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Artificial Intelligence and Infertility

Aricha Suriya, Sunil Kumar, Dipneet Kaur

*M.Sc. Student Department of Clinical Embryology & Reproductive Genetics,
Rayat Bahra University, Mohali, Kharar Punjab 140301
Research Scientist, Origin LIFE, Health Care Solution & Research Centre LLP,
SCO-181, First Floor Sector-38-C, D Chandigarh-160036*

ABSTRACT:

The inability to conceive after a year of unprotected sexual activity is known as infertility and affects both men and women worldwide. Although ovarian dysfunction, tubal difficulties, endometriosis, and spermatogenesis disorders are known causes, 85% of cases are still undiagnosed. It is advised to evaluate and treat both couples at the same time. Ovulation-stimulating medications such as letrozole and clomiphene citrate, intrauterine insemination (IUI), and in vitro fertilization (IVF) are used as treatments. Artificial intelligence (AI) is transforming the of infertility by enhancing diagnosis, tracking the development of folliculogenesis, evaluating endometrial receptivity, and choosing viable embryos. AI improves patient outcomes, lab productivity, and treatment regimens, but there are still issues with data quality and ethical considerations. Personalized care and increased success rates are promised by AI integration in reproductive medicine.

***Keywords**: Letrozole, clomiphene citrate treatment, spermatogenesis, ovarian dysfunction, in vitro fertilization, intrauterine insemination, artificial intelligence.*

INTRODUCTION:

Advances in artificial intelligence (AI) applications in reproductive medicine are increasingly based on the availability of medical information. Decision making for infertile patients based on the analysis of such data appears as an optimal clinical approach.[1] To bridge the gap between research and clinical practice, it is important to focus on the integration of artificial intelligence and artificial insemination technology (ART). Artificial intelligence and machine learning models allow fertility specialists to determine the best treatment for individual cases of infertility, leading to significant advances in ART. This approach not only increases successful pregnancies and reduces the financial burden on patients, but also reduces the unnecessary use of medical resources, thus reducing healthcare costs.[2],[3]

Artificial intelligence is currently used in several key areas of ART, including sperm selection and prediction, evaluation of embryo and egg quality, and the development of ART prediction models. These applications aim to improve implantation speed and treatment efficiency by defining good non-invasive markers and integrating artificial intelligence components into image analysis [4]. This integration improves detection efficiency, reduces errors and minimizes manual classification workload by automating the classification of sperm, embryos and oocytes. However, the main limitations of current AI research are the quantity and quality of data, which affects model performance and generalizability. Many studies are based on small; single-source, retrospective datasets, and large-scale randomized controlled trials lack algorithm validation and optimization of resource use. Despite these challenges, there have been significant technological advances in reproductive medicine, such as preimplantation genetic screening, endometrial receptivity testing, late embryo tracking, egg vitrification, and laser hatching. [5] Artificial intelligence is poised to bring a revolutionary paradigm shift in ART success rates based on the advanced computer tools and vast amount of knowledge available today.[6] Artificial intelligence has been used in reproductive medicine since the 1990s, but its potential to improve ART outcomes is only now being fully realized. [7]

The integration of AI into IVF and reproductive medicine promises to improve various aspects of ART, from sperm selection and ovarian reserve to embryo selection and new IVF treatments. Artificial intelligence also offers important opportunities for data storage, processing, quality control and minimizing human errors in embryology laboratories. In addition, artificial intelligence can help match egg and sperm donors to recipients using, for example, facial symmetry.[8],[9] Currently, AI is used in IVF in three main forms: natural language processing (NLP), machine learning and robotics. NLP extracts relevant information from extensive data, machine learning creates decision models from training data, and robotics automates various processes.[10] AI is a powerful tool to supplement the knowledge of doctors and embryologists, but it is unlikely that it will completely replace human decision-making. Instead, AI aims to improve clinical practice by providing robust evidence-based algorithms to guide ART, ultimately benefiting reproductive medicine professionals and patients.[11],[12]

OBJECTIVE:

To investigate the potential of Artificial Intelligence in enhancing the effectiveness, efficiency, and accessibility of Artificial Reproductive Technology.

LITERATURE REVIEW:

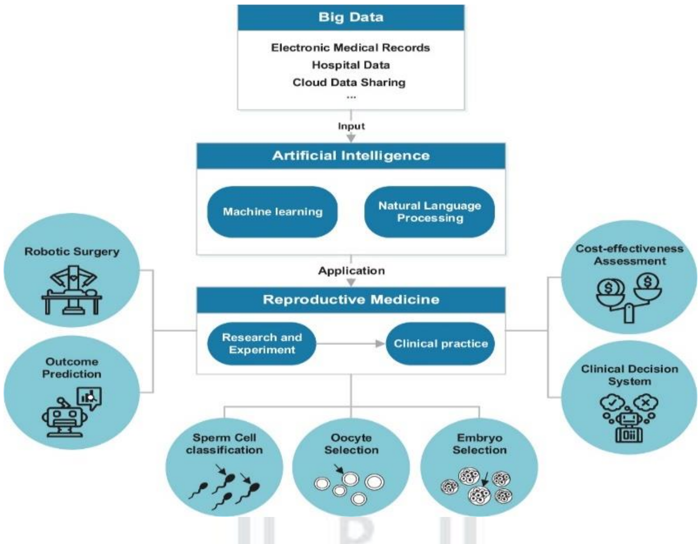
ARTIFICIAL INTELLIGENCE IN THE PRESENT ART PRACTICE

Artificial intelligence has been used into ART using algorithms that forecast the quality of gametes and embryos based on specific data sets. Because the evaluation is currently completed manually by embryologists, bias and human error are possible. Any evaluation that involves people is subjective and based on the operator's individual conclusions and experience.[13] Furthermore, these evaluations just take into account morphology. Oocyte quality is the most significant predictor of pregnancy. Currently, there is no non-invasive technique to identify aneuploidy in oocytes since aneuploid oocytes resemble normal oocytes in most morphological aspects. Oocytes are currently evaluated according to their cytoplasmic inclusions, polar body, perivitelline space, homo/heterogeneity, and maturity.[14]
It might be feasible to create an algorithm to assess an oocyte's developmental competence through the use of artificial intelligence. The currently accessible techniques, such as time-lapse, metabolomics, or transcriptomics, can be tailored for this use. Spindle abnormalities in the oocytes can be non-invasively detected using polarized microscopy.[15]
Even if an egg has extruded its polar body, it has poor developmental competence if it remains in the telophase I stage. Similar to this, time-lapse bright-field microscopy in conjunction with particle image velocimetry allows for an image study of the oocyte's transition from the germinal vesicle to the metaphase II stage, yielding important details about the oocytes' capacity for development.[16]

Like oocytes, embryos are frequently ranked according to their morphology by embryologists. When the goal is to transfer a single embryo in order to prevent multiple pregnancies, choosing the most viable embryo from the cohort is essential. Extending the culture of the nonviable embryos to blastocysts is a practical method of eliminating them. This is the initial method of selecting a viable embryo for transfer. This does not imply that all blastocysts are euploid and have the same capacity for implantation. [17] Based on their expansion, trophectoderm, and inner cell mass, they are ranked sequentially. Grading of blastocysts has shown to be extremely subjective and vulnerable to vary between and among observers. Even the correct evaluation time chosen for evaluation will affect evaluation because the blastocyst is a dynamic entity. Automating the scoring system using computer graphics and precise algorithm can eliminate variability between and within servers. Computer imaging with time-lapse tracking combined with a modern machine learning algorithm can also take into account morpho kinetic events when determining embryo viability.[18]

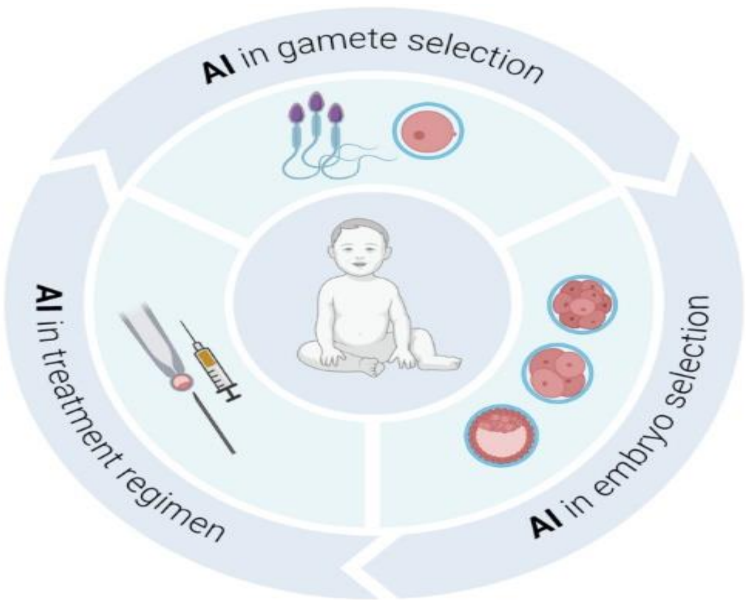
Artificial intelligence was recently applied to PGT-A (Cooper Surgical PGTai) in the form of a machine learning approach, to eliminate operator subjectivity, for reporting and interpreting next-generation sequencing results. Artificial intelligence-based programs like computer-assisted semen analysis (CASA) exist to [19] sperm morphology and kinetics subjectively. However, it is riddled with some problems like its inability to distinguish between debris and dead sperm.6 It has also been stated that the CASA program perhaps needs further improvement before it can be confidently put to mainstream clinical use. [20]

Robotic surgery has been used in reproductive surgeries like tubal reanastomosis, myomectomy, endometriosis surgery, and ovarian transplantation. Presently, robotic surgery poses certain problems like cost, bulky equipment, lack of tactile feedback, and locking of patient position, scientists around the world are working to improve the precision and ergonomics of existing systems.[21],[22]



The role of artificial intelligence in Reproductive Medicine. Big data include electronic medical records (EMRs) and other data. EMRs can capture data from various ways and the data is analyzed using AI such as machine learning and natural language processing (NLP). AI has been used in the many aspects of reproduction, from research and experiment to clinical practice. These schematic reviews the seven main applications of AI in reproductive medicine.

APPLICATIONS OF ARTIFICIAL INTELLIGENCE IN REPRODUCTIVE MEDIC



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Evaluation and selection of oocytes

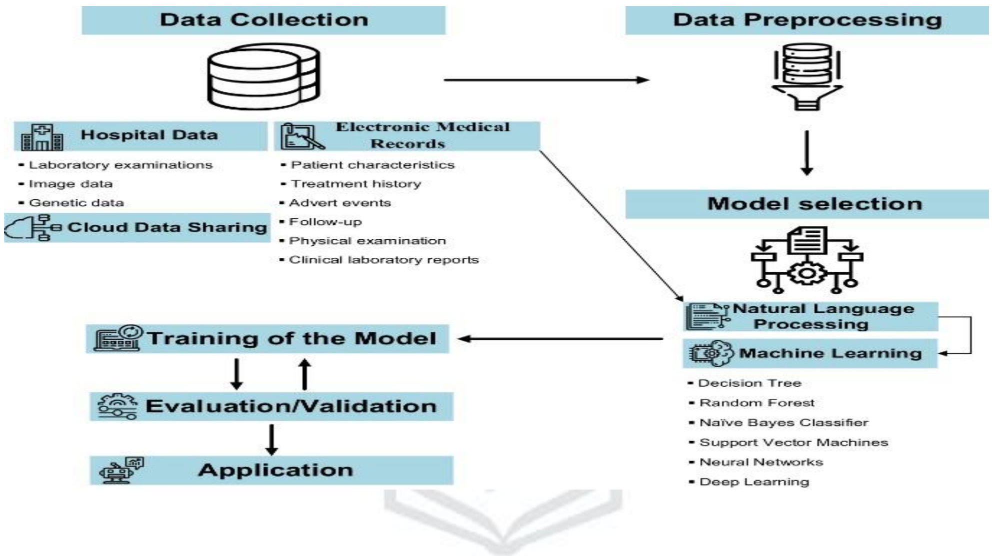
The general success of reproduction, either spontaneously or after ART, is very dependent on the quality of the oocyte. Currently, the pregnancy rate per oocyte retrieved is estimated at 4.5% [44]. A better understanding of oocyte developmental competence will help guide the development of new strategies to improve IVF success and the development of new biomarkers to predict oocyte quality and select the optimal oocyte for IVF [44]. Various strategies have been proposed to evaluate and select the oocyte with the best developmental potential, but with different limitations, such as the possibility that an oocyte or embryo that appears normal may still hide its aneuploidy [45] further research to obtain accurate standards and methods. Thus, the use of artificial intelligence methods for selection of eggs in IVF programs can bring new opportunities. [38] tracked mouse cells during their in vitro maturation from the germinal vesicle (GV) to metaphase II and captured images for time-lapse analysis. They calculated a profile of cytoplasmic movement speeds by analysing the images with the PIV method, after which the data were analysed with a feedforward artificial neural network to identify competent or incompetent oocytes with 91.03% accuracy. In addition, some researchers have used non-invasive approaches to predict the developmental potential of human oocytes. [46] reported that viscoelastic properties of human zygotes, measured non-destructively within hours of fertilization, could reliably predict viability and blastocyst formation with >90% accuracy, 95% specificity, and 75% sensitivity. In addition, the researchers examined RNA-seq data and found that non-viable embryos had significantly different transcriptomes, particularly in the expression of genes important for oocyte maturation. An ideal method for oocyte selection would be non-invasive, inexpensive, and could be incorporated into the embryology workflow with minimal impact [47]. There is still room for improvement in ART, for example for more reliable prediction of oocyte quality and more accurate quantification of germ cell developmental competence. In addition, the application of artificial intelligence methods to the evaluation of human oocytes, which use delay [48] or evaluate gene expression through transcriptomics or genomics [49] can have a good development perspective. and additional benefit to ART.

Sperm selection and semen analysis

Sperm analysis is the first step in the evaluation of infertile couples. Sperm morphology reflects various abnormalities in human sperm samples. The ability to recognize the morphology of sperm cells and observe changes in sperm motility is extremely important in evaluating the potential fertility of a sample. Currently, computer-assisted sperm analysis (CASA) systems are used for human or animal research and routine analysis. The system can report motility rate and kinematic parameters and identify subpopulations of sperm cells [50] Due to the lack of objectivity and the complexity of manual evaluation of sperm morphology, as well as the high variability between laboratories, automated methods based on image analysis should be developed to obtain more objective and accurate results. In addition, up to a third of male factors of infertility are idiopathic [51] meaning that current sperm evaluation methods fail to identify multiple causes of infertility. Goodson et al. (2011) developed an automated and quantitative method to classify mouse sperm motility patterns based on 2043 sperm tracks obtained from the CASA system. In 2017 (Goodson et al. 2017), the same method was applied to human sperm. This model has an overall accuracy of 89.92% and retrospectively used data from 425 human spermatozoa to develop this model and diagnose chromosomal abnormalities. Height, total testicular volume, follicle-stimulating hormone, luteinizing hormone, total testosterone and ejaculate volume were used, and the prediction of chromosomal abnormalities reached more than 95% accuracy. Data mining methods can also be used to predict seed quality based on information from lifestyle and environmental characteristics. Girela et al. (2013) developed two special neural networks using questionnaires to predict human sperm concentration and motility based on environmental factors and lifestyle. Although this method appeared to be an alternative to more expensive laboratory tests, it can be a useful tool for early diagnosis. Sahoo and Kumar (2014) used five artificial intelligence techniques and eight feature selection methods to predict human fertility to find suitable features that can more accurately predict male fertility. Feature selection can improve performance, visualize information needed for model selection, reduce dimensions, and effectively remove noise. Finally, feature selection methods increased the accuracy of AI techniques, and support vector machine and particle swarm optimization increased the accuracy and AUC index.

Embryo selection

Accurate assessment of embryo viability is crucial to optimize IVF treatment.[52] Embryologists usually select embryos by non-invasive visual inspection based on morphology and development at the blastocyst stage. This assessment is subjective and varies according to the experience and knowledge of the embryologist, which can affect the success rate [53] In addition, transferring multiple embryos to increase success increases the risk of complications such as preeclampsia and maternal haemorrhage [54] Artificial intelligence and automatic morphological analysis offer promising alternatives. Santos Filho et al. (2012) used SVM classifiers to classify blastocyst images, which achieved good characterization of morphological features. Singh et al. (2015) improved TE region detection with the Retinex algorithm, achieving an accuracy of 87.8%. Saeedi et al. (2017) developed an automatic method for joint segmentation of TE and ICM, reporting accuracies of 86.6% and 91.3%, respectively. These methods provide a more objective and quantitative evaluation of embryos. Continuous developmental information is provided by Age-Lapse (TL) systems for monitoring the dynamic embryo.



The workflow of artificial intelligence in Reproductive Medicine. This flowchart provides a brief overview of the AI workflow. The first step is the collection of data. The data includes electronic medical records (EMRs), hospital data and cloud data sharing. The second step is data pre-processing. The third step is the selection of the appropriate model. The data is analysed using artificial intelligence methods such as machine learning and natural language processing (NLP). Then the training dataset is used to train the model. The final steps include the evaluation and validation of the model.

iDAScore®- The Future of AI-based Embryo Evaluation
By Dr. Tine Qvistgaard Kajhoj.

IDAScore is a metric used to assess embryo viability and quality during in vitro fertilization (IVF). It stands for Intelligent Data Analysis Score and is derived from advanced algorithms that analyse various parameters of embryonic development, including morphology and morpho kinetics, to predict the probability of successful implantation and pregnancy. IDAScore typically incorporates information from time-lapse imaging and other non-invasive monitoring methods to provide a quantitative and objective assessment of embryonic potential. This score helps embryologists make more informed decisions about embryo transfer, which can improve IVF success.

IDAScore uses advanced data analysis and machine learning algorithms to assess embryo viability and quality.
Here is a step-by-step overview of the process:

1. **Data collection**: -

   Time-lapse imaging: embryos are continuously monitored and imaged at regular intervals using time lapse imaging system.

Morphological Assessment: The system records detailed images of embryos at various stages of development.

2. **Feature Extraction**: -

Morpho kinetics: Slow system captures key developmental milestones (eg cell division times, blastocyst).
Morphology: The system evaluates morphological characteristics such as cell shape, size, symmetry and the quality of the internal cell mass (ICM) and trophectoderm (TE).

3. **Algorithmic Analysis**: -
Machine Learning: The collected data is processed by machine learning algorithms trained on large datasets of primitive images and their results. These algorithms identify patterns and correlations associated with successful implantation and pregnancy. -
Scoring: Algorithms assign a score to each element based on the extracted features. The IDAScore reflects the probability that the embryo will lead to a successful pregnancy.
4. **Prognosis and Ranking: -**

Viability Prediction: IDAScore provides a predictive measure of each embryo's potential for successful implantation.
Grading: embryos are graded according to their score, which helps embryologists select the most viable embryos for transfer.

5. **Clinical Decision Making**: -

Objective Scoring: IDAScore provides objective, data-driven scoring that reduces the subjectivity inherent in manual scoring.
Informed Choices: Embryologists can use the score to make more informed decisions about which embryos to transfer, which can improve IVF success rates and reduce the risks associated with multiple embryo transfers. Integrating advanced image analysis, machine learning and extensive data on embryo development, IDAScore aims to improve the accuracy and consistency of embryo selection in IVF treatment.
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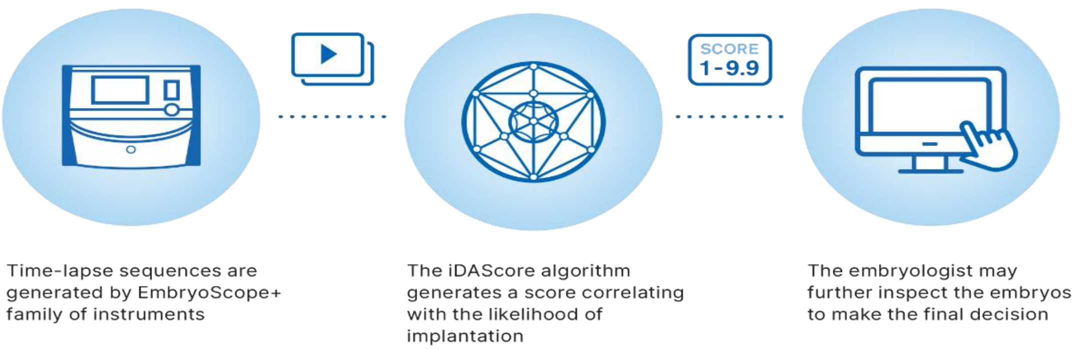

Image: vitrolife https://www.vitrolife.com/our-products/idascore-intelligent-data-analysis-for-embryo-evaluation/

The Prediction of IVF outcome

Today, many infertile couples try to conceive a child using the ART method [55]. However, due to low clinical pregnancy rates and high cycle costs many childless families are under enormous pressure. By creating a functional IVF prediction model combined with artificial intelligence, clinicians can tailor individual treatment for infertile couples and improve ART pregnancy outcomes. Several publications have described models to predict IVF outcomes [56],[57] where various methods of artificial intelligence were used with 59 accuracy [58] to 84.4% [59] Although the prediction accuracy is gradually improving, there are still various problems and the model cannot be well applied in clinical practice. Further research is needed. Hafiz et al. (2017), they used previous IVF/ICSI records to predict an outcome with an AUC greater than 80%. They found that the age of the woman, the number of developed embryos and the serum estradiol level on the day of human chorionic gonadotropin administration were optimal predictors. A limitation of their work was the number of IVF/ICSI records and missing values, which reduced the accuracy of the classifiers. Even a methodologically excellent model is limited by the quality and size of the input data on which it is trained. These difficulties need to be addressed in future studies.

Future of Artificial Intelligence in Artificial Reproduction Technology

Creating a viable embryo in the lab involves several critical steps: selecting the best sperm for fertilizing the oocytes, grading oocytes, culturing and grading embryos, grading blastocysts, and tracking the development from oocyte to blastocyst to assess an embryo's potential based on the time taken to reach each milestone. Various AI programs are already available to facilitate each step of embryo culture. This raises the question of whether skilled embryologists could be entirely replaced by AI. It seems plausible.

Reproductive Surgeries:
For a couple diagnosed with fibroids or endometriosis affecting fertility, minimally invasive robotic surgery can be offered to address the issue.

Hormone Analysis:
Many pathology labs are automated, enabling hormone profiles to be generated with the help of AI.

Ovarian Stimulation Protocol:
A 2018 literature review established a clear relationship between serum AMH levels and the ovary’s response to stimulation. Key criteria for determining a stimulation protocol include age, AMH, BMI, and previous response to stimulation (if applicable). Software could be developed using this nomogram, taking into account all relevant aspects of a woman’s ovarian status to recommend the most suitable protocol for ovarian stimulation.[60]

Evaluation of the Oocytes:
Assessing the quality of oocytes is crucial for the success of assisted reproductive technology (ART) cycles. Ideally, a method for determining oocyte quality would be affordable, non-invasive, and minimally disruptive. Morphological assessment alone is limited in accurately predicting oocyte potential.

By capturing images of oocytes from the germinal vesicle to the metaphase II stage using time-lapse imaging, it becomes possible to analyse their cytoplasmic movement velocity (CMV) profiles using particle image velocimetry. This method has shown promise in identifying the competency of mouse oocytes with an accuracy exceeding 91%. Additionally, research by Yanez et al. demonstrated that non-destructive measurement of the viscoelastic properties of zygotes in the hours following fertilization could predict blastocyst formation with over 90% precision. Furthermore, they found that transcriptomic evaluation of developing embryos could provide a reliable assessment of viability. Integrating these techniques collectively may aid in identifying the most promising oocyte within a cohort.[61]

Embryos have traditionally been cultured in static medium within Petri dishes, which do not mimic natural conditions. In vivo, embryos experience a dynamic environment with changing medium composition along the fallopian tube, and metabolites like ammonia are constantly removed. Meseguer et al. proposed a dynamic microfluidics system that continuously changes the culture medium surrounding the developing embryo. Coupled with time-lapse imaging, this system may offer an optimal culture environment for assessing embryo development and milestones.[62]

Current time-lapse programs utilize algorithms based on morpho kinetic parameters and embryo morphology to predict embryos with the lowest implantation potential.

In the realm of embryo freezing, automated devices are available to assist with embryo vitrification. These devices claim to reduce the labour and skill intensity of the process while also decreasing interoperate variance.[63]

Conclusion

The integration of AI into assisted reproductive technology (ART) laboratories presents immense potential across various stages, from hormone assessment to embryo vitrification. AI offers advantages such as automating tedious tasks with high reproducibility, reducing errors, maintaining records, and providing mechanical judgment. However, challenges include cost implications and ethical considerations regarding delegating decision-making to computers, as machines may lack the human touch and compassion.

This paper outlines current and proposed AI programs applicable to the IVF lab, foreseeing a future where these tools collectively optimize embryo selection and standardize pregnancy rates globally. As AI techniques evolve with more data and case studies, they are expected to self-learn and improve over time.

The rise of automation in ART raises concerns about potential job displacement among embryologists and the need for ethical guidelines to ensure a smooth transition. Questions arise regarding the role of embryologists in decision-making, the advantages of fully automated labs, and the extent to which humans or machines should have the final say.

Coexistence and collaboration between humans and machines are proposed, with a gradual allocation of responsibilities based on ethical considerations and evolving capabilities. The paper emphasizes the importance of shaping the role of embryologists within AI-integrated ART labs, considering the evolving landscape of technology and medicine.

In summary, the paper covers the basics of AI and machine learning, explores their applications in reproductive medicine, and discusses limitations, challenges, and future trends. Despite limitations, AI technologies have the potential to enhance pregnancy outcomes and patient care in infertility treatment, paving the way for more effective and accurate healthcare delivery.

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