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Artificial intelligence algorithms for optimizing assisted reproductive technology programs: A systematic review

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Abstract

Artificial intelligence (AI) has been experiencing rapid growth in recent years, and numerous applications are improving the single-step efficiency of the whole assisted reproductive technology (ART) procedure. In this review, we collected all the algorithms supplying ART and selected those supporting the clinical assistance to the procedure up to the successful attempt. Those with a clear role in improving ART performances were further selected. We found a questionnaire-based algorithm identifying patients at risk for endometriosis with early management and better fertility outcome. An algorithm can detect the values of simple gamete production (male) and reservoir (female) according to gradual scale allocation, and display themas normal or abnormal, spontaneousor stimulated gamete production. This can provide significant benefits for infertile couples undergoing diagnostic and therapeutic journeys. The calculators for the starting dose of gonadotropins and the trigger timing during controlled ovarian stimulation make clinical management more efficient. With the application of AI in ART, the ability to determine the optimal number of metaphase II oocytes required for blastocyst formation and number of oocytes needed for embryo production has been significantly improved. The calculation of the implantation rate as proposed in different calculators, using the ultrasound of endometrial vascularization or the age and euploidy of the embryo transferred, may provide further advancement in managing the ART procedure with more participation from the couples to increase the efficacy of the procedures. Finally, the calculator of presumptive success with an ART program based on couples or medical center profiling and efficiency is of tremendous comfort to couples. In conclusion, algorithms and machine learning development in human reproduction are growing daily with evident benefits. Infertility treatments by *in vitro* fertilization (IVF) are assisted by several algorithms that improve the efficiency of each procedure step, making IVF program's management more effortless.

Keywords: Assisted reproductive technology; Fertilization; Blastocysts development; Embryo implantation

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1. Introduction

Artificial intelligence (AI) in medical issues management can improve the accuracy, efficiency, and effectiveness of health-care delivery, leading to better patient outcomes and improved public health. AI leads to deep analysis of complex systems detection and to building up provisions to prospectively manage dynamic changes in our society. The future fertility outcomes are a key input to estimating future population size, depending on the social custom and economic safe of populations of different countries. Population size and age structure modifications might have dramatic economic, social, and geopolitical impacts in many countries. On the other hand, forecasting mortality, fertility, infertility treatments, migration, and population are the necessary prerequisite for the sustainable development of the human condition. Infertility, defined as a failure to achieve pregnancy after 1 year of regular unprotected sexual intercourse, affects 8.8% of US women aged 15 – 49 years[1] and is often associated with significant psychological distress[2].

The highest and lowest fertility rates in countries reported by World Bank in 2021[3] are shown in Table 1. In close association with that data, the infertility rates were reported differently in developed regions compared to non-developed ones. The prevalence rate of infertility has been reported to elevate from 3.5% to 16.7% in more developed nations and 6.9% to 9.3% in less-developed ones[4].

There has been an increase in the literate population using contraception and assisted fertilization techniques to generate a family plan. The birth of over 8 million babies through *in vitro* fertilization and embryo transfer (IVF-ET) programs in the world has been registered following the born of Luise Brown, Robert Edwards's first successful human application of this procedure[5]. An IVF program is divided into four separate phases, each responsible, at different percentages, for the final result: Controlled ovarian stimulation (COS) to obtain multiple oocytes[6,7], laboratory treatments for fertilization[8], embryo differentiation[9], and ET[10]. Key performance index (KPI) detects optimal single-step performance compared with good medical and laboratory standard procedures leading to optimizing chances of implantation and live birth[11,12]. The gold standard of the single steps of this procedure is now entering the era of being managed by AI rather than human controls. However, there have been mixed results, presented with some positive evidence and some ineffective applications. To optimize the results, periodic internal and external checks of these KPIs are essential. This has already been established as a standard by various registers in the world, and reports are sent for diagnosis of various parameters such as entry, age of the partners[13], type of therapeutic approach, supply of gametes, and accessory pathologies[14].

The improvement of assisted reproductive technologies (ART) through AI applications is crucial in the perspective of declines in fertility and slow population growth related to the increased trend of female educational attainment[4]. AI may be one of the most important solutions to counteract the global population decline observed in the last decades[15].

This review aims to focus on the already published AI algorithms and mathematical models that have been found to influence IVF efficiency, specifically embryo implantation, with data extracted from the evidence or convincing experimental promises. This review prioritizes the clinical algorithms rather than those applied in the laboratory because of their evident superiority with the help of the entire program.

Table 1. The highest and lowest fertility rates in countries reported by World Bank in 2021

Countries with the highest fertility rates (by births per woman)	Countries with the lowest fertility rates (by births per woman)
1. Niger – 6.8	1. South Korea – 0.9
2. Somalia – 6.0	2. Puerto Rico (US territory) – 1.0
3. Congo (Dem. Rep.) – 5.8 (tie)	3. Hong Kong (China SAR) – 1.1 (tie)
4. Mali – 5.8 (tie)	4. Malta – 1.1 (tie)
5. Chad – 5.6	5. Singapore – 1.1 (tie)
6. Angola – 5.4	6. Macau (China SAR) – 1.2 (tie)
7. Burundi – 5.3 (tie)	7. Ukraine – 1.2 (tie)
8. Nigeria – 5.3 (tie)	8. Spain – 1.2 (tie)
9. Gambia – 5.2	9. Bosnia and Herzegovina – 1.3 (tie)
10. Burkina Faso – 5.1	10. San Marino – 1.3 (tie)
	11. Moldova – 1.3 (tie)
	12. Italy – 1.3 (tie)
	13. Andorra – 1.3 (tie)
	14. Cyprus – 1.3 (tie)
	15. Luxembourg – 1.3 (tie)

2. Methods

We performed PubMed and Cochrane searches for English publications from January 2013 to March 2023 with keywords: "Assisted reproductive technology," "ART," "embryo implantation," "embryo nidation," "endometrial receptivity," "endometrial decidualization," "aneuploidy," "embryo loss," "implantation failure," "repeated implantation failure," "RIF," "microbiome," "early embryos miscarriage," "early abortion," "endometrial omics," "endometrial genetic assessment," "endometriosis," "endometritis," "uterine abnormalities and implantation failure," "uterine abnormalities and early miscarriage," "adenomyosis and embryo implantation," "thyroid," "thrombophilia," "immunology," "myomas," "polyps," "difficult embryo transfer," "ART management," "mathematical models," "embryology and algorithms," "good embryo transfer," and "artificial intelligence." Algorithms included all published diagnostic, timing, and therapeutic tools to optimize assisted fertilization program.

3. Results

We found 44 publications, with 15 papers including supporting diagnostic and/or predicting tools to upgrade the levels of medical assistance to the ART programs (Table 2). We excluded the others because they were ineffective in improving diagnostic penetrance, clinical compliance, and/or prediction capability[16]. The elaborations of how the AI tools assist in the particular management/diagnosis/treatment of ART-related areas are as follows:

3.1. Endometriosis

Endometriosis is a disease-causing pain and infertility[17], encountered in nearly 50% of infertile women. Medical efforts do not help treat endometriosis-caused infertility, for which the only options are surgery and/or ART[18]. Surgery enhances the chances of conceiving naturally during the 12–18 ensuing months, irrespective of the stage of the disease but does not improve ART results[18]. Therefore, ART is the primary option for women whose infertility is associated with endometriosis and/or over 35 years of age[19]. However, unfortunately, patients who had longer diagnostic delays for endometriosis had more pre-diagnosis endometriosis-related symptoms and higher pre-diagnosis health-care utilization and costs compared with patients diagnosed earlier after symptom onset, providing evidence in support of earlier diagnosis[20]. In other words, time to pregnancy is a crucial prognostic factor inversely related to the success of the treatments; thus, it is crucial to anticipate the diagnosis of this disease at present, occurring several years after the symptoms appear[6]. Recently a new validated algorithm was introduced as a screening for the diagnosis of endometriosis based on a

Table 2. Diagnostic and therapeutic algorithms useful in the diagnosis and treatment of infertile couples

Diagnosis/treatment	Algorithms	References
Endometriosis	Presumptive diagnosis by questionnaire	[21]
Sperm evaluation according to WHO criteria: WHO Semen Analysis 2021	Sperm evaluation by WHO criteria, 2021	[25]
An ovarian reservoir according to AMH	Classification of the ovarian reservoir according to AMH and age	[26,27]
Ovarian reservoir according AFC	Classification of ovarian reservoir according to the AFC	[44]
Starting dose gonadotropins	Gonadotropin starting dose calculator	[28]
Trigger time calculation: Day/hour	To develop an interpretable machine learning model for optimizing the day of trigger in terms of mature oocytes (MII), fertilized oocytes (2PNs), and usable blastocysts	[30]
Number of oocytes exposed to sperm during ART cycle	A prediction tool was developed to aid clinicians in determining the optimal number of oocytes to expose to sperm, reducing the number of unused embryos created, and immediately addressing current patient and clinician concerns.	[44]
ART calculator	Blastocyst presumptive calculation from recruited MII oocytes	[32]
Nomograms	Blastulation rate prediction in specific infertile groups selection	[9]
Endometrial receptivity score	Endometrial scoring for implantation prediction	[34]
Algorithm predicting implantation efficiency according to the effects of female age and anticipated blastocyst euploidy rates on cumulative implantation rates	Estimation of implantation of euploid and aneuploid embryos after transfer according to the age of the women and number of embryos transferred	[33]
Chance to have a baby	Presumptive successful IVF treatment stratified for the infertile couple's features	[33] [35] [36] [37]
The working group achieved consensus on a list of KPIs, PIs, and RIs useful for internal and external controls of ART treatments	KPIs, PIs, and RIs to ascertain good medical practice in ART	[12]

Abbreviations: KPIs: Key performance indicators; PIs: Performance indicators; RIs: Recommendation indicators; ART: Assisted reproductive technology; AMH: Anti mullerian hormone; AFC: Antral follicular count; MII: Metaphase II, 2PN: 2 pronuclear patient questionnaire with good prognostic value[21]. This screening can distinguish patients at risk of endometriosis early, with bigger treatment possibilities (Table 2).

The algorithm introduced by Chapron *et al.*[21] is known as well as the endometriosis fertility index (EFI)[22] and is used as a screening tool for the diagnosis of endometriosis in women with infertility. The algorithm introduced by Chapron *et al.* is known as the EFI and is used as a screening tool for the diagnosis of endometriosis in women with infertility[21]. The risk calculator is based on a patient questionnaire that includes several factors related to endometriosis, such as symptoms, clinical history, and imaging findings. The risk calculator questionnaire includes six questions related to age, duration of infertility, history of surgery for endometriosis, ovarian reserve, anatomical factors such as tubal patency and uterine anomalies, and the severity of endometriosis based on imaging findings. Each factor is assigned a score, and the total score is used to predict the likelihood of endometriosis and the chances of achieving a pregnancy. The risk calculator has been shown to have good predictive value. For example, the higher the score, the lower the chances of achieving a pregnancy and the greater the likelihood of endometriosis. However, it is important to note that the risk calculator is not a definitive diagnostic tool and should be used with other diagnostic methods, such as laparoscopy and histological analysis.

The added value of this presumptive diagnosis obtained with a simple but effective algorithm is obtaining an early diagnosis with the benefit of its surgical treatment or slowing down its potential evolution. To validate the benefits of adopting the algorithm, an initial population of 2527 patients was used to test its development. The population was divided into two groups, including 1,195 patients in the study group with histologically proven endometriosis, and 1332 patients in the control group who did not have any endometriotic lesions during surgery. However, the use of these algorithms is still too recent to further validate the advantages of their adoption[21].

It should be emphasized that patients with clinically diagnosed endometriosis reportedly experience a decrease in endometrial receptivity[23,24]. Although the exact mechanism by which endometriosis impairs endometrial receptivity is not fully understood, ongoing research is investigating changes in endometrial gene expression, sex hormone receptors, and cell adhesion molecules[24]. However, the role of specific gene expression mutation (HOXA 10) in the cyclical endometrial growth and differentiation may affect the steroid hormones' effects on the tissue for progesterone resistance[24].

3.2. Gamete production estimation

Gamete production and reservoir are prerequisites for couples' fertility and the efficiency of infertility treatments (Table 2).

3.3. Sperm

The gold standards for sperm counts and motility assessment are already established by continuous time-related adjustment according to the big data collection[25], and a simple algorithm is implemented to ease the diagnostic procedure (Table 2). More specifically, the user is required to enter details such as seminal volume, nemaspermic concentration, progressive motility, vitality, and morphology; then, for each of these parameters, the algorithm automatically checks whether any seminal alteration is present. According to the 2021 guidelines of the World Health Organization, the threshold values separating the normal range from abnormally low values are defined, for each parameter, to represent the fifth percentile in a sample of almost 3500 fertile men of different ages and from 12 different countries around the globe.

3.4. Oocytes

Oocyte reservoir was more recently divided as hypo-, poor, normal, and hyper-responders in terms of specific values of anti-mullerian hormone (AMH) and/or antral follicular count (AFC) for a potential response to the ovarian stimulation with gonadotropins[26,27]. A simple algorithm based on the collected data of large communities of fertile and infertile women eases the decision-making for ART (Table 2). Similarly to the previously described algorithm for seminal alteration, the user simply needs to specify the AMH blood level (in ng/mL) to implemental classification into one of five possible tiers, ranging from "very low" to "very high" level.

3.5. COS

COS is a medical procedure used to stimulate the ovaries to produce multiple eggs, typically for use in ART such as IVF. Monitoring the response to COS is essential to ensure optimal outcomes. Several algorithms have been developed to adequately monitor COS, including predicting the response to COS, optimizing treatment protocols, and personalizing treatment based on individual patient characteristics.

Machine learning is an approach to optimizing COS monitoring using the dynamics simulation of ovarian response to COS. Machine learning algorithms can be trained on large datasets of patient characteristics, including age, body mass index, hormonal levels, and other factors, to predict the likelihood of a successful response to COS. These algorithms can then be used to inform treatment decisions, such as selecting the appropriate dose of ovarian stimulation medication (Table 2). By adjusting treatment protocols based on these algorithms, clinicians can optimize outcomes while minimizing risks such as ovarian hyperstimulation syndrome (OHSS). For example, the follicle-stimulating hormone (FSH) dosing algorithm has been used to predict response to COS with progressive improvement using large datasets of patient characteristics.

Another approach that has been used to optimize COS treatment protocols is reinforcement learning. Reinforcement learning algorithms can learn to optimize treatment protocols by iteratively adjusting treatment parameters based on feedback from previous patients. For example, an algorithm could learn to adjust the dose and timing of stimulation medication to maximize the number of eggs retrieved while minimizing side effects.

Real-time monitoring algorithms can be used to develop personalized treatment plans that optimize outcomes while minimizing risks. For example, a deep learning algorithm could analyze ultrasound images of ovarian follicles to predict the number and quality of oocytes that will be retrieved. By integrating these predictions into treatment protocols, clinicians can optimize outcomes while minimizing risks.

These algorithms can optimize COS in ART, improving the efficiency and effectiveness of treatment while minimizing risks and improving patient outcomes[26,27] (Table 2).

3.6. Starting dose of gonadotropins

A recent development involves the creation of machine learning models that are interpretable and designed to optimize the selection of starting gonadotropin doses based on criteria such as mature oocytes (metaphase II [MII]), fertilized oocytes (2 pronuclear [2PN]), and viable blastocysts[28,29]. Fanton *et al.* have proposed a machine learning model for selecting the initial FSH that can deliver optimal laboratory results while minimizing the use of starting and total FSH[30]. Another machine learning model has been introduced by Correa *et al.* as a training and educational resource for new clinicians and as a means of quality control for experienced clinicians. This model is helpful in the adequate calibration of the personalization of the treatment to obtain the best number of oocytes and avoid OHSS[28] (Table 2).

3.7. Optimal day of the trigger

The model suggested by Fanton *et al.*[30] optimize the day of trigger for mature oocytes (MII), fertilized oocytes (2PNs), and usable blastocysts. This model can potentially improve outcomes for many IVF patients (Table 2). After providing input information about the total amount of follicles binned by size (<11 mm, 11–13 mm, 14–15 mm, 16–17 mm, 18–19 mm, and >19 mm) and the estradiol level on a given examination day, the number of MII oocytes is predicted through two different linear regression models corresponding to two distinct scenarios hypothesizing triggering the same day and triggering the day after, respectively. If the predicted number of MII oocytes "today versus tomorrow" shows a decreasing trend, triggering is recommended; otherwise, if the number of MII oocytes is expected to be higher if triggering the day after, it could be worth waiting one more day before updating the follicle count and the estradiol level and repeating the previous step. A third linear regression model can also be used to predict the estradiol level 1 day after. The trigger calculation to optimize trigger time and oocyte retrieval is a strong advantage in clinical practice.

3.8. The number of oocytes exposed to fertilization

The number of oocytes that should be exposed to fertilization during an ART cycle needs to be decided to minimize the number of unused embryos and optimize the probability of live birth. A tool for prediction was developed during a study on IVF cycles, which can assist clinicians in determining the most suitable number of oocytes to be exposed to sperm. This can help reduce the number of unused embryos generated and effectively address any existing concerns of both the patients and clinicians involved[31] (Table 2). The optimization of the number of oocytes exposed to sperm and the number of unused embryos represent a concrete improvement of the IVF procedure.

3.9. ART calculator

In IVF/intracytoplasmic sperm injection (ICSI), an ART calculator has been developed to estimate the minimum number of MII oocytes required for obtaining at least one euploid blastocytes for each patient, serving as a useful tool for counseling and planning treatments[31,32]. This prediction tool is highly beneficial for clinical and embryological daily practice. In addition, Jin *et al.* have created a nomogram to predict blastocyst formation rates based on the range of clinical characteristics in patients with different types of infertility, aiming to minimize the possibility of wasting embryos and accurately predict the likelihood of blastocyst formation[9]. The patients were categorized into three groups: tubal factor, polycystic ovary syndrome, and endometriosis, with each group further divided into a training set and a validation set. The nomogram was constructed using the training set, while the performance of the model was tested using discrimination and calibration on the validation set. The models showed satisfactory results, with acceptable calibration in each model.

The process of predicting embryo implantation in the human endometrium is complicated and involves multiple factors[23]. To address this challenge, various algorithms have been created to forecast the probability of successful embryo implantation[32]. A new definition of recurrent implantation failure (RIF) that accounts for the effects of female age and anticipated blastocyst euploidy rates on cumulative implantation rates was recently proposed, and a calculator has been developed and provided to estimate a 95% cumulative implantation probability by taking into account the blastocyst euploid rates from published data across different female age categories. The estimation was done under the assumption of the absence of any other factor affecting implantation. However, the assumption is not true, as this estimation is a great system to establish the focus areas of clinical research in the RIFs after euploid embryos transfer (Table 2).

3.10. Endometrial receptivity score

Numerous markers signify the readiness of the endometrium for successful implantation, and these become apparent during the implantation window. At present, transvaginal ultrasound color Doppler is a dependable method for displaying the rise in blood flow during the peri- and postovulatory phases and objectively evaluating these flows to anticipate endometrial receptivity[33-35]. Our view is that none of the individual parameters that indicate suitable endometrial conditions for embryo nidation can be utilized as a predictive score. However, the method to collect all the known parameters into a single score, with weighting of each parameter determined by a big database collection, may help promote a model for predicting implantation of total embryos (both euploid and aneuploid) in the endometrium.

3.11. Prediction of IVF program results

Several algorithms can be used to predict the success of IVF treatments. A study reported that in women who experience unexplained RIF after IVF/ICSI treatment, the cumulative incidence of live birth and mean time to pregnancy (through conception after IVF/ICSI or natural conception) over a follow-up period of up to 5.5 years was 49%. In addition, the calculated median time to pregnancy leading to a live birth was 9 months after the RIF diagnosis[33-38].

The authors conducted a population-based cohort study using data from the Society for ART (SART) Clinic Outcome Reporting System[14] to develop IVF prediction models. These models estimate the probability of cumulative live birth for individual patients at two different time points: Pre-treatment (before commencing the first complete IVF cycle) and post-treatment (before starting a second complete IVF cycle in cases where the first cycle was unsuccessful). The pretreatment prediction models provide estimates of the probability of achieving a live birth over a maximum of three complete cycles of IVF, whereas the post-treatment model predicts the probability over the second and third complete cycles. A complete cycle is defined as all ETs (both fresh and frozen) resulting from one round of ovarian stimulation, and the models take into account the first live birth episode, including both singletons and multiple births. Unlike previous IVF prediction models in the US, which focused solely on cumulative live birth rates and excluded cycles involving frozen embryos, these innovative models are clinically relevant and can assist clinicians and couples in planning IVF treatment at different stages of the process[33-39]. Other attempts at IVF estimation results are based on couples' profiling and medical center performances as shared with their national registers as disaggregate (Table 2).

3.12. Key performance indicators (KPIs), performance indicators (PIs), and recommendation indicators (RIs)

Through its own working group, the Italian Fertility Society and Reproductive Medicine (SIFES-MR) achieved consensus on a list of clinical and laboratory KPIs such as KPIs, PIs, and RIs useful for internal and external controls of ART treatments in IVF settings[12]. Each parameter was assigned a score, and the cumulative score resulted from the collection of a stratified database of that parameter from Italian clinical and laboratory ART programs. Algorithms identifying good medical practice and laboratory procedures will be built up when the database is consistent and the single-step prediction coherent (Table 2).

To further improve this practice for the collective benefit, non-aggregated data collection registers are increasingly accessible to the use of these algorithms to evaluate the individual's performance compared with classes of collectivity given by these databases whose reliability is a function of its size[36].

4. Discussion

Evidence suggests that female educational attainment is a cofactor of female infertility, although the exact mechanisms underlying this relationship are complex and multifactorial. One possible explanation is that women pursuing higher education levels may delay childbearing to focus on their careers or educational goals. As women age, their fertility declines, and delaying childbearing may increase the risk of infertility due to factors such as decreased ovarian reserve and increased risk of conditions such as endometriosis. Another potential explanation is that women with higher levels of education may be more likely to engage in behaviors that can contribute to infertility, such as smoking, excessive alcohol consumption, and exposure to environmental toxins.

On the contrary, education may impact access to healthcare and reproductive technologies. Women with higher levels of education may have greater knowledge of and access to fertility treatments such as IVF. In comparison, women with lower levels of education may face barriers to accessing these treatments, leading to a higher risk of infertility. Finally, socioeconomic factors such as income and access to healthcare may also play a role in the relationship between education and female infertility. Women with higher levels of education may have higher incomes and greater access to healthcare, which can improve their overall reproductive health and decrease the risk of infertility. While the relationship between female educational attainment and infertility is complex, it highlights the need for comprehensive reproductive health education and access to fertility treatments for all women, regardless of their educational background.

AI can potentially transform infertility diagnosis and treatment by enabling more accurate diagnoses, personalized treatment plans, and improved patient outcomes. There are several algorithms that can be used to predict the success of IVF treatments. Here are some of the most common ones:

i. Logistic regression: This algorithm is used to predict the probability of success or failure of IVF treatments based on patient and treatment characteristics. It uses a mathematical model to analyze data from previous IVF cycles and identify the factors that are most predictive of success or failure.
ii. Decision trees: This algorithm is used to analyze complex data sets and create decision trees that map out the most likely outcomes based on various factors. In IVF, decision trees can be used to predict the probability of success or failure based on patient age, ovarian reserve, embryo quality, and other factors.
iii. Neural networks: This algorithm is designed to simulate the function of the human brain and can be used to analyze large and complex data sets. In IVF, neural networks can be used to analyze patient data and identify patterns that are predictive of success or failure.
iv. Support vector machines (SVM): This algorithm is used to analyze and classify data based on complex patterns. In IVF, SVM can be used to predict the probability of success or failure based on patient characteristics and treatment data.
v. Random forest: This algorithm is used to analyze data sets with many variables and identify the most important factors that influence the outcome. In IVF, random forest can be used to predict the probability of success or failure based on patient and treatment characteristics.

These algorithms can be trained using large data sets of IVF treatment outcomes, patient characteristics, and treatment data. Once trained, they can be used to predict the probability of success or failure for a given patient based on their individual characteristics and treatment plan. These predictions can help doctors to personalize treatment plans and improve IVF success rates.

Increasing AI applications in the field of reproductive medicine to improve the treatment of infertility are already established. Some of the applications are elaborated as follows:

i. Oocyte ovarian reservoir estimation: This can help fertility specialists to make more accurate predictions about the number of oocytes that can be retrieved during the IVF cycle.
ii. Sperm analysis: AI can analyze and classify sperm morphology, motility, and concentration with greater accuracy and speed than manual methods, improving the diagnosis of male infertility.
iii. COS: It is done by predicting the optimal dose and duration of gonadotropin administration.
iv. Fertilization: AI can help embryologists to identify the best quality embryos by analyzing various morphological and kinetic parameters of the developing embryos.
v. Blastulization: AI can help to identify which embryos are more likely to develop into blastocysts, improving the success rates of IVF treatments.
vi. Implantation of human embryo: AI can assist fertility specialists in selecting the best clinical and embryological parameters to optimize the implantation rate.

In the present review, we analyzed the most promising applications to improve results and compliance with IVF procedures, leaving those without clear validation out of our focus[16].

IVF programs require a high degree of laboratory efficiency to optimize outcomes and ensure the safety of patients. Several algorithms have been developed and validated to improve the laboratory efficiency of IVF programs, including:

i. Time-lapse imaging algorithms: Time-lapse imaging algorithms use computer vision techniques to analyze time-lapse images of developing embryos. These algorithms can predict which embryos are most likely to develop successfully, allowing embryologists to prioritize these embryos for transfer and reducing the time required for manual embryo selection[39].

ii. Embryo scoring algorithms: Embryo scoring algorithms use machine learning techniques to predict the likelihood of successful embryo implantation based on a range of factors, such as morphological characteristics and developmental stage. These algorithms can prioritize embryos for transfer and reduce the time required for manual embryo selection[39,40].

iii. Fertilization prediction algorithms: Fertilization prediction algorithms use patient-specific data, such as age, hormonal levels, and sperm quality, to predict the likelihood of successful fertilization. These algorithms can optimize the timing of procedures and reduce the time required for manual monitoring and intervention[8].

iv. Quality control algorithms: Quality control algorithms use statistical techniques to monitor laboratory performance and ensure the safety and accuracy of procedures. These algorithms can detect anomalies and deviations from established protocols and alert laboratory staff to potential issues before they affect outcomes[12].

v. Cryopreservation algorithms: Cryopreservation algorithms use machine learning techniques to predict the likelihood of successful embryo or gamete cryopreservation based on a range of factors, such as age, hormonal levels, and clinical history. These algorithms can optimize the timing and methods of cryopreservation and reduce the time required for manual monitoring and intervention[41,42].

However, even if these algorithms could still improve the laboratory efficiency of IVF programs, reducing the time required for manual procedures, optimizing the use of resources, and improving outcomes for patients, they still do not exhibit evidence of an improvement in the procedure's efficiency. By integrating these algorithms into clinical practice, IVF programs could achieve higher success rates and provide safer and more effective treatment. But still, randomized and controlled trials are needed for full validations.

The use of AI in infertility treatment can improve the accuracy, efficiency, and success rates of reproductive medicine, leading to better patient outcomes and increased access to fertility care. We reported available tools and algorithms focused to personalize medical efforts.

Specific algorithms have the potential to improve the effectiveness and safety of COS by providing personalized treatment recommendations, optimizing treatment protocols, and predicting responses to treatment. However, these approaches are still in the early stages of development, and further research is needed to validate their effectiveness in clinical practice.

These new instruments are improving the experiences of both clinicians and patients, with a larger applicative in gamete, embryo selection, and egg/embryo storage. Nevertheless, the application of AI in the IVF laboratory to streamline patient care is a growing but not yet fully realized concept. This is why we still believe that, in clinical rather than laboratory, AI applications are more immediately useful in medical practice for ART. The question of accurately estimating the overall probability of a medical outcome resulting from two independent events still remains for clinicians. While it is possible to do so in certain cases, such diagnostic and prognostic decisions often require the consideration of multiple probabilities or steps. However, in cases where multiple independent events are involved, the misestimation of the overall probability of success (known as the conjunction fallacy) is likely to lead to diagnostic and prognostic errors[32].

That happens in the diagnosis and treatment of RIF where several factors are concurring to the failure, one independent from the other[43].

The diagnostic tool by questionnaire of Chapron *et al.*[21] is a real improvement of the clinical approach to this disease because it is able to shorten the first diagnosis and accelerate the possible treatment with an improved prognostic value for prospective fertility treatment results in those women (Table 2). The assessment of male[25] and female[26-29] gametes with specific automatic prognostic grading allocation according to the production and/or reservoir is a substantial help in the clinical management of the infertile couple without adding some new potential improvement in pregnancy outcome (Table 2). The starting dose of gonadotropins in the COS represents a great help in the same management, improving the clinical effort in that management[28,29], as well as the trigger timing calculation that avoids mistakes and delays or anticipation leading to reduced oocyte pick up (OPU) efficiency (Table 2). There is still discussion about the efficiency of picking up and fertilizing the maximal oocytes as possible for each aspiration or performing mild stimulation and partial fertilization of oocytes. Thus, the model for calculating the magic number to maximize results and reduce the number of oocytes to pick up remains to be established for efficiency contribution and the use of this algorithm, but it is useful to follow the concern of clinicians that refuse to collect as many embryos as possible in the perspective of better efficiency of this procedure[44] (Table 2). The ART calculator proposed by Esteves *et al.* is a great algorithm that gives both embryologists and clinicians more information for clinical choice orientation[27] (Table 2). The nomograms to predict blastocysts rate following cycles of IVF in patients with tubal factor infertility, polycystic ovary syndrome, or endometriosis is another useful algorithm helping the decision-making of the clinician, embryologist, and couples together to follow-up on the procedure[9] (Table 2).

The endometrial receptivity estimation based on the only parameter of ultrasound and vascularization of the endometrium in its own layers is not actually being the factor contributing to the endometrial receptivity more complex and determined by several independent parameters rather than this one. However, the establishment of each parameter with its own specific score in a database supporting an algorithm inclusive of all those factors is, from the methodological point of view, the right direction for future studies[34].

An algorithm was developed to predict implantation efficiency by taking into account the impact of both female age and anticipated blastocyst euploidy rates on cumulative implantation rates, as published in a hands-on tool, is very attractive. Moreover, despite its estimation of implantation for euploid and aneuploid embryos after transfer according to the age of the women and the number of embryos transferred did not consider the value of the extra embryo factors, this tool remains of great value for clinicians[33] (Table 2).

The prediction of personalized cumulative live birth following IVF as published by MacLernon *et al.*[37] and adopted by the Sars registry and American Society for Reproductive Medicine (ASRM)[38] (Table 2) is very helpful for all involved in the ART programs, from the couples to the medical doctors. The attempt of other algorithms proposed for the same finality, which include both the couple's profiling and the medical center's performances, is a great improvement in medical practice for the transparency by which the performances are released and for the "True" informed consent to undergo IVF program in one center instead of the other[36]. Public services rather than private companies should provide for that. Unfortunately, we assist in medical center's promotion by media with declared results that are not obtainable. This phenomenon leads to making money on the emotional fragility of these couples. These AI application models can reduce a doubly reprehensible practice on a deontological and human level. Couples seeking information should make it a habit to avoid centers that do not release their results as disaggregated and verifiable data to national registries in a transparent manner. The study of the Italian Group of the SIFES e MR (SocietàItaliana di Fertilità, Sterilità e MedicinadellaRiproduzione) focused on the Key Performance Indicators (KPI) useful for internal and external control of each procedural step of the ART programs may improve the quality of the entire procedure by generating algorithms establishing the gold standards procedures as well as their laboratory and clinicians' coherence[12]. Many other predictive tools are published day by day in the literature, such as the natural conception prediction application[45] or an AI model developed to predict gestational age more accurately than standard fetal biometry-based estimates which was achieved by utilizing both standard plane ultrasonography images and fly-to ultrasonography videos[46]. Moreover, the progress in performing studies and AI models are ongoing with an enthusiastic perspective for patient management.

5. Conclusion

After an impressive increase from 1960 to 2010, the world population is decreasing. The total fertility rate is in inverse relationship to the literate couples population being lower in the high alphabetization communities. The use of infertility treatments by IVF is now a worldwide phenomenon, with 2%–8% of newborns using this technique. The recent use of mathematical models and/or real-time monitoring algorithms designed to improve the diagnostic power of specific tests as well as the best management of the treatments is describing a new clinical era where the improvement of efficiency and the reduction of complications will be the most evident phenomenon.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

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