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TITLE: Ethical Issues of Artificial Intelligence & Assisted Reproductive Technologies

Author: Prof Rev Dr Raymond Zammit
ORCID: https://orcid.org/0000-0001-6352-3253
AFFILIATION: University of Malta, Malta
correspondence: ray.zammit@um.edu.mt

ABSTRACT

The downward trend in fertility rates has not surprisingly led to an increase in assisted reproduction techniques (ART), and assisted reproduction today is characterised by high-tech, high-end investment and international fertility companies, with the global fertility services market expected to grow beyond US$25 billion by 2026. Much has happened since the birth of the first test tube baby in 1978, including personalised ovarian stimulation, extended embryonic culture, intra cytoplasmic sperm injection (ICSI), pre-implantation genetic diagnosis, embryo selection (leading to elective single embryo transfer) and oocyte vitrification. Nevertheless, the success rate of IVF currently stands at around 30%, even though this depends heavily on a number of factors, such as age and changes in the physical and psychosocial environments. Many women, therefore, have to go through multiple rounds of IVF such that the process can be time-consuming, and challenges patients both financially and emotionally. Research is thus increasingly focused on how to improve treatments and outcomes, and rapid advancements in Artificial Intelligence look promising and are increasingly being utilised in fertility clinics around the world.

Keywords:

Reproductive technologies, ART, IVF, ICSI, AI, Artificial Intelligence, ethics, bioethics, infertility, ovarian stimulation, embryo, gamete, oocyte, selection, sperm, semen, donor gametes, inequalities, DNA

Introduction

ART currently presents a number of ethical issues, and these have been debated extensively. These mostly centre around (i) the value and meaning of the transmission of human life; (ii) the moral status of the human embryo, including the ethics of freezing or discarding human embryos, and the related problem of surplus, or orphan, embryos; (iii) the expressivist critique of pre-implantation diagnosis put forward by the Disability Rights Movement; and (iv) what is the best environment for the upbringing of children and their rights, such as the right to know one's genetic parents, gamete donation, and surrogacy. Employing AI in the field of

ART, however, presents its own ethical complexities. Thus, having outlined the potential benefits of AI in ART, the clinical, social, and ethical risks related to this 'brave new world' will be discussed.

1. Infertility and Reproductive Technology

1.1 Infertility

Infertility is a medical and social concern worldwide. Defined as the inability to conceive after 12 months or more of unprotected regular intercourse,[1] infertility affects between 8 and 12% of reproductive-aged couples worldwide.[2] In some regions, however, the infertility rate can be as high as 30%.[3] While infertility can be the result of many factors, 10–20% of cases are unexplained, or 'idiopathic'.[4]

1.2 Assisted Reproductive Technologies

The downward trend in fertility rates has not surprisingly led to an increase in assisted reproduction techniques (ART),[5] and assisted reproduction today is characterised by high-tech, high-end investment and international fertility companies, with the global fertility services market expected to grow beyond US$25 billion by 2026.[6] Much has happened since the birth of the first test tube baby in 1978, including personalised ovarian stimulation, extended embryonic culture, intra cytoplasmic sperm injection (ICSI), pre-implantation genetic diagnosis, embryo selection (leading to elective single embryo transfer) and oocyte vitrification. Nevertheless, the success rate of IVF currently stands at around 30%,[7] even though this depends heavily on a number of factors, such as age and changes in the physical and psychosocial environments.[8] Many women, therefore, have to go through multiple rounds of IVF such that the process can be time-consuming, and challenges patients both financially and emotionally. Research is thus increasingly focused on how to improve treatments and outcomes, and rapid advancements in Artificial Intelligence look promising and are increasingly being utilised in fertility clinics around the world.[9]

2 Role of AI in IVF

As an article in *Time* magazine points out, "getting pregnant requires a complex calculus of ovulation cycles, hormone levels and lifestyle changes. But increasingly, women - and their doctors - are asking artificial intelligence (AI) to do that math for them."[10]

Introduced by John McCarthy in 1955,[11] AI can be defined as the ability of machines to learn and display intelligence, allowing them to automatically detect subtle but important patterns in large and complex data sets and to use these patterns to make predictions. While for the past 50 years, decision making in reproductive medicine has been a clinician-centred process based on the expertise of clinicians, and on evidence-based medicine, AI is increasingly being used as a "third way of knowing", shifting the decision making process from one centred on the provider, to a data-centric, quantitative model which generates probability estimates for various treatment options and offers the prospect of personalised care.[12] AI, in fact, promises to prove useful in several key parts of the IVF procedure.

2.1 Evaluation of female reproductive function

One of the most important phases in treating infertility is the evaluation of the female reproductive function such as the evaluation of ovarian reserve and endometrial receptivity.

Diagnosis aided by Artificial Intelligence may be one of the effective ways to assess female reproductive function,[13] and to provide guidance for diagnosing infertility conditions.[14]

2.2 Ovarian stimulation

Ovarian stimulation necessary for oocyte retrieval, and AI is being used to attempt to offer a more refined stimulation protocol and cycle management.[15] Machine learning models have been used to predict the prognostic results for ovarian response, thus enabling a customised controlled ovarian stimulation;[16] and to recommend first Follicle Stimulation Hormone doses for ovarian stimulation.[17] Since retrospective results show that over half of IVF cycles had possible early or late trigger injections which effected oocyte retrieval outcomes, researchers have developed an interpretable machine learning model to optimise the day of trigger,[18] as well as a decision support system with an algorithm trained to be identify the ideal time for oocyte retrieval.[19] Researchers have also developed a suite of integrated management tools related to management, scheduling and decision-making which reduced monitoring to a single best day during ovarian stimulation, thereby reducing the workflow and in patient care visits, without any decrease in response or outcomes.[20]

2.3 AI in gamete selection

The outcome of ART is also highly dependent on gamete health and the identification of early markers of quality are important. Currently, these are assessed by highly trained staff and automatic methods based on AI image analysis would allow more objective and precise results.

2.3.1 Ooctye selection

Oocyte quality is typically observed using a microscope, and each retrieved oocyte has a 4.5% chance of resulting in pregnancy.[21] The retrieved oocytes are at various stages of their meiotic maturity, and since those at the early stages of meiosis have a low embryonic development potential, they are therefore either rejected or matured in vitro.[22] The labour intensity of oocyte assessment "precludes daily application in a busy lab and constrains uptake."[23] Moreover, aneuploidy may exist even when oocytes appear normal.[24] Research is therefore ongoing on how to use AI image analysis to reliably predict which oocytes to fertilise or cryopreserve, depending on their reproductive potential.[25] AI may also help identify new biomarkers, to obtain precise standards and methods, and to identify predictive patterns which cannot be discernible visually.[26] Non-invasive and inexpensive methods which are easily assimilated into the clinical workflow would be the best.[27]

Elective oocyte freezing has become increasingly popular for fertility preservation. Comparable fertilisation and pregnancy rates have been obtained with fresh and frozen-thawed oocytes in ICSI and the evidence to date shows that children born through vitrified oocytes do not have a higher incidence of congenital abnormalities.[28] AI software has been used on images of mature oocytes before freezing to instantaneously grade their probability of reaching the blastocyst stage and live birth by comparing it to a large dataset of previously frozen eggs that successfully reached the blastocyst stage.[29] Automated vitrification is also being developed in order to overcome the diverse outcomes of oocyte cryopreservation.[30]

2.3.2 Sperm selection and semen analysis

IVF success is also linked to sperm morphology, concentration and motility. At the same time, up to one-third of male factor infertility are idiopathic, that is of unknown cause.[31] AI can thus

be employed to analyse and select the best specimens for fertility treatments. Researchers, for example, have used data mining to predict human sperm concentration and motility from questionnaires on lifestyle and environmental factors, offering a useful alternative to more expensive laboratory tests,[32] while others have used five AI techniques on eight feature selection methods to improve prediction of male fertility.[33] Researchers have also applied a computer aided sperm analysis system (CASA) developed on mouse sperm[34] to diagnose chromosomal abnormalities in human sperm with a prediction accuracy of more than 95%.[35]

Sperm quality, however, fluctuates over time and it is therefore crucial that sperm concentration and motility be monitored frequently in both spontaneous and assisted reproduction. Semen analysis is usually performed at a doctor's office, and it is not only time-consuming but also embarrassing for men.[36] Researchers have therefore developed and tested several home sperm tests,[37] some of which utilize platforms based on smartphone systems.[38] These systems allow men to monitor the health of their sperm over the course of several months, and clinicians may offer guidance in lifestyle changes to enhance their fertility both if they intend natural or assisted conception.[39] Frequent at-home testing also allows epidemiological research.[40]

Sperm selection would be particularly useful in intracytoplasmic sperm injection (ICSI), and unsupervised AI learning may not only discover new markers for sperm assessment, but may also predict the best sperm-ooctye pair for fertilisation.[41]

2.4 Embryo selection

In order to increase success rates, the most viable embryo is prioritised for elective single embryo transfer. The conventional approach involves assessing embryo implantation potential on the basis of their developmental rate and morphological characteristics and whether any aneuploidies are present. Such assessments are complicated, time consuming and highly dependent on the embryologist's experience and judgement, resulting in subjective grading which varies considerably not only among clinics and embryologists, but also when done by the same individual (e.g. observer fatigue).[42] Standardisation even within a clinic is challenging, and it becomes near impossible between institutions. The subjectivity is further increased due to the fact that morphological cut off values are not clearly defined, and notwithstanding the proposal of standard criteria, consensus has remained elusive. Even if agreement were to be reached about this, however, these criteria would need to be interpreted and applied, and since embryos develop dynamically, their classification might vary between observation times.[43]

Researchers have therefore introduced time-lapse imaging (TLI), allowing sustained microscopical monitoring of developmental milestones with time and therefore the assessment of morphokinetics.[44] These systems have now been integrated with an incubator,[45] allowing "uninterrupted embryo culture, flexibility in timing, improvement of documentation procedures, quality control and management and, in particular, the introduction of dynamic markers of embryo quality."[46] A retrospective study utilising a prediction model on a large combined set of transferred embryos with known clinical outcome from 7 independent clinics in 3 different countries reported a relative 30% increase in the implantation rate of the embryos selected by the model, but the model rejected a large number of the embryos from the test cohort which had actually implanted and resulted in pregnancy. The researchers thus conclude that both sensitivity (the ability to designate an embryo as 'unhealthy' with few false negatives) and specificity (the ability to designate an

embryo as 'healthy' with few false positives) need to be taken into account when developing embryo selection models for future clinical use.[47] Controversy still remains, in fact, about the clinical efficiency of such systems,[48] and whether the price of the equipment and its consumables, as well as the significant modifications to the clinical work routine are justified.[49] A review of this technology reports that TLI did not provide a statistically significant increase in pregnancy rates when compared to conventional assessment, and that it may not offer information about euploidy as pre-implantation genetic screening. The review thus concludes that the majority of embryologists do not yet trust this technology which may therefore be more of a gadget than a necessity.[50] The UK Human Fertilisation and Embryology Authority in fact does not recommend its routine use until further research.[51] At the same time, however, there have been several attempts to develop an AI based TLI system that is better than the standard scoring system in predicting pregnancy rates,[52] as well as attempts to standardise the media culture environment by utilising AI and TLI.[53]

2.5 Analysis of cell free DNA

Cell free DNA (cfDNA) are (nucleic or mitochondrial) DNA fragments released by cells into their extracellular environments. In a reproductive context, they are mainly found in seminal plasma, follicular fluid, serum, spent culture medium, and blastocoel fluid, and researchers have been exploring their profiles and correlations as well as postulating the variety of mechanisms from which they originate. cfDNA may therefore serve to diagnose infertility disorder, identify reliable biomarkers to predict ART outcomes, as well as for non-invasive genetic or epigenetic diagnoses which are currently done via embryo biopsies performed by highly-experienced technicians using expensive equipment. A recent review by Qassami and colleagues has provided a summary of the research so far,[54] but much more research is needed for clinical application and AI deep learning can certainly be part of this.[55]

2.6 The arrival of the omics era

The success of ART depends heavily on gamete and embryo selection and the determination of the best time for embryo implantation. While current practices rely mostly on the morphology of the gametes and embryos, and the histology of the endometrium, the emergence of genomic, transcriptomic, proteomic and metabolomic tools (collectively known as 'the omics') is leading to new research on mammalian physiology in general and are now also been researched in assisted reproduction in the profiling of sperm, oocytes, granulosa or cumulus cells, embryos or spent blastocyst media. An early review has analysed the different omics approaches, presenting their unique advantages and potential applications as well as their disadvantages and current shortcomings,[56] and a later review also considered lipidomics, secretomics (secreted proteins), interactomics (relationships between genes, proteins, ligands and metabolites), implantomics (molecules related to embryonic implantation), as well as epigenomics (genomic imprinting).[57]

Omics analyses can differentiate between morphologically identical embryos and can potentially identify ploidy status non-invasively, thereby reducing the risk of harming embryos and their environment, while reducing costs by eliminating the need for biopsies and decreasing the number of cycles.[58] The large amount of data which omics generates from a sample, however, presents a major challenge for researchers.[59] A combination of statistical models with an artificial neural network has therefore been proposed to integrate omics and artificial intelligence, to clarify the pathophysiology behind recurrent implantation failure,

and propose optimal treatment options, thus enhancing treatment success rates even in cases of unexplained infertility."[60]

2.7 Clinical Workflow

Future AI applications will also move beyond clinical care, extending to operational management and workflow, including data-entry, management and processing, which will become more efficient and less prone to errors.[61] Currently, for example, patient specific embryos are tracked and identified using manual identification, barcodes, or radio frequency identification technology. Researchers have now reported using a convoluted neural network as a witness system with 100% accuracy based on the unique morphological features of each embryo.[62]

AI driven tools might also help in automated scheduling of appointments and retrievals, leading to efficient scheduling.[63] AI based Decision Support Systems could also be incorporated into Electronic Medical Records for immediate assessment by an algorithm which issues a recommendation to a provider, possibly also on a smartphone display. The recommendation would be generated by the dataset of the clinic or network of clinics, but the provider might disagree with the recommendation in which case the application would migrate to a larger dataset for a review of the original recommendation.[64] AI-powered solutions can also be used to reply to customer inquiries and complaints with very specific replies via 'chatbots' and natural language processing, which can be used to answer common questions about scheduling, medication management, or questions about IVF cycle options.[65]

2.8 Towards a personalised care plan

AI is particularly fit as a technology to be applied to complex and multifactorial problems such as poor stimulation response and repeated miscarriages or implantation failure.[66] When analysed deeply, the numerous data points possible allows clinicians to draw up a personalised treatment plan.[67] AI tools would not only be able to offer recommendations at the start of treatment, but AI analytics would be able "to adjust predictions throughout treatment in a continuous, feedback loop of data collection, assessment and predictions"[68] taking into account patients' unique genetics and the molecular mechanisms of their infertility to personalise optimal treatment. It also allows "a more systematic recording of the process calling out unusual or outlier lab results for expert re-evaluation."[69] Care can thus be delivered with greater precision, enabling a treatment regimen that is "predictive, preventive, personalized, and participatory."[70]

AI is also being used in facial recognition technology (e.g., Fenomatch)[71] to identify donor gametes and embryos which are most likely to result in a child with similar facial features to the social parents. Facial recognition AI in donor selection could allow IVF children to 'pass' as one's own genetic child.[72] Rich Vaugn, the founder of the International Fertility Law Group, believes that this may help reduce the number of abandoned frozen embryos,[73] but that is highly improbable.

Moreover, AI's propensity to lead to automation offers hope that recurring, time-consuming and monotonous tasks which require a great deal of skill and attention[74] – such as semen analysis, oocyte and embryo grading and vitrification, biopsy sample loading, etc – would no longer need to be done manually and occupy most of the lab workflow.[75] Administrative or laboratory errors related to patient identification, chain of custody of gametes and embryos,

and their cryopreservation inventory would be reduced, and robotics would also make more efficient use of raw materials such as culture media and reagents.[76] Moreover, rather than requiring years of experience and labour-intensive medical training, such AI systems only require training on a dataset.[77] Trained clinicians would have more time on their hands to train junior staff, considering the increased need of experienced embryologists,[78] and to concentrate on the human foundations of medical care, such as better communication and counselling based on the evidence reported by new research.[79] It would also make the latest technology more widely available, offering a remote medical expert system even across borders via telemedicine. Combined with telehealth, clinicians would also be able to offer advice "without the need for in-person office visits bringing to life the dream of the 'quasi-DIY' (do it yourself) IVF cycle that reduces costs, increases convenience, and democratizes access for everyone."[80]

3. Ethical complexities

ART currently presents a number of ethical issues and these have been debated extensively. These mostly centre around (i) the value and meaning of the transmission of human life; (ii) the moral status of the human embryo, including the ethics of freezing or discarding human embryos, and the related problem of surplus, or orphan, embryos; (iii) the expressivist critique of pre-implantation diagnosis put forward by the Disability Rights Movement;[81] and (iv) what is the best environment for the upbringing of children and their rights, such as the right to know one's genetic parents, gamete donation, and surrogacy. Employing AI in the field of ART, however, presents its own ethical complexities. Thus, having outlined the potential benefits of AI in ART, the clinical, social and ethical risks related to this 'brave new world' will now be discussed.

3.1 Harm due to AI errors and misuse

Notwithstanding the increase in data availability and machine learning, AI is still prone to errors in sensitivity and specificity (false positives and false negatives) which can lead to missed diagnosis, unnecessary treatments or unsuitable interventions or prioritisation.[82] Even with large scale datasets and sufficient training, errors in clinical practice may be introduced by three main factors.[83] The first is noise during the inputting of data during usage, such as issues with image quality or ultrasound scanning.[84] Errors could also occur due to dataset shift,[85] which occurs when the statistical distribution of the clinical data is even slightly different from that used for algorithm training. Differences in population groups and acquisition protocols between service providers, as well as the use of machines from different manufacturers can confuse AI systems and lead to consequential errors.[86] Finally, AI algorithms adapt clumsily to unexpected alterations in the context or environment in which they are used.[87] AI solutions should therefore be extensively evaluated for their generalisability to new populations and sensitivity to noise, and should be designed and utilised as assistive tools such that clinicians could still be able to detect and report potential errors.[88]

The increasing availability of medical AI apps for the general public leads to further concerns related to harm. Though easily accessible, limited information is given on how these have been developed and validated, and their clinical efficiency has not been demonstrated.[89] A recent study concluded that "the current regulatory process for awarding the CE marking for algorithm-based apps does not provide adequate protection to the public."[90] While most

parts of the ART process necessarily requires clinician intervention and oversight (e.g. oocyte retrieval and embryo implantation), home semen analysis tests are already available, and wearable bioadhesive ultrasound stickers the size of postage stamps might soon be available for long-term imaging of diverse organs, including during pregnancy.[91] Health care professionals, however, should be an essential part of the team designing and developing these devices, and regulation of this sector is becoming increasingly necessary.[92]

3.2 Transparency

AI systems need to be trustworthy,[93] and transparency is an important ethical requirement both (i) in terms of their design, development, evaluation and deployment linked to traceability (transparency in the development and usage of these processes) and (ii) in terms of their explainability (transparency of the decisions reached by such systems).[94]

With respect to the former, new mechanisms are needed to increase transparency in medical AI systems beyond their development and testing phase throughout their lifecycle. The Panel for the Future of Science and Technology (STOA) of the European Parliament suggests that this could take the form of an AI passport issued by regulatory bodies which would offer standardised descriptions and traceability across countries and health care organisations.[95] This should describe and monitor (i) model related information (such as owners, developers and reviewers, algorithmic details, and intended clinical uses); (ii) data related information (such as datasets and their origin); (iii) evaluation related information (such as model accuracy, robustness, biases and limitations); (iv) usage related information (such as statistical distributions, agreements or disagreements with clinicians, identified failures); and (v) maintenance related information (such as last updates and evaluation).[96] Such a passport would continuously monitor how the AI system functions in clinical practice, considering the continuous introduction of new data, new equipment, and new users, and identify possible errors or changes in performance. Live, user-friendly interfaces are therefore important for the continuous surveillance and auditing of such tools.[97]

Transparency is also needed in terms of the decisions reached. Most algorithms in fact are developed using neural networks or machine learning which are uninterpretable (or 'black box'), that is, end users are unable to explain why the system has reached a particular decision. This may either be due to the fact that the decision making process is too complicated to explain, or else because the algorithm is proprietary and therefore cannot be understood by outsiders, that is, by doctors, embryologists or patients.[98] Such opaque, or "black box" models present significant epistemic and ethical issues.[99] According to Afnan and colleagues, knowledge-based concerns, on one hand, revolve around asymmetries of information between developers and users (including clinicians and patients); the risk of bias introduced during the training process; difficulties in error checking in real time; buying commercial, and therefore, proprietary models; as well as difficulties related to troubleshooting.[100] On the other hand, ethical concerns focus on the risk of misrepresentation of patient values; concerns for the wellbeing and health of children born as a result of these technologies; the risk of devaluing disability; possible societal implications; and the accountability gap in cases of bad decisions.[101]

3.3 Need for rigorous clinical trials

While support for AI in the field of ART has been steadily increasing, AI has not yet attained gold standard status.[102] Currently, there are considerable variations in outcomes and results,

probably due to different protocols and study designs which compromise certainty.[103] Different data point definitions, patient demographics and heterogenous clinical procedures may all lead to data bias such that AI models would be only applicable in the clinic in which they were trained.[104] Calibration,[105] or standardisation,[106] of AI models is therefore necessary but this requires much larger and unbiased databases for robustness, which need to be generated from several clinics (reproducibility) to reduce variability in data and avoid dataset heterogeneity.[107] This brings up issues of data confidentiality, cooperation/competitiveness between clinics, and intellectual property protection.[108]

Summarising the current limitations of studies to date, Wang and colleagues argue that the quantity and quality of current data significantly affects the applicability and generalisability of current models whose data is "small in number, single in source, and retrospective."[109] There are no prospective studies which demonstrate better patient outcomes or cost reductions over current practice,[110] and any meaningful application would need large-scale randomised clinical trials and meta-analyses of their data.[111]

Indeed, researchers have reported that they found no trials evaluating clinical effectiveness,[112] arguing that it is too early to adopt AI for embryo selection outside of a clinical trial. For example, while studies report that AI can distinguish between good and bad embryos, algorithms may not necessarily be able to differentiate embryos of similar quality which is needed clinically.[113] Much more work is therefore necessary in order to ethically deploy AI in ART.

3.4 Privacy and confidentiality

Ai based systems are computer based and more systems today rely on information uploaded to a cloud based system. This allows patients to be able to receive, retrieve or access their test results on their own computer or smartphone, as well as allowing them to share this with a clinic of their choice, regardless of lab location or whether that clinic has access to AI technology.

At the same time, however, such systems are vulnerable to cyberattacks, which compromise the safety of highly sensitive personal data, such as names, addresses, medical records, and insurance policy numbers,[114] and ransomware[115] which, apart from financial and criminal concerns, delays time-sensitive care to patients, such as the monitoring of hyperstimulation, oocyte retrieval and embryo transfer. Cyberattacks might also allow the medical tools to continue to work, but the systems would provide erroneous conclusions.[116] AI systems employed in ART, as well as any personal medical devices, must therefore be engineered to monitor safety hazards, detect malicious use and withstand attacks.[117]

Patient privacy and confidentiality may also be violated by the sharing of personal data without fully informed consent, such as in cases of data repurposing,[118] sometimes also referred to as 'function creep'.[119] It may also occur when clinical data is shared with researchers outside the clinic. Patients are increasingly finding it difficult to comprehend complicated informed consent forms, how their data can possibly be used, and how they can choose not to allow the sharing of their personal data.[120]

Awareness and literacy on privacy, security risks and informed consent should therefore be increased, especially in the context of digital platform based health data research.[121] Research on how to increase cybersecurity, and regulations and legal frameworks to address both privacy and accountability are therefore needed. Decentralised, federated approaches to AI

would still allow the use of big data from different clinical centres while avoiding unsafe data transfers.[122]

3.5 Bias, inequality and justice

AI technology depends heavily on both the algorithms used as well as on the datasets on which they are modelled and trained. This means that AI technology faces the risk of magnifying any existing systemic bias in the data, turning AI into what one author called Augmenting Inequality.[123] Some researchers have started to study the social determinants of health in infertility and fertility outcomes following ART,[124] while others have questioned what types of data diversity would be biologically relevant, and whether diversity in the data depends on the AI model being developed such as, for example, being adequately diverse for diagnosis, but not for embryo selection.[125]

Both clinicians and patients need to be able to trust the system and ensure that both fairness and equality are met. Models should therefore use diverse, high-quality datasets and developers should pay close attention to the selection, labelling and annotation of the data and variables which will be used during model training. Datasets should thus be representative of key factors such as age, socioeconomics, ethnicity, geographical location,[126] and lifestyle, as well as unequal access to equipment and digital technologies.[127] The diversity and interdisciplinarity in the technological, scientific, clinical and policy making teams is also important, which should also include social scientists, bioethicists, public health experts as well as patients and citizens.[128] In parallel with the ethical and just use of similar scientific databases, researchers have questioned whether such datasets ought to be publicly available, which would allow reproducible research as well as serve as a performance baseline.[129] If that were to be the case, a number of ethical issues would arise, such as who should host and act as gatekeeper to the dataset, who should access the data, and for what purposes can that data be put to use.[130] Examples of past practices utilised in other areas, such as genetic and biobank databases, can serve as examples of best practice, and an expert consortium could be established to oversee such an initiative.[131]

3.6 Gaps in accountability

'Algorithmic accountability' is crucial if AI is to be trustworthy. The multiplicity of actors involved in the whole AI pipeline (from design to data collection and development, to preclinical stages, to deployment and use) makes the definition of roles and responsibilities very difficult, and at present, national and international regulations contain legal lacunae on who should be held accountable or liable for the failures or errors of AI systems. This is particularly concerting in the case of medical AI, placing clinicians and other healthcare professionals particularly susceptible to liability, especially when the AI tool they use is not fully transparent.[132] It is therefore important to determine the boundaries between the physician and the machine's role in patient care,[133] and to develop frameworks to define accountability, responsibility and liability while enforcing any relevant consequences.[134] Though GDPR establishes transparency in data processing and privacy, this is not enough to outline algorithmic accountability and experts see the need for a new regulatory body for AI.[135]

3.7 Need for regulation

Even though there have been some initiatives, ethical guidelines and policies for AI technology lag behind medical progress and the medical community is not well-informed about the ethical complexities that the nascent AI technology can introduce.[136] Risk assessment should therefore go beyond accuracy, and should be evaluated "on a case-by-case basis for each new AI algorithm and application."[137]

In the US, AI driven medical tools are regulated by the Food and Drug Administration which usually requires that these are 'locked', that is, that they cannot be changed once placed on the market.[138] Such an approach promotes safety, but prevents these devices from using clinical data to learn, adapt and improve.[139] Similarly, across the EU, the *Medical Device Regulation* 2017/745 (which includes software) and the *In Vitro Medical Devices Regulation* 2017/746 (diagnostics), do not consider the endless learning of AI models or the possibility of algorithmic biases.[140] Several authors have therefore called for these regulatory approvals of AI-based medical devices to be updated.[141]

In 2021, the FDA proposed an *Artificial Intelligence and Machine Learning (AI/ML) Software as a Medical Device Action Plan* to promote "regulatory science efforts to develop methodology for the evaluation and improvement of machine learning algorithms."[142] That same year, the European Commission published a draft AI regulation with the aim of harmonising rules across the EU,[143] but this is similarly general and does not take into account the specific requirements of health care, and once again fails to address the dynamic and ongoing learning of medical AI devices.[144]

The draft European framework categorises risk on three main levels (minimal, high and unacceptable). While unacceptable risks (such as manipulation, exploitation or social scoring) are by definition unacceptable, it seems that most AI driven medical devices would be categorised as high risk, especially systems which are autonomous. For such systems, the proposal would require: (i) high-quality training, validation and testing data (relevant, representative); (ii) technical documentation and logging capabilities (traceability & auditability); (iii) an appropriate degree of transparency with users being versant on the system's capabilities and limitations; (iv) human oversight; and (v) robustness, accuracy and cybersecurity. It would also create obligations such as to (i) register the AI system in a EU database; (ii) affix CE marking and sign declaration of conformity; (iii) conduct post-market monitoring; (iv) collaborate with market surveillance authorities; (v) inform the provider or distributor about any serious incident or any malfunctioning; (v) continue to apply existing legal obligations (e.g. under GDPR).[145]

It is conceivable, however, that not all medical AI tools are high risk, and if so, it would be essential to differentiate between them.[146]

3.8 Marketing, conflicts of interest, and post-marketing monitoring

The cost/benefit ratio of adding AI technology in ART should also be evaluated, considering unfair marketing practices,[147] and the aggressive marketing of new technologies which, at least according to some, are unnecessary (see the discussion on time lapse images above). Unless such technologies lead to an improvement in live birth rate, their deployment would not serve the best interest of patients but rather the careers of researchers and the commercial interests of technological companies,[148] or the financial interests of clinicians if used as a way to advertise their services.

For example, the deployment of time lapse imaging, the endometrial receptivity assay and preimplantation genetic analysis for aneuploidy, even if they may ultimately turn out to be beneficial, were clearly introduced early due to commercial interests.[149] Moreover, even evidence based 'add on's increase the already expensive costs of ART, and the question arises as to whether one ought to increase access to 'normal' infertility treatments rather than offer more sophisticated and costly treatments to the few who can afford them.[150]

Moreover, once deployed in a clinic, AI tools need to be monitored via longitudinal databases so that users can be confident that they are safe and effective. Embryos with a higher implantation potential for clinical pregnancy, for example, might correlate with some unfavourable conditions, such as large foetal size or cardiovascular complications.[151] The health and well-being of offspring born after the adoption of any new technology should therefore be monitored long term.[152] Considering the importance of such databases, ways of relieving this burdensome task from embryologists and clinicians is needed.[153]

3.9 Publication and research standards

Scientific developments thrive on research and publication of results. Their value, however, depends on the study design, and the pitfalls of fertility-related study designs have been well outlined in the literature.[154] Moreover, reviewers may find evaluating study designs difficult and a critical appraisal framework for this type of research may be needed.[155] One also needs to address questions of authorship and conflicts of interest such as whether simply providing access to a dataset would be sufficient to be listed as an author, and the possibility of conflicts of interest,[156] such as when an executive of an IVF clinic hands over access to medical records in exchange for pecuniary gain such as start-up shares.[157]

3.10 Medical education

As novel AI methods and ideas make their way into research and clinical practice, researchers have called for medical education to be updated in the context of AI.[158] This will allow future professionals to be adequately trained for a career integrating AI,[159] as well as using AI in their education,[160] with a focus on the advantages, limitations and risks of this new field. Medical education should thus be rethought in a way that medical students would be trained to manage AI machines rather than concentrate on knowledge recall, with careful attention given to the ethical and clinical complexities involved, while improving communication and empathy.[161] Of course, there is a concurrent need to deepen the AI literacy of the general public in order to empower patients, especially during remote monitoring and care management.[162]

4. A better experience for patients and clinicians

AI is extremely promising in its potential to improve outcomes in ART, which would translate into decreased patient anxiety and distress, as well as the optimisation of human and technical resource allocation, thus lowering costs for patients, insurance companies or national health services. An integrated approach is needed, however, for advances in gamete and embryo selection need to be coupled with improved safety of ovarian stimulation and oocyte retrieval, as well as advances in endometrial receptivity and early pregnancy management.[163] It is also auspicial that these advances would lead to less surplus human embryos.[164] Research in these fields will need to rely on unsupervised learning, yet, as previously pointed out, AI driven applications need to be explainable.[165] Uninterpretable

decisions lead to a new form of paternalism which replaces human decisions with those taken by machines, and this inability to explain medical decisions to patients is exacerbated in the case of failed IVF cycles.[166] It is interesting to note, in fact, that the American Medical Association has adopted the term Augmented Intelligence, rather than Artificial Intelligence, in order to focus on AI's assistive role to enhance human intelligence rather than replace it.[167]

Indeed, as human reproduction become more technical and automated, it is important to retain a humanistic rather than a robotic approach, with physician patient interactions based on both science and art, for an empathetic relationship in this highly sensitive and emotional journey can go a long way in offering a better experience for both patients and clinicians.[168]

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