COMMENTARY

Proceedings of the first world conference on AI in fertility

Carol Lynn Curchoe¹

Received: 21 December 2022 / Accepted: 22 December 2022 / Published online: 4 January 2023 © The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2023

The first international conference on artificial intelligence (AI) and fertility, AI Fertility, was held on September 15–18, 2022, in Dubrovnik, Croatia. The objective of the AI Fertility Conference was to provide a forum for scientists and researchers from academia and industry to discuss critical strengths, weaknesses, challenges, and opportunities for AI and fertility. The summit was co-chaired by Nikica Zaninovic, PhD and Zev Rosenwaks, MD (Weil Cornell Medical College), Cristina Hickman, PhD (Apricity), and Velimir Šimunić, MD (Medical Faculty in Zagreb) and the newly formed AI Fertility Society. The meeting was sponsored by a number of AI, related vendors, without which a meeting of this caliber would not have been possible.

The conference opened with a celebratory and sobering presentation by Professor Dr. Simunić. As a field, we have accomplished so much, but we have a long way to go in terms of worldwide IVF access, technology implementation, and success rates [1]. Worldwide, comparisons are difficult, because ART presents with different technologies, populations (age, OB, DOR, POR), mild or minimal ovarian stimulation vs goal of more oocytes retrieved, and embryo selection methods, transfer timing (ET vs FET), eSET, blastocyst culture, and a myriad of other variables, resulting in countryto-country differences in success rates. It was noted that the 3.2 million ART cycles performed yearly grows at a 10% rate and that just 10 countries (China, Japan, USA, Spain, Russia, France, Germany, Italy, Australia, and UK) perform 80% of all cycles (ICMART/ESHRE 2022), with Europe and China accounting for a stunning 50% of those cycles. Some continents, such as Africa, perform just 1-2% of all ART cycles. The ICMART World Collaborative Reports for assisted reproductive technology (ART) for 2018, the latest year that data are available, shows delivery success rates of 22% per autologous oocyte aspiration, 31% per frozen embryo transfer, and 46% per "PGT" embryo transfer. The

Carol Lynn Curchoe carolc@aivf.co

reported autologous ART cumulative delivery rate per aspiration varies from 21 (Africa) to 49% (North America). The mean age of IVF patients has risen worldwide, and while success rates have increased, the rate of multiple gestations has decreased, that is amazing progress! There are still significant opportunities to improve certain metrics, such as cycle cancellation, multiple gestation, and cumulative delivery rates. We must ask, what are top performing regions doing differently?

Iman Hajirasouliha, PhD (Weill Cornell Medicine), spoke about the promise of precision medicine and tailoring the best treatments to individuals based on their own genetic uniqueness [2]. The precision medicine of the future will transcend a single source of data, such as DNA sequencing, include a variety of data types (imaging, electronic health records), and make use of artificial intelligence. IVF can benefit from AI to combine the pros of morphology selection (quick and cost effective) with the precision of PGT.

David Sable's, MD, discussion (former REI turned investor and reproductive economist) covered the strengths, weaknesses, opportunities, and strategies for startups and the technology investment landscape. Women's health and IVF are poised to move from an "organ and systems" approach to a cellular, biochemical, and personalized genetic approach [3]. Unlike other fields of medicine, like oncology, we are just now at the cusp of moving away from the slow, incremental, "analog" human intelligence method to problem-solving, to digitalizing the diagnoses, prognosis, and treatment pathways for infertility. This epistemological shift is necessary to accomplish the "missing" 20 million IVF babies per year that he estimates we need, 40 times the efficiency of the current IVF industry! What would the world look like if IVF were as common as eye glasses are now? Digitization has the ability to provide value propositions for strict outcome measures: dollars to baby, time to baby, and "life-disruption" to baby, while informing risk management with big data. Investments in technology and commercialization of solutions will benefit from focus on "big ticket" items that may make the most difference in overcoming the barriers to IVF care. We must target with our inventions and



¹ ART Compass, an AIVF Technology, Tel Aviv, Israel

our funds the "bottlenecks" of the industry: medical labor (clinical and embryology), laboratory space and complexity, and reliance on generic drugs. The future of IVF is a parallel industry that is built from the ground up to provide the enormous numbers of "missing" IVF babies. The industry as it stands now has some serious limitations; data are heterogenous and not at all "large"; too much of IVF is "unobservable" (sperm genetics, the embryo after transfer); there are few baselines and biased initial data, subjecting all of our work to confounders.

Santiago Munné, PhD (Overture Life), well known for co-developing one ART revolution (reproductive genetics), now focuses his efforts on technology automation in the in the IVF lab. Automated platforms can solve the problem of inconsistency, provide labor savings, and convenience. Variability between IVF centers is high: embryo aneuploidy rates from egg donor oocytes vary from 20 to 60% [4]; pregnancy rates in egg donor recipients varies from 10 to 80% [5]; methods and skills vary from center to center and from operator to operator [6]. Automation is now enabled by affordable robotics, microfluidics, miniaturized imaging systems, and "IoT" connectivity (internet of things). Freezing oocytes and embryos and performing ICSI are two processes where automation can increase the efficiency of the IVF lab to scale the industry, possibly even to the aspirational 40-fold goal mentioned above. The automated systems to achieve these complex procedures are now in development [7].

The second session focused on AI in fertility as it is today. The audience enjoyed a communal laugh as we all considered where we were 5 years ago, where we are today, and where we might be in the next 5 years.

Evaluating reproductive cells is essential to fertility treatments. Dan Nayot, MD (Future Fertility and The Fertility Partners) pointed out that every sperm sample is evaluated, every embryo is graded at every milestone from 2PN to blastocyst, and every endometrium is evaluated prior to embryo transfer; however, oocyte scoring systems are rare in clinical practice. Artificial intelligence applications have been successfully developed to predict fertilization potential, blastocyst formation, and embryo quality from oocyte images [8]. These predictions can be useful for patients and clinicians. The contribution of the oocyte to a failed cycle can start to be parsed and quantified. Embryo choice can be augmented with this additional information. Patients undergoing oocyte cryopreservation can use the information to make choices (undergo additional retrievals or not), and oocytes from donors can be divvied up and distributed based on potential. Future directions for oocyte AI will extend the predictive capabilities to pregnancy, confirm nuclear maturity, automatically label dysmorphisms, and uncover new metrics and clinical variables of success.

In the same sense and despite every semen sample being evaluated, the semen analysis is also ripe for an overhaul. It is manual, time-consuming, and subjective, and while requiring highly skilled, trained, and experienced technologists, it is also a "routine" and repetitive task. Alejandro Chavez Badiola, MD presented the case for AI to digitize and optimize sperm analysis and selection [9]. Sperm are a particular challenge to image and select for ICSI. At less than 6 microns, the healthiest sperm are highly motile, and the particulars of imaging for ICSI, i.e., optics that must be able to glimpse through embryo-safe plastics, media, and PVP, must be considered. Current solutions (IMSI, MSOME, DFI) are inadequate or too expensive. AI automation can be useful for other time-consuming andrology tasks, such as differentiating rare sperm cells from other cellular debris in the case of vasectomy or a surgical semen sample.

Daniella Gilboa, MSc discussed how AI is ushering in a new era of embryology, *computational embryology*, and a new type of *computational embryologist*. The computational embryologist will have a different tool kit [10] at their disposal and use a different vocabulary that includes measures of true PN scoring, halo effects [11], cytoplasm rearrangement, values and ratios of time events, cell edges [12] and dynamics, speed of blastulation and hatching, embryo pumping [13], and non-invasive predictions of ploidy [14], among others [15]. The promise of AI-mitigated freedom for the computational embryologist is not just a new toolkit but the re-acquisition of free time, free time to perform at the higher levels as only humans can, higher order data analysis, research, intellectual work, training, mentoring, and quality functions.

Piotr Wygocki, PhD (MIM Solutions) is advancing reproductive ultrasonography with AI. Follicle ultrasound is used to predict the number of MII oocytes, 2PNs, and blastocysts and to adjust the dosage of exogenous gonadotrophins or the timing of the trigger shot. Ultrasound appointments account for over half of the patients in person fertility clinic visits, and it has been estimated that the human eye misses one out of every three follicles. AI can not only reduce the number of patient visits, but also allow the procedure to be performed by a greater number of medical professionals, such as at a general gynecological office.

There is an underappreciated reluctance to use well-established ART, despite high levels of reimbursement in some countries. This indicates that cost is not the only barrier to treatments, but stress and other factors play a significant role. Due to high stress associated with ART treatment, patients can also prematurely discontinue ART, even when further treatment is likely to be beneficial [16]. Mylene Yao, MD (Univfy) is using AI to improve empathetic, patient centric care and increase access to IVF through AI-driven patient conversion and retention. Many IVF prediction models are based in large part on age, even though 86% of patients have a significantly different probability of live birth than predicted by age alone [17]. AI provides advantages, such as accurate and personalized prognostics, over other modeling methods. It is simple for fertility clinics to present success rates against age; it becomes increasingly difficult to include additional factors to improve prognostication. Machine learning can link outcomes from fresh and frozen embryo transfers; relevant clinical variables, such as age, body mass index, ovarian reserve, reproductive history, clinical diagnosis, and male partner's health data; semen analysis; and clinical outcomes, to build truly accurate prognostic tools for patient counselling.

Embryo and oocyte DNA content, growth patterns, and morphology are not the only signals by which to predict potential. Samuel Ojosnegros, PhD (Institute for Bioengineering of Catalonia), an expert in using photo-stable imaging in the near-infrared (NIR) [18] biological transparency window, is applying AI to the spectral signatures of small molecules to create three-dimensional renderings to metabolically classify embryos and oocytes non-invasively. Small molecules like metabolites can also offer tantalizing clues to potential. The hyper spectral imaging presented can excite six metabolites (FAD, NADH, retinal, and protoporphirins, for example) in a single shot, significantly enriching our view of the embryo.

High-performing technology, like AI, relies on big data [19, 20], which can be supported by government-funded databases [21], but its clinical adoption has been slow. Three main challenges, explainability [22], actionable insights, and integration into clinical workflows, can slow successful adoption of AI-driven clinical decision support systems. Hyejun Lee, MD (Kai Health) led an insightful discussion about the opportunities and weaknesses in each of those domains. For example, AI companies should not just provide an embryo prediction but explain the decision by showing with a visual tool, like a heat map, what the AI is looking at to provide clinicians with a measure of explainability.

Big data are necessary and so are new methods to streamline data processing and digitize the vast reams of data collected during a single IVF cycle. For decades, Jonas Malmstem, DPS (Weill Cornell Medical) has been interconnecting hardware devices in the IVF lab to databases, cleaning those data with AI, and transforming those data into research for many years [23]. He knows well the curse of too many data files. As an example, a timelapse incubator will take images at 11 different focal planes, every 20 min for 5 days. A thousand patients, each with 10 embryos, become 40 million images or about 1.2 terabytes of data. Instruments can also generate poor data (up to 2% of all images); embryo images can be "missing"; there can be translocated wells and out of focus embryos. An AI model can be trained to select the best images for future AI projects and separate out the "noise." Every part of an IVF lab has the ability to evolve over time; therefore, models must be robust enough to handle data gathered over time and subject to longitudinal biases. Lastly,

the concept of "AutoML," an emerging technology that can create AI models without prior art, could one day combine data types, tabular, image, video, and natural language, to predict a single outcome.

Data quality, quantity, and diversity are central to machine learning's ability to generalize and perform well at any IVF Clinic. Jens Rimestad, MSc (Vitrolife) advised the audience from the perspective of developing the iDAScore, AI embryo selection support tool for the Embryoscope, a timelapse incubator that is available for use worldwide [24, 25]. The performance of an AI Model (area under the curve) relates to image data quality (resolution), and confounders (bias from embryo hatching), as well as the "ground truth" or the outcome label used, the selection of which can be noisy and uncertain (Gardner score) or somewhat cleaner (known implantation). Increasing the size and diversity (FETS and fresh transfers, day of transfer, media type, age) of data is important to increase AI model performance.

Hadi Shafiee, PhD (Harvard) has published more than forty publications and patents using neuronal networks for IVF applications [26] and is an expert on overcoming data bias and those stubborn confounders of AI decision-making [27]. The selection of an AI model for a certain task, data imbalances, type of training or the evaluation, and interpretation of the model can distort the meaning of the results. The performance of AI models can change for subgroups of a population due to bias, for example, based on insurance status or skin tone. AI system performance can be improved by forcing the system to focus on clinically relevant features in high-quality images before being trained on lower quality images (MD-Nets), in order to tackle "domain shift" and "under-specification" data quality issues [28].

Tony Gordon, PhD (Cooper Surgical) is bringing the technology of AI to PGT to tackle subjectivity, human error, and bias (PGTai 1.0 and 2.0) [29]. Five to ten cells are taken during trophectoderm biopsy. The DNA from those cells needs to be amplified a million times, and some areas of the genome amplify better than others, introducing bias. There is also subjectivity in traditional next-generation sequencing (NGS) "calling" (i.e., distinguishing which base-indicating "peak" signal is true from the noise). Errors in base calling are rare, but the sheer volume of high-throughput data means that a "one in a thousand" mistake will be made once every 10 days. Human interpretation can be subjective and vary from lab to lab, and data entry clerical errors can occur. Machine learning algorithms can be trained to decipher the difference between true signal and noise patterns for "statistical calling" of next-generation sequencing data.

The third session focused on responsible innovation, taking ideas and turning them into useful products. There are several steps along that timeline, from inception of an idea to running randomized clinical trials and collecting clinical trials data to finally introduction into clinical practice.

Ze'Ev Bomzon, PhD (AIVF) has led the transition of several ideas from inception to product and discussed the quality control of responsible innovation for AI product development. AI products, like AIVF's EMA embryo evaluation software [30], need to extract data from hardware (timelapse incubators) and software (EMRs), which have many different formats. In general, products need to have a user interface and backend software, all connected to the AI model(s). However, those are not what make a successful product. On top of the product, lots of "extras" are needed for proper functioning. The product must be easy to install, collect, and store training and validation datasets (proper version control); there must be system monitoring tools to ensure proper functioning, algorithm monitoring tools, automated model re-training, and "MLOPS" (a set of practices that aims to deploy and maintain machine learning models in production reliably and efficiently. The word is a compound of "machine learning" and the continuous development practice in the software field), and lastly, cybersecurity.

Taking a 30,000 foot view on the implementation of AI in healthcare, Michelle Perugini, PhD (Life Whisperer, Presagen) spoke about the significant challenge of aligning incentives across multiple stakeholders with diverse needs. Clinicians and embryologists have an ultimate duty to patient outcomes but also desire time efficiency and operational improvements. Patients need access, affordability, better outcomes, and treatment transparency. AI technology can align those needs via support of clinical decision-making, standardization [31], and by improved accuracy [32]. Introducing these AI innovations to the market is all about building trust; how does AI work and can we explain it? Does it meet legal requirements to be marketed? Does it solve practical clinical problems? Does it benefit patients and improve outcomes? Does the value outweigh the costs to the patient and the provider? Can we mitigate the risks (data security and regulation)? And how can we as an industry educate the clinicians and the patients on these new technologies, help them verify and validate the innovations, and explain the results?

The randomized clinical trial (RCT) is the so-called gold standard to determine the efficacy of a treatment or intervention. Usually, an intervention that undergoes a clinical trial quickly gains trust through transparency of the trial design, data collection, and analysis. For AI research, one of the salient questions is if the RCT is indeed the appropriate vehicle. Cristina Hickman, PhD bravely led the discussion to thoroughly challenge the notion that an RCT is the only acceptable way to validate a new technology [33] and deftly countered the narrative that live birth rate is the only acceptable benefit of technology. Despite being the gold standard, RCTs present with a number of challenges. They are expensive and time-consuming, designed to benefit the most patients possible, and may not be appropriate for "precision" medicine applications; the population of an RCT may not reflect the real population of patients (biasing the results), and are not designed explicitly for prognostic tools. Prognostic tools are based on data; they are a precursor to an intervention [34]. The performance of AI specifically is based on training datasets, meaning the more diverse data you feed the model, the more accurate it becomes, and it is optimized in real time and can be personalized per patient. There is a range of autonomy in AI technologies; from low risk "assistive" AI (data presentation, clinical decision support) to medium risk (conditional automation) and higher risk "autonomous AI" (high automation and full automation), but it seems as though regulators are demanding the same level of rigor across the board, no matter what the level of autonomy and risk is.

Clinical trials data are shifting from tabular to image based, and drug development companies like Ferring have the resources to power large RCTs in the domains of ART that can be shaped by image analysis, antral follicle count, follicle development, fertilization, embryo selection, and embryo transfer. Patrick Heiser, PhD and Thomas Ellebaek, MSc (Ferring) are using new and innovative ways to apply AI to clinical trials databases to extract every bit of clinical and scientific data from expensive, large, and rigorous RCTs with dozens of endpoints [35]. Novel AI-driven data monitoring techniques can learn patterns of good quality data in unstructured clinical trials datasets, allowing for real-time surveillance of data from study sites and correction before it can compromise the trial's results.

The fourth session focused on driving connected intelligence. Artificial Intelligence is connected intelligence, and those connections impact everything from data collection for clinical trials, to generalizability, AI publications, and complete "end to end" workflows from; stimulation, gamete production and collection, through IVF, and from start-up through IPO.

If we are to apply AI to precision medicine, Gaurang Daftary, MD (Ferring) postulates that data collection, annotation, and structure must transcend the population level and achieve the personal level. Individualized biomarkers recognize that each and every one of us is different and unique in our own special way. For example, every ovary is different; it has different supply and demands for pharmacological molecules [36]. Concomitantly, drug dosage and bioavailability of fertility treatments should reflect that [37]. AI for clinical trials can incorporate digital biomarker signatures, adverse events form data, trial surveillance (incomplete or spurious data), end-point adjudication, and missing data (impute specific values or interpret meaning of missing values. AIdriven analyses for improved inclusion and exclusion criteria, selection, and stratification of patient populations for clinical trials can allow for higher success rates, smaller trials, improved efficiency, and success. Looking to other areas

of medicine, such as the COMPANION cardiac clinical trial [38], provides an excellent roadmap for how AI can bring precision medicine to fertility.

When a brilliant physicist like Jonathan Hall, PhD (Presagen, Life Whisperer) takes the stage, he puts mathematics vocabulary to work ("asymptotes off") and uses his knack for analogizing to make hard concepts accessible. Untrainable Data Cleansing (UDC) is a concept, whereby AI is turned on itself to flag suspected or apparent mislabeled data, to identify and clean datasets, remove suspected noise, and improve performance. Having BIG data is not good enough. Real-world data tends to be messy, noisy, and confounded. Ultimately, "noise" in the training and test sets (misdiagnosis, rare confounding variables) can removed so that the AI can be retrained and avoid learning the wrong things [39]. Combined with Federated Learning approaches, UDC can boost the performance of AI on diverse data [40].

In 2018, Carol Lynn Curchoe, PhD (ART Compass, AIVF) et al. noted a significant increase in AI abstracts at ASRM and ESHRE and a high variance in reporting (data types, sizes, accuracy, etc.) [41]. As our field grows, the challenges with AI Publication standards for reporting, acceptance criteria, risk of bias, and the availability of welltrained reviewers to quickly and accurately review AI-related work increase. Further, our EMRs were designed for billing and revenue generating activities. They are missing the features necessary to collect, structure, and access big data for fertility AIs, and there is no question that data entry and computational scientists will be part of the twenty-first century IVF care team [42]. Questions of authorship may arise, as the use of databases [43] grows, and in some cases, access to these data is sold for shares in private start-up companies. Additionally, while several checklists exist (TRIPOD, PROBAST, PRISMA), our field may benefit from convening a working group to establish a fertility-specific checklist that includes, for example, data annotations for repeated implantation failure, sibling embryos and oocytes, and clustered observations. It could combine the best elements of exiting checklists (presence of an item, with a measure of the quality of that item, and the risk of bias, plus a full description of these data) for publication standards, referees, and readers.

In lieu of a fertility-specific AI checklist, how we read AI papers is critical. Assaf Ben Meir, MD (Fairtility) led an insightful discussion on how biologists and clinicians can understand where the pitfalls and numerous biases in AI publications lie. The quality of AI research hinges on the scope of inclusion criteria, balance of data, sample size, and the performance metrics reported [44]. The so-called confusion matrix beautifully demonstrates in a single graph the classes predicted, true positive, false negative, false positive, true negative, precision, negative predictive value, sensitivity, specificity, and accuracy. The critical reader must consider the size and distribution of the dataset, how it was annotated, if there is "overfitting" of the model, and the transparency of the results.

Gerard Letterie, DO (Seattle Reproductive Medicine), could have continued along in the same vein by presenting his excellent AI compendium [45], "Three Ways of Knowing," and we, the audience, would have been greatly enriched in our understanding of AI manuscripts. However, he presented another pressing aspect, legacy decision-making [46] and smarter workflows [47], enabled by better decisions, analyzed, and adjusted in real time by AI systems. To adjust AI models optimally, we may need to actually reduce input and plumb the depths of what is necessary and sufficient (can we reduce our complex models to the one variable that is the driving force?).

Our technologies must make it to the market in order to help others. David Sable, MD gave a condensed masterclass on how to turn an idea into an "IPO" (initial public offering) and reminded us not to "make stuff up, to know our denominators, biology always wins, and to always tip the waitstaff well!" Pitching technology ideas, corporate communications and structures, funding cycles, and intellectual property protection are not necessarily in the wheel house of embryologists and REIs, and it takes strength in all of those elements to get funded.

The last session of the conference focused on AI Development. The embryologist plays an essential role in the evolution of technology and the implementation of "The Digital Future" in the IVF clinic. AI promises to make IVF safer, more accessible, and patient centric. We are tasked not to lose the emotional intelligence during the application and integration of AI technology to IVF patient care.

Occasionally, people fret that AI could "take our jobs." Borut Kovacic, PhD has a vision for the role of the embryologist in the high-tech lab of the future. The role of the clinical scientist has always evolved along with technology [48]. It has changed in the past and will certainly keep changing in the future. Embryologists do many more adjunct tasks than embryology. We organize the flow of work and manage the risk and quality of the lab, perform extraordinary procedures (IVM, TESE, IMSI), audit data, perform research, write abstracts and papers, grant applications, and mentor, teach, and train the new generations of embryologists.

We are all familiar with seeing reproductive tissues in two dimensions, using Hoffman Modulation Contrast or bright field microscopy. Timelapse incubator users can see embryos both over time and in two dimensions. Chloe He (PhD Student, Imperial College, London) is one of the new generation of scientists bringing new three-dimensional imaging technologies to embryology. Who knows what profound future insights may be gleaned from such technologies? Certainly, high-tech imaging is a foundational and rapidly advancing technology for our field [49]. How can the IVF lab prepare for a digital future? We are likely far from ready to accept and adapt these technologies into our labs. Marcos Messeguer, PhD (IVI, Valencia) is an expert at introducing and validating timelapse and AI technologies into a clinical workflow [50, 51]. Implementing a new technology requires an investment of time to learn (for example, preparing growth chambers for timelapse incubators) but can save a significant amount of time once proficiency is achieved (3 h of manual labor and observations to 6 min with automation). Internal correlation studies comparing new technologies (EMA Score) with the outcome measure of interest will give a high degree of confidence for clinical use [10].

Making IVF safer, accessible, and more patient-centric is a top goal of Charles Bormann, PhD (Massachusetts General Hospital). He noted that with just practicing 13,000 REIs in the USA and 50 completing fellowships per year, like all of healthcare in general, fertility is impacted by workforce shortages. There is debate in the field for how exactly to address this significant problem. Some suggestions, such as shortening the RE fellowship period and using "generalists" (if they really can be called that...) gynecologists and midlevel providers, but these are not ideal solutions. Just "one" solution probably does not exist; we need to tackle these problems from many angles. We must apply technology to solve the pain points and inefficiencies in fertility healthcare. Bormann and collaborators have created and validated AI-driven technologies to address accessibility and safety at almost every point in the IVF life cycle [52], from home semen analysis devices connected to mobile phones [53], to quality control and assurance in the IVF lab [54], to upending the current mode of "witnessing" embryos [55].

The application and integration of AI in fertility were presented by early adaptor of AI and technology for the IVF patient flow [56], Amber Cooper, MD (Kindbody). There are treatment "dropout hotspots" along every step of the patient flow, from becoming a new patient, to evaluation, diagnosis, and financial counseling, to successful transfer. The bulk of new IVF patients are now "digital natives": Millennials, Gen Z, and increasingly Gen Alpha. AI-driven technologies can turn treatment dropout hotspots into opportunities to engage. Virtual visits, consenting, medications education, and coping support to allay anxiety are opportunities to offer compassionate care and shared decision-making through technology.

The final talk of the meeting addressed mental health, perhaps one of the final frontiers in ART treatment. IVF and infertility are a major life crisis; the distress (depression, anxiety) felt by those suffering from infertility is equivalent or worse than cancer, divorce, or death of a family member. The risk for suicide in infertility patients is quite high; however, there are serious barriers to accessing mental healthcare for infertility [57]. Elizabeth Grill, PsyD (Weill Cornell) brings the patient's voice to the forefront of "emotional AI" research. Mobile health apps like Ferticalm and Fertistrong are putting a therapist in the pocket of the IVF patient to overcome challenges of access, cost, and psychological barriers to care. Virtual reality, mobile, and AI-driven chat bots and psychological tools can reduce patient drop out, increase pregnancy rates, provide coping strategies, and help IVF patients regain a sense of control.

Summary

The inaugural AI Fertility World Conference concluded with a call to create an AI Fertility Society that can take the lead in creating an ongoing international forum to discuss frameworks and validations; discuss ethical uses of AI, peer review, and publication standards; help inform decisions by national policymakers and others; formulate regulatory recommendations and guidelines; and promote coordination for key stakeholders (patients, startups, industry) and for robotics, automation, and integration with software.

Data availability Recordings of the AI Fertility oral presentations will be made available through the AI Fertility Society at https://aifertility.org/.

Declarations

Conflict of interest The author is a shareholder for ART Compass, an AIVF technology, a big data and artificial intelligence software platform for IVF lab management.

References

- Adamson GD, Dyer S, Chambers G, Ishihara O, De Mouzon J, Kupka M, et al. O-151 ICMART preliminary world report 2018. Hum Reprod. 2022;37.
- Hajirasouliha I, Elemento O. Precision medicine and artificial intelligence: overview and relevance to reproductive medicine. Fertil Steril. 2020;114:908–13.
- Hariton E, Sable D. SUMMIT:IVF discussing the future of assisted reproduction. F S Rep. 2020;1:54–5.
- Munne S, Alikani M, Ribustello L, Colls P, Martinez-Ortiz PA, McCulloh DH, et al. Euploidy rates in donor egg cycles significantly differ between fertility centers. Hum Reprod. 2017;32:743–9.
- Coates A, Bankowski BJ, Kung A, Griffin DK, Munne S. Differences in pregnancy outcomes in donor egg frozen embryo transfer (FET) cycles following preimplantation genetic screening (PGS): a single center retrospective study. J Assist Reprod Genet. 2017;34:71–8.
- Guzman L, Nunez D, Lopez R, Inoue N, Portella J, Vizcarra F, et al. The number of biopsied trophectoderm cells may affect pregnancy outcomes. J Assist Reprod Genet. 2019;36:145–51.

- Costa-Borges N, Giralt G, Albó E, Alvarez A, Ramos J, Hernandez I, et al. O-122 ICSI in a box: development of a successful automated sperm injection robot with external supervision and minimal manual intervention. Hum Reprod. 2021;36.
- Fjeldstad J, Mercuri N, Meriano J, Krivoi A, Campbell A, Smith R, et al. O-204 Non-invasive AI image analysis unlocks the secrets of oocyte quality and reproductive potential by assigning 'Magenta' scores from 2-dimensional (2-D) microscope images. Hum Reprod. 2022;37.
- Mendizabal-Ruiz G, Chavez-Badiola A, Aguilar Figueroa I, Martinez Nuno V, Flores-Saiffe Farias A, Valencia-Murilloa R, et al. Computer software (SiD) assisted real-time single sperm selection associated with fertilization and blastocyst formation. Reprod Biomed Online. 2022;45:703–11.
- Lorena Bori PD, Daniella Gilboa M, Ron Maor B, Thamara Viloria P, Ilya Kottel B, Seidman DS, et al. Could the EMA ertificial neural network grade blastocysts as an embryologist? In: ASRM: Fertility and Sterility; 2021. p. E84.
- 11. Marcos Meseguer P, Ron Uriel Maor B, Lucia Alegre P, Raquel Del Gallego P, Antonio Pellicer M, Seidman DS, et al. Automated halo identification: a novel predictive feature for IVF success identified through an artificial intelligence (AI) algorithm. In: ASRM: Fertility and Sterility; 2019. p. E157.
- Meseguer Estornell F, Bori L, Maor R, Kottel I, Gilboa D, Seidman D, et al. O-085 In-depth analysis of embryo development: Differences among monosomic, trisomic and chromosomally chaotic embryos compared to euploid embryos. Hum Reprod. 2021;36.
- 13. Daniella Gilboa M, Seidman DS, Liron Kedar M, Ron Maor B, Ilya Kottel B, Goldberg JM, et al. Blastocyst "pumping" is a detrimental feature predicting implanation failure: highly accurate assessmet by computer analysis of time-lapse videos. In: ASRM: Fertility and Sterility; 2021. p. E181.
- Meseguer M, Bori L, Ron Maor B, Liron Kedar M, Desai N, Daniella Gilboa M, et al. Can computer vision algorithms noninvasively recognize aneuploidy in blastocysts?: "Pumping" appears to be a strong predictive feature. In: ASRM: Fertility and Sterility; 2021. p. E153.
- Lorena Bori PD, Ron Maor B, Fernando Meseguer P, Ilya Kottel B, Daniel S. Seidman, Daniella Gilboa M et al. Artificial intelligence is moving closer to reproductive medicine: prediction of blastulation and embryo implanation In: ASRM: Fertility and Sterility; 2021. p. E154.
- Jenkins J, van der Poel S, Krussel J, Bosch E, Nelson SM, Pinborg A, et al. Empathetic application of machine learning may address appropriate utilization of ART. Reprod Biomed Online. 2020;41:573–7.
- Choi B, Bosch E, Lannon BM, Leveille MC, Wong WH, Leader A, et al. Personalized prediction of first-cycle in vitro fertilization success. Fertil Steril. 2013;99:1905–11.
- Ploschner M, Denkova D, De Camillis S, Das M, Parker LM, Zheng X, et al. Simultaneous super-linear excitation-emission and emission depletion allows imaging of upconversion nanoparticles with higher subdiffraction resolution. Opt Express. 2020;28:24308–26.
- Lee HJ, Ko T, Park JH, Kim HM, Woo S. Deep ensembles-based AI as a tool to support embryo grading and clinical pregnancy prediction. Hum Reprod. 2022;37.
- Lee H, Woo S, Park JH, Jung J, Ko T, Choi S, et al. Deep learning algorithms using embryo morphology can more accurtaly predict gestational sac (G-SAC) than fetal heartbeat possibly due to non embryo factors. ASRM: Fertility and Sterility. 2022;(Supplement):E114–E5.
- Ko T, Lee H, Jung J, Park JH, Kim HM, Woo S, et al. Generation of big data for fertility treatment at the national level in South Korea. ASRM: Fertility and Sterility. 2022;(Supplement):E262–E3.

- 22. Kundu S. AI in medicine must be explainable. Nat Med. 2021;27:1328.
- Zhan Q, Sierra ET, Malmsten J, Ye Z, Rosenwaks Z, Zaninovic N. Blastocyst score, a blastocyst quality ranking tool, is a predictor of blastocyst ploidy and implantation potential. F S Rep. 2020;1:133–41.
- Berntsen J, Rimestad J, Lassen JT, Tran D, Kragh MF. Robust and generalizable embryo selection based on artificial intelligence and time-lapse image sequences. PLoS One. 2022;17:e0262661.
- 25. Ueno S, Berntsen J, Ito M, Uchiyama K, Okimura T, Yabuuchi A, et al. Pregnancy prediction performance of an annotation-free embryo scoring system on the basis of deep learning after single vitrified-warmed blastocyst transfer: a single-center large cohort retrospective study. Fertil Steril. 2021;116:1172–80.
- 26. Shafiee H, Kanakasabapathy MK, Bormann C. Digitising the human embryo. The Lancet. 2022;400:1577.
- Bormann CL, Kanakasabapathy MK, Thirumalaraju P, Gupta R, Pooniwala R, Kandula H, et al. Performance of a deep learning based neural network in the selection of human blastocysts for implantation. Elife. 2020:9.
- Kanakasabapathy MK, Thirumalaraju P, Kandula H, Doshi F, Sivakumar AD, Kartik D, et al. Adaptive adversarial neural networks for the analysis of lossy and domain-shifted datasets of medical images. Nat Biomed Eng. 2021;5:571–85.
- Sanders KD, Silvestri G, Gordon T, Griffin DK. Analysis of IVF live birth outcomes with and without preimplantation genetic testing for aneuploidy (PGT-A): UK Human Fertilisation and Embryology Authority data collection 2016-2018. J Assist Reprod Genet. 2021;38:3277–85.
- Papatheodorou A, Gilboa D, Seidman D, Oraiopoulou C, Karagianni M, Papadopoulou MI, et al. P-197 Successful implementation of an end-to-end artificial intelligence (AI) platform in a busy IVF clinic: A prospective observational study. Hum Reprod. 2022;37.
- Diakiw SM, Hall JMM, VerMilyea MD, Amin J, Aizpurua J, Giardini L, et al. Development of an artificial intelligence model for predicting the likelihood of human embryo euploidy based on blastocyst images from multiple imaging systems during IVF. Hum Reprod. 2022;37:1746–59.
- Diakiw SM, Hall JMM, VerMilyea M, Lim AYX, Quangkananurug W, Chanchamroen S, et al. An artificial intelligence model correlated with morphological and genetic features of blastocyst quality improves ranking of viable embryos. Reprod Biomed Online. 2022;45:1105–17.
- Khosravi P, Kazemi E, Zhan Q, Malmsten JE, Toschi M, Zisimopoulos P, et al. Deep learning enables robust assessment and selection of human blastocysts after in vitro fertilization. NPJ Digit Med. 2019;2:21.
- 34. De Gheselle S, Jacques C, Chambost J, Blank C, Declerck K, De Croo I, et al. Machine learning for prediction of euploidy in human embryos: in search of the best-performing model and predictive features. Fertil Steril. 2022;117:738–46.
- 35. Fernandez Sanchez M, Visnova H, Larsson P, Yding Andersen C, Filicori M, Blockeel C, et al. A randomized, controlled, firstin-patient trial of choriogonadotropin beta added to follitropin delta in women undergoing ovarian stimulation in a long GnRH agonist protocol. Hum Reprod. 2022;37:1161–74.
- 36. Witz CA, Daftary GS, Doody KJ, Park JK, Seifu Y, Yankov VI, et al. Randomized, assessor-blinded trial comparing highly purified human menotropin and recombinant follicle-stimulating hormone in high responders undergoing intracytoplasmic sperm injection. Fertil Steril. 2020;114:321–30.
- 37. Robins JC, Khair AF, Widra EA, Alper MM, Nelson WW, Foster ED, et al. Economic evaluation of highly purified human menotropin or recombinant follicle-stimulating hormone for controlled ovarian stimulation in highresponder patients: analysis

of the Menopur in Gonadotropin-releasing Hormone Antagonist Single Embryo Transfer-High Responder (MEGASET-HR) trial. F S Rep. 2020;1:257–63.

- 38. Anand IS, Carson P, Galle E, Song R, Boehmer J, Ghali JK, et al. Cardiac resynchronization therapy reduces the risk of hospitalizations in patients with advanced heart failure: results from the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial. Circulation. 2009;119:969–77.
- Dakka MA, Nguyen TV, Hall JMM, Diakiw SM, VerMilyea M, Linke R, et al. Automated detection of poorquality data: case studies in healthcare. Sci Rep. 2021;11:18005.
- 40. Nguyen TV, Dakka MA, Diakiw SM, VerMilyea MD, Perugini M, Hall JMM, et al. A novel decentralized federated learning approach to train on globally distributed, poor quality, and protected private medical data. Sci Rep. 2022;12:8888.
- Curchoe CL, Bormann CL. Artificial intelligence and machine learning for human reproduction and embryology presented at ASRM and ESHRE 2018. J Assist Reprod Genet. 2019;36:591–600.
- 42. Curchoe CL. The paper chase and the big data arms race. J Assist Reprod Genet. 2021.
- 43. Curchoe CL, Tarafdar O, Aquilina MC, Seifer DB. SART CORS IVF registry: looking to the past to shape future perspectives. J Assist Reprod Genet. 2022;39:2607–16.
- 44. Cimadomo D, Soscia D, Casciani V, Innocenti F, Trio S, Chiappetta V, et al. How slow is too slow? A comprehensive portrait of Day 7 blastocysts and their clinical value standardized through artificial intelligence. Hum Reprod. 2022;37:1134–47.
- 45. Letterie G. Three ways of knowing: the integration of clinical expertise, evidence-based medicine, and artificial intelligence in assisted reproductive technologies. J Assist Reprod Genet. 2021.
- 46. Letterie G, Mac DA. Artificial intelligence in in vitro fertilization: a computer decision support system for day-to-day management of ovarian stimulation during in vitro fertilization. Fertil Steril. 2020;114:1026–31.
- 47. Letterie G, MacDonald A, Shi Z. An artificial intelligence platform to optimize workflow during ovarian stimulation and IVF: process improvement and outcome-based predictions. Reprod Biomed Online. 2022;44:254–60.
- Gianaroli L, Veiga A, Gordts S, Ebner T, Woodward B, Plas C, et al. ESHRE certification of ART centres for good laboratory and clinical practice. Hum Reprod Open. 2022;(2022):hoac040.

- Gill ME, Quaas AM. Looking with new eyes: advanced microscopy and artificial intelligence in reproductive medicine. J Assist Reprod Genet. 2022. https://doi.org/10.1007/ s10815-022-02693-9.
- Paya E, Bori L, Colomer A, Meseguer M, Naranjo V. Automatic characterization of human embryos at day 4 post-insemination from time-lapse imaging using supervised contrastive learning and inductive transfer learning techniques. Comput Methods Programs Biomed. 2022;221:106895.
- Bori L, Meseguer F, Valera MA, Galan A, Remohi J, Meseguer M. The higher the score, the better the clinical outcome: retrospective evaluation of automatic embryo grading as a support tool for embryo selection in IVF laboratories. Hum Reprod. 2022;37:1148–60.
- 52. Dimitriadis I, Zaninovic N, Badiola AC, Bormann CL. Artificial intelligence in the embryology laboratory: a review. Reprod Biomed Online. 2022;44:435–48.
- Kanakasabapathy MK, Sadasivam M, Singh A, Preston C, Thirumalaraju P, Venkataraman M, et al. An automated smartphonebased diagnostic assay for point-of-care semen analysis. Sci Transl Med. 2017:9.
- 54. Bormann CL, Curchoe CL, Thirumalaraju P, Kanakasabapathy MK, Gupta R, Pooniwala R, et al. Deep learning early warning system for embryo culture conditions and embryologist performance in the ART laboratory. J Assist Reprod Genet. 2021.
- 55. Cherouveim P, Jiang VS, Kanakasabapathy MK, et al. Quality assurance (QA) for monitoring the performance of assisted reproductive technology (ART) staff using artificial intelligence (AI). J Assist Reprod Genet. 2022. https://doi.org/10.1007/ s10815-022-02649-z.
- Cooper AR. Intravaginal embryo culture: a successful alternative to standard IVF that may improve access to care. Curr Opin Obstet Gynecol. 2022;34:179–83.
- 57. Grill E. Role of the mental health professional in education and support of the medical staff. Fertil Steril. 2015;104:271–6.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.