play a role in generating and using of synthetic oocytes [31].

Semen Analysis and Preparation

Male factor contributes to 50% of infertility cases, 80% of which are due to sperm motility [32]. This is why robust semen analysis ad preparation form is necessary for diagnosis and management of infertility. There is a computer-assisted sperm analysis systema (CASA), but recently an automated version of the same system CASAnova has been developed. It looks promising and accurate n classify alteration in sperm motility [33]. Scientists have also tried to perform semen analysis preparation for treatment automatically, by using microfluidics, an emerging technology in biomedicine that employs the use of minute volumes of solvents manipulated on a chamber or chip [34]. In addition, microfluidic chips give the opportunity to allow synthesis of mechanical barriers, which have been suggested to better imitate natural barriers of female reproductive tract, reassuring that only normal in shape and gradually mobile sperm are isolated [35]. A microfluidic chamber will potentially give the opportunity of a non-invasive, highly-precise, and rapid means of performing semen preparation. In the same time, the risk of DNA damage will be reduced [36]. A relevant example is the FERTILE (Zymot) device (DxNow Inc., Gaithersburg, MD, USA). This single-use filtered chip, with inlet and outlet chambers, connected by a microfluidic channel helps to improve the selection of sperm with better motility and DNA Fragmentation Index [36]. With further integration of AI this partial automation, is possible to pass to full automation since a remodelling could optimise fluid flow and displacement further personalising the process. A close example is the AI and robotics-powered microscopy system, the Mojo©-AISA (Mojo, Sweden), which promises to perform rapid analysis of raw semen samples within ten minutes, compared to the usual 30 min by trained andrologists. The system agrees with values of 2010 World Health Organization (WHO) semen analysis values. It is a way to make automated and standardised semen analysis, which is restricted by the different observers [29]. However, further clinical training of the CNN-based AI algorithm will be necessary to decreases the high false positive prediction rates, mainly when there is low samples' concentration.

Endometrial Evaluation for Personalised Embryo Transfer

Molecular techniques have allowed detailed study of endometrial receptivity [37-40] resulting in a genomic diagnostic tool, Endometrial Receptivity Array (ERA)[41], and as result more personalised embryo transfer (pET). The ERA is based on the endometrial gene expression analysis, which, integrated with AI and its main goal Is to increase accuracy and reproducibility when compared with conventional histological analysis of endometrium [42]. Although ERA continues to be used clinically, there is conflicting evidence on its clinical benefit [43-48] and more prospective multicentral studies are necessary .

Preimplantation Genetic Testing and Metabolomics

Pre- implantation genetic testing (PGT) is used widely in many IVF clinics, despite the conflicting evidence of the effectiveness on improving ART success rates [49-51]. This growing demand for PGT has led to the development of AI integrated platforms such as PGTai^{SM} (CooperSurgical, Denmark). It is a predictor algorithm that increases sensitivity, efficiency, and objectivity of PGT-aneuploidy (PGT-A) sequencing data analysis by reducing human involvement in the process. Interestingly, to avoid the breach of PGT-A altogether, a new AI algorithm has been developed, ERICA® (Embryo Ranking Intelligent Classification Algorithm). This is an image based system, that detects the embryo ploidy and also predicts the success rates independently of the developmental stage. ERICA® has been shown to be superior in its ability to predict blastocyst ploidy status and selection of embryos with best clinical outcome with a 92.5% success rate, when compared with trained embryologists [52]. Additionally, this dynamic ERICA® algorithm has recently been tested for its ability to be personalised according to individual clinic protocols and procedures [53] and a positive correlation has also been shown between lower ERICA® grades and chances of early miscarriage, independent of patient age [53]. However, further training of the algorithm is necessary with diverse data seta.A different less invasive technique to PGT-A (NIPGT) is able to test with accuracy the ploidy status by using cell-free DNA in culture system, with remarkable harmony to routine invasive trophectoderm biopsy [54]. In the same time, a non-invasive metabolomic method has been used to develop a predictive algorithm based on 60 potential biomarkers of embryo aneuploidy, found through spent culture media analysis. The algorithm showed a 97.5% accuracy rate in selecting aneuploid over euploid embryos [55]. This approach of using AI for non-invasive embryo selection has been commercialised by the Overture© Metabolomics (Overture Life, USA). Additionally, Raman spectroscopy–based metabolic profiling combined with AI for ploidy prediction has also been demonstrated [56]. It is obvious that there is a range for embryo selection based on its ploidy status; what remains to be seen, is if and how we could take advantage of the combination of NIPGT and metabolomics through AI algorithms and how this will improve clinical outcomes, thus making them undeniably cost effective.

Limitations and Clinical Feasibility

Implementation of any novel technology is challenging. Despite the efforts to automate the steps of ART, there has been relatively small penetration into the clinic due to practical restrictions, ethical concerns, and importantly lack of further research and clinical trials. This review is emphasized on a prominent change in ART, about the more frequent use of a combination of self-acting and self-determined deep learning algorithms with higher computational ability. This will decrease human bias, even there is always a possibility of algorithmic bias. Every type of supervised learning is biased and potentially can interfere with the result of this process. A possible solution is the self-supervised learning approach, as this includes the adverse networks (AANNs)s, where in the same time another AI system is made to evaluate and surpass the original one.An example of AANNs successfully tested in the field of reproductive medicine was presented by Kanakasabapathy et. al., where they subjected an AANNs to evaluate embryos, sperm, and blood cells using a range of images from different image qualities [57]. Even the results of this study need to be evaluated, this is an interesting proposal about the use of AI systems in IVF. In a clinical setting, the safety and outcome of utilising a predictive algorithm based on what cannot be fully understood by a healthcare practitioner can be both questionable, thereby regular assessment of system's performance is necessary [58]. Nowadays, AI is still an assisting tool, rather than a replacement, for embryologists and clinicians, and must only be implemented through well- designed researched processes. Moreover, a combination of an expert human, a machine, and a well-designed process is highly likely to outperform either machine or human, alone [59]; such combined approach may avoid the possibility of not being able to control the clinical decision-making going against the native human nature of an experienced embryologist.

One more flow limitation in practice is the effect on cost-effectiveness. For example, the semi- automated Gavi® cryopreservation system is much more costly compared to manual cryopreservation. This is reflected in the poor clinical use of the system, where, despite this novel technique being available since 2013, live birth rates were only recorded by 2017 in Europe [60]. Usability and integrability of many of these automated approaches are also limited in certain cases, such as the Gavi® system. This system operates with its own only consumables rather than existing consumables, further limiting its accessibility while also increasing its cost. Similarly, microfluidic approaches, can play an important role in semen analysis and preparation, but there are less viable in high-capacity laboratories, because of the fact that large volume of raw semen examination needs multiple chips. It is difficult to determine the safety and efficacy of AI systems, because of the lack of robust clinical evaluation through Randomised Control Trials (RCT). Further research is necessary. Data insufficiency, variability in data sets, and bias within individual studies, such as the long time between the conception of the idea of an RCT and the publication of results can be the reason of lack of quality in evidence [58].

Again, bias greatly limits transferability of study approaches between groups due to inter-clinic variation including laboratory conditions and heterogeneous data points such as different input and output measures [61]. Data insufficiency, particularly prospective data, don't allow the use of large and data sets in many of these studies. These issues reduces reliability and reproducibility of AI, which is essential prior to generalised clinical use [61]. There is no specific number about the size of data sets, so synthetic data has been suggested as a possible approach to the above limits, with concerns though [62]. As with many initial advancements and especially within IVF, ethical regulations must be addressed. With the high processing power of big data brought about using general processing units (GPUs) in AI, it is important to have

Health Insurance Portability and Accountability Act (HIPAA)–compliant patient data protection software in place and perhaps the development and implementation of AI-driven defence mechanisms [62]. Furthermore, user transparency and responsible disclosure systems must also be in place prior to clinical use of AI systems [58].

Future of ART

As we enter the era of Web 3.0, more and more new technologies are implemented in medical sciences, based on the integration of computer and biomedical sciences. The areas under study reviewed here together with future new areas of interest from other fields such a robotics and telesurgery [63] may change ART. Mixed reality (MR), is a combination of virtual reality (VR) and augmented reality (AR). It can be the answer to fully automate consultations with patients, something that is absolutely necessary especially at the era of global pandemics. Operative procedures such as embryo transfer may also be performed with mixed reality, the main benefit of which removes physical limitations of consultants to one clinic [64]. Synergy between microfluidics [65], AI, and robotics may indeed achieve a fully automated, intelligent, single-step device for the entirety IVF treatment pathway. This idea of 'IVF in a box' has been drafted by NaturaLife (Overture Life, USA), which currently offers three limited features including cryopreservation of oocytes and embryos and non-invasive testing of embryos.

Conclusion

In conclusion, it looks like the automation of ART will be soon a reality. Its role is not to replace the embryologists or practitioners involved, but to provide support and improvement. As result the role of embryologists will be developed differently, so from performing repetitive mechanical tasks to precise logical decision-making. Indeed, it would be interesting to see, if, clinical embryologists of present will be transformed to research embryologists in near future. AI in ART will help to standardise procedures, increase efficacy and accessibility. It is necessary though to think about the gap between research and clinical implementation of innovative technologies, before being able to generalised its use in ART.

Reference

1. Kumar N, Singh AK (2015) Trends of male factor infertility, an important cause of infertility: A review of literature. J Hum Reprod Sci 8: 191-196.
2. Vander Borght M, Wyns C (2018) Fertility and infertility: Definition and epidemiology. Clin Biochem 62: 2-10.
3. HFEA. Fertility treatment 2018: trends and figures. 2020.
4. CDC. 2018 Assisted reproductive technology fertility clinic success rates report. In: Prevention CfDCa, editor 2020.
5. Gandhi S, Mosleh W, Shen J, Chow C-M (2018) Automation, machine learning, and artificial intelligence in echocardiography: A brave new world. Echocardiography 35: 1402-1418.
6. Grace K, Salvatier J, Dafoe A, Zhang B, Evans O When Will AI Exceed Human Performance? Evidence from AI Experts.
7. Wang R, Pan W, Jin L, Li Y, Geng Y, Gao C, et al. (2019) Artificial intelligence in reproductive medicine. Reproduction 158: 139-154.
8. Dosovitskiy A, Beyer L, Kolesnikov A, Weissenborn D, Zhai X, Unterthiner T, et al. AN IMAGE IS WORTH 16X16 WORDS: TRANSFORMERS FOR IMAGE RECOGNITION AT SCALE].
9. Curchoe CL, Malmsten J, Bormann C, Shafiee H, Flores-Saiffe Farias A, et al. (2020) Predictive modeling in reproductive medicine: Where will the future of artificial intelligence research take us? Fertil Steril 114: 934-940.
10. Cirillo F, Patrizio P, Baccini M, Morenghi E, Ronchetti C, et al. (2020) The human factor: does the operator performing the embryo transfer significantly impact the cycle outcome? Hum Reprod 35: 275-282.
11. Franco JGJ, Petersen CG, Mauri AL, Vagnini LD, Renzi A, et al. (2017) Key performance indicators score (KPIs-score) based on clinical and laboratorial parameters can establish benchmarks for internal quality control in an ART program. JBRA Assist Reprod 21: 61-66.
12. Topol EJ (2019) High-performance medicine: the convergence of human and artificial intelligence. Nat Med 25: 44-56.
13. View of A Web of IOT Sensors to Automate Quality Control in an IVF Embryology Lab 2023.
14. Palmer GA, Kratka C, Szvetecz S, Fiser G, Fiser S, et al. (2019) Comparison of 36 assisted reproduction laboratories monitoring environmental conditions and instrument parameters using the same quality-control application 2019.
15. Hammond ER, Morbeck DE (2019) Tracking quality: can embryology key performance indicators be used to identify clinically relevant shifts in pregnancy rate? Hum Reprod 34: 37-43.
16. Lu Z, Zhang X, Leung C, Esfandiari N, Casper RF, et al. (2011) Robotic ICSI (intracytoplasmic sperm injection). IEEE Trans Biomed Eng 58: 2102-2108.
17. Jensen AK, Kristensen SG, MacKlon KT, Jeppesen J V, Fedder J, et al. (2015) Outcomes of transplantations of cryopreserved ovarian tissue to 41 women in Denmark. Hum Reprod 30: 2838-2845.
18. Park J, Jung S-H, Kim Y-H, Kim B, Lee S-K, et al. (2005) Design and fabrication of an integrated cell processor for single embryo cell manipulation. Lab Chip 5: 91-96.
19. Lai D, Ding J, Smith GW, Smith GD, Takayama S (2015) Slow and steady cell shrinkage reduces osmotic stress in bovine and murine oocyte and zygote vitrification. Hum Reprod 30: 37-45.
20. Roy TK, Brandi S, Tappe NM, Bradley CK, Vom E, et al. (2014) Embryo vitrification using a novel semi-automated closed system yields in vitro outcomes equivalent to the manual Cryotop method. Hum Reprod 29: 2431-2438.
21. Swain JE, Smith GD (2011) Advances in embryo culture platforms: novel approaches to improve preimplantation embryo development through modifications of the microenvironment. Hum Reprod Update 17: 541-557.

22. Smith GD, Swain JE, Bormann CL (2011) Microfluidics for gametes, embryos, and embryonic stem cells. Semin Reprod Med 29: 5-14.

23. Gupta S, Fauzdar A, Singh VJ, Srivastava A, Sharma K, et al. (2020) A Preliminary Experience of Integration of an Electronic Witness System, its Validation, Efficacy on Lab Performance, and Staff Satisfaction Assessment in a Busy Indian in vitro Fertilization Laboratory. J Hum Reprod Sci 13: 333-339.

24. Bormann CL, Kanakasabapathy MK, Thirumalaraju P, Gupta R, Pooniwala R, et al. (2020) Performance of a deep learning based neural network in the selection of human blastocysts for implantation. Elife 2020.

25. Nelson SM, Fleming R, Gaudoin M, Choi B, Santo-Domingo K, et al. (2015) Antimüllerian hormone levels and antral follicle count as prognostic indicators in a personalized prediction model of live birth. Fertil Steril 104: 325-332.

26. Nelson SM, Klein BM, Arce J-C (2015) Comparison of antimüllerian hormone levels and antral follicle count as predictor of ovarian response to controlled ovarian stimulation in good-prognosis patients at individual fertility clinics in two multicenter trials. Fertil Steril 103: 923-930.

27. Yovich JL, Alsbjerg B, Conceicao JL, Hinchliffe PM, Keane KN (2016) PIVET rFSH dosing algorithms for individualized controlled ovarian stimulation enables optimized pregnancy productivity rates and avoidance of ovarian hyperstimulation syndrome. Drug Des Devel Ther 10: 2561-2573.

28. Ishikawa M, Nakata T, Yaginuma Y, Nishiwaki K, Goishi K, et al. (1993) Expression of superoxide dismutase (SOD) in adenomyosis. Am J Obstet Gynecol 169: 730-734.

29. Abdullah KAL, Atazhanova T, Chavez-Badiola A, Shivhare SB (2023) Automation in ART: Paving the Way for the Future of Infertility Treatment. Reprod Sci 30: 1006-1016.

30. Barnes J, Brendel M, Gao VR, Rajendran S, Kim J, et al. (2023) A non-invasive artificial intelligence approach for the prediction of human blastocyst ploidy: a retrospective model development and validation study. Lancet Digit Heal 5: 28-40.

31. Hendriks S, Dancet EAF, Van Pelt AMM, Hamer G, Repping S (2015) Artificial gametes: a systematic review of biological progress towards clinical application. Hum Reprod Update 21: 285-296.

32. Katz DJ, Teloken P, Shoshany O (2017) Male infertility - The other side of the equation. Aust Fam Physician 46: 641-646.

33. Goodson SG, White S, Stevans AM, Bhat S, Kao C-Y, et al. (2017) CASAnova: a multiclass support vector machine model for the classification of human sperm motility patterns. Biol Reprod 97: 698-708.

34. Nikshad A, Aghlmandi A, Safaralizadeh R, Aghebati-Maleki L, Warkiani ME, et al. (2021) Advances of microfluidic technology in reproductive biology. Life Sci 265: 118767.

35. Jafek A, Feng H, Brady H, Petersen K, Chaharlang M, et al. (2020) An automated instrument for intrauterine insemination sperm preparation. Sci Rep 10: 21385.

36. Quinn MM, Jalalian L, Ribeiro S, Ona K, Demirci U, et al. (2018) Microfluidic sorting selects sperm for clinical use with reduced DNA damage compared to density gradient centrifugation with swim-up in split semen samples. Hum Reprod 33: 1388-1393.

37. Gómez E, Ruíz-Alonso M, Miravet J, Simón C (2015) Human Endometrial Transcriptomics: Implications for Embryonic Implantation. Cold Spring Harb Perspect Med 5: a022996.

38. Díaz-Gimeno P, Ruíz-Alonso M, Blesa D, Simón C (2014) Transcriptomics of the human endometrium. Int J Dev Biol 58: 127-137.

39. Evans GE, Martínez-Conejero JA, Phillipson GTM, Simón C, McNoe LA, et al. (2012) Gene and protein expression signature of endometrial glandular and stromal compartments during the window of implantation. Fertil Steril 97: 1362-1365.

40. Enciso M, Carrascosa JP, Sarasa J, Martínez-Ortiz PA, Munné S, et al. (2018) Development of a new comprehensive and reliable endometrial receptivity map (ER Map/ER Grade) based on RT-qPCR gene expression analysis. Hum Reprod 33: 220-228.

41. Díaz-Gimeno P, Horcajadas JA, Martínez-Conejero JA, Esteban FJ, Alamá P, et al. (2011) A genomic diagnostic tool for human endometrial receptivity based on the transcriptomic signature. Fertil Steril 95: 50-60.

42. Díaz-Gimeno P, Ruiz-Alonso M, Blesa D, Bosch N, Martínez-Conejero JA, et al. (2013) The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity. Fertil Steril 99: 508-517.

43. Hashimoto T, Koizumi M, Doshida M, Toya M, Sagara E, et al. (2017) Efficacy of the endometrial receptivity array for repeated implantation failure in Japan: A retrospective, two-centers study. Reprod Med Biol 16: 290-296.

44. Mahajan N (2015) Endometrial receptivity array: Clinical application. J Hum Reprod Sci 8: 121-129.

45. Ruiz-Alonso M, Blesa D, Díaz-Gimeno P, Gómez E, Fernández-Sánchez M, et al. (2013) The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure. Fertil Steril 100: 818-824.

46. Ben Rafael Z (2021) Endometrial Receptivity Analysis (ERA) test: an unproven technology. Hum Reprod open 2021.

47. Riestenberg C, Kroener L, Quinn M, Ching K, Ambartsumyan G (2021) Routine endometrial receptivity array in first embryo transfer cycles does not improve live birth rate. Fertil Steril 115: 1001-1006.

48. Simón C, Gomez C, Ruiz M, Mol BW, Valbuena D (2021) Response to: Comments on the methodology of an endometrial receptivity array trial. Vol. 42, Reproductive biomedicine online. Netherlands 284.

49. Lee M, Lofgren KT, Thomas A, Lanes A, Goldman R, et al. (2021) The cost-effectiveness of preimplantation genetic testing for aneuploidy in the United States: an analysis of cost and birth outcomes from 158,665 in vitro fertilization cycles. Am J Obstet Gynecol 225: 55.e1-55.e17.

50. Rosenwaks Z, Handyside AH, Fiorentino F, Gleicher N, Paulson RJ, et al. (2018) The pros and cons of preimplantation genetic testing for aneuploidy: clinical and laboratory perspectives. Fertility and sterility. United States 2018: 353-361.

51. Theobald R, SenGupta S, Harper J (2020) The status of preimplantation genetic testing in the UK and USA. Hum Reprod 35: 986-998.

52. Chavez-Badiola A, Flores-Saiffe-Farías A, Mendizabal-Ruiz G, Drakeley AJ, Cohen J (2020) Embryo Ranking Intelligent Classification Algorithm (ERICA): artificial intelligence clinical assistant predicting embryo ploidy and implantation. Reprod Biomed Online 41: 585-593.
53. Chavez-Badiola A, Farias AF-S, Mendizabal-Ruiz G, Griffin D, Valencia-Murillo R, et al. (2021) O-235 ERICA (Embryo Ranking Intelligent Classification Assistant) AI predicts miscarriage in poorly ranked embryos from one static, non-invasive embryo image assessment. Hum Reprod 2021.
54. Rubio C, Navarro-Sánchez L, García-Pascual CM, Ocali O, Cimadomo D, et al. (2020) Multicenter prospective study of concordance between embryonic cell-free DNA and trophectoderm biopsies from 1301 human blastocysts. Am J Obstet Gynecol 2020.
55. Zhou J, Xu H, Liang C, Zhang L, Hao Z, et al. (2015) A Comparative Study of Distinct Ocular Symptoms After Performing Laparoscopic Surgical Tasks Using a Three-Dimensional Surgical Imaging System and a Conventional Two-Dimensional Surgical Imaging System. J Endourol 29: 816-820.
56. Liang B, Gao Y, Xu J, Song Y, Xuan L, et al. (2019) Raman profiling of embryo culture medium to identify aneuploid and euploid embryos. Fertil Steril 111: 753-762.
57. Kanakasabapathy MK, Thirumalaraju P, Kandula H, Doshi F, Sivakumar AD, et al. (2021) Adaptive adversarial neural networks for the analysis of lossy and domain-shifted datasets of medical images. Nat Biomed Eng 5: 571-585.
58. Curchoe CL, Flores-Saiffe Farias A, Mendizabal-Ruiz G, Chavez-Badiola A (2020) Evaluating predictive models in reproductive medicine. Fertil Steril 114: 921-926.
59. Cabitza F, Campagner A, Sconfienza LM (2021) Studying human-AI collaboration protocols: the case of the Kasparov's law in radiological double reading. Heal Inf Sci Syst 9: 8.
60. Dal Canto M, Moutier C, Brambillasca F, Guglielmo MC, Bartolacci A, et al. (2019) The first report of pregnancies following blastocyst automated vitrification in Europe. J Gynecol Obstet Hum Reprod 48: 537-540.
61. Hickman CFL, Alshubbar H, Chambost J, Jacques C, Pena C-A, et al. (2020) Data sharing: using blockchain and decentralized data technologies to unlock the potential of artificial intelligence: What can assisted reproduction learn from other areas of medicine? Fertil Steril 114: 927-933.
62. Chen RJ, Lu MY, Chen TY, Williamson DFK, Mahmood F (2021) Synthetic data in machine learning for medicine and healthcare. Nat Biomed Eng 5: 493-497.
63. Taylan E, Oktay KH (2017) Robotics in reproduction, fertility preservation, and ovarian transplantation. Robot Surg 4: 19-24.
64. Fida B, Cutolo F, di Franco G, Ferrari M, Ferrari V (2018) Augmented reality in open surgery. Updates Surg 70: 389-400.
65. Le Gac S, Nordhoff V (2017) Microfluidics for mammalian embryo culture and selection: where do we stand now? Mol Hum Reprod 23: 213-226.