



# ACE NEWSLETTER

ACADEMY OF CLINICAL EMBRYOLOGISTS

Volume 15

September 2022



Artist : Emb Arathy P Sudhar

## MESSAGE FROM THE PRESIDENT



Greetings from Academy of Clinical Embryologists, India.

We started ACE a decade ago, with the dream of having a society for us embryologists – a society that would take care of our growth and continued improvement; a society that will harbor a feeling of brotherhood amongst us; a society that will get us the recognition that is due to all of us; a society that will fight for our rights when required.

As you all are aware, last year it had become very difficult to organize the in-person meetings. So we tried our best to continue to organize online events to share knowledge and experience with our members.. All the online programs were very well attended and appreciated by all the participants. In the last year, we have added more than 150 new members to our society. Today, the society has 725 members and it is increasing day by day. It was not possible without the support of my team members.

In view of third wave of covid, as a responsible society we organized our International Conference ACE Kolkata 2021 online, which was planned in-person earlier. It was attended by more than 1800 delegates from across the world. I would like to congratulate the Local organizing committee ACE Kolkata headed by Dr Gautam Khastgir and Dr Ratna Chattopadhyay for organizing a very successful 9th international ACE Kolkata conference 2021.

Those we love can never be more than a thought away; for as long as there's a memory, they live on in our hearts. This year we lost three great scientists Dr Daniel Franken, Dr Patrick Quinn and Indian Reproductive medicine scientist, Teacher of teachers Dr B N Chakarborty. We all learned so many things by reading their books or listening them in conferences. We cannot forget their contribution in our field. ACE Team wishes them farewell in their journey to eternity. They'd never be forgotten, rest in peace.

After so many up and downs, finally the situation is slowly improving and we are moving from online to in person meetings. I know you all are very excited to meet each other and interact. ACE is coming up with 10th International ACE conference to be held in Delhi from 23<sup>rd</sup> Sept to 25<sup>th</sup> Sept 2022. Local organizing committee headed by Dr Gaurav Majumdar and myself invite you all to ACE Delhi 2022 conference. We assure you that it will be full of scientific knowledge.

Once again I congratulate team ACE for their hard work to bring out this newsletter. Special thanks to Dr Rajvi Mehta and Dr Sanjay Shukla for their hard efforts and guiding the enthusiasm of our young ACE members Dr Rahul Sen and Dr Sanketh Dhupal.

I am indebted to Zydus Health Care Ltd. for their support in the production of this newsletter and a special thanks to Mr. Deepak Mishra and his team for their effortless commitment towards us.

Thank you all

**Yours truly,**

**Dr Ved Prakash President, ACE**



## MESSAGE FROM THE SECRETARY

Since the beginning of this year, there have been lots of discussions and conversations regarding the new ART rules and we, the IVF community are at a crossroad. These regulations appear to be daunting only because for the last three decades, we did not have to adhere to any framework or answer to any authority. But this change would streamline IVF work and improve the quality, and this will also give our work international recognition. ACE, as your representative is all geared up to give the necessary information and support regarding ART rules during these trying times.

We are also getting ready for our annual conference and since this physical meeting is happening after three years, efforts are made to bring great scientific talent from across the world, so that all of us go back enriched with latest, proven, validated information in reproductive medicine. Sharing knowledge has been our primary motto, which you will also experience by reading our newsletter. This edition has articles on Y chromosome, news on interesting studies and details of presentations done by our embryologists in the recent times. Any field would progress only when dialogues are initiated and not by one way flow of information and so we welcome your thoughts and feedback on the content.

Thank you all,

**Sujatha Ramakrishnan**

**Secretary, ACE**

# ACE NEWSLETTER

Volume 15, September 2022

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Academic Chair

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Associate Editors

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**Sanketh Dhumal Satya**





## EDITORIAL

As we celebrate 10 years of ACE, it gives me a sense of joy and pride to see how our profession has grown. The credit for this goes to all the ACE members especially all the office bearers and committee members who have really worked hard over the years. As one of the very early embryologists in India, in an era where communication took place over mail and not e-mail and phone and not messages; where we attended conferences to “find out” who else shared our interests, there was a time when I personally knew more clinicians than embryologists. I often tried to get the names and contacts of their embryologists but failed in almost all instances. There was a time when I have even participated in a debate on “why a clinician cannot be the embryologist”. I even attempted to visit ART Clinics and requested the Clinicians to divulge the names of their embryologists, rather those who worked in the IVF laboratory, as the word embryology was barely used. The idea was to form a group to “discuss” about laboratory issues but the idea failed miserably as it was mis-read as wanting to create a “union.” However, with the advent of the nascent e-mail technology, few embryologists tried to get together to share concerns/ideas but we later moved in participating in email groups of that time - embryomail and ivf.net. I must admit that I was not persistent and gave up the idea of getting a group of embryologists together in India. Thus, more than a decade later, when ACE was formed, I was thrilled but I was still skeptical on how it would progress? Would the passion of the early founders continue? Would it motivate all to join and participate to share their knowledge and skills were the questions that came to mind? Or, would there be individual egos which would surface once the goal of the forming an organisation was completed?

The growth of ACE is phenomenal in terms of number of members, respect as well activities. With this strong foundation of ACE, it has a long long way to go not only in India but the world. Like true scientists, we need to be critical of our ourselves so that complacency does not set in and we retain the same zeal and passion with which the organization was formed. Happy 10th birthday to ACEians!

Regards

**Rajvi H Mehta**

## Ten years of ACE

[Voices of some of our Ex-Presidents]



**Charudutt Joshi**

***Can you give a background of embryologists status, position and interactions prior to the formation of ACE? What were the difficulties faced by embryologists then?***

When I started working in 1993, embryology and IVF was at a very preliminary state. There were very few embryologists at that time. It was not a recognized profession. When I saw a advertisement in the paper for reproductive biologists - I thought that I would qualify as I had studied reproduction and I was a biologist! It was unknown profession. So, even when I applied for a home loan and said that I was an embryologist - the question was - what is that? There is no such recorded profession! Even the clinicians felt that we ourselves can do this work and don't need an embryologists.

At that time, we did ALL the work from cleaning the laboratory to all the work. After 2005, there were more clinics and embryologists but they were often seen as people who took care of the laboratory. I think it was after 2007, many more centres came up and ICMR made guidelines. Then, people starting understanding the role of the embryologists.

ACE has played a very important role. It is Srinivas who gave the idea, the idea clicked, we spoke to a few people in one of the conferences; a few people got together and that is how the journey of ACE started. This is our 10th year and people still remember many of our conferences, workshops.



**Dr. Alex Varghese**

***How important for embryologists to consistently analyse their data?***

"In God we trust. All others must bring data." This famous quote, by W. Edwards Deming- The Guru of Quality management, refers mainly to the importance of data measurement and analysis when doing business. In IVF, like in business, the data analysis is equally important. Interestingly, keeping the data in IVF refers to everything related to "what one does with treatment, eggs, sperm and embryos". Data registry should be considered equally important from the embryology as well as the clinician's side, which helps in measuring the process outcomes, troubleshooting, analysing the data for research outputs etc.

***How can we motivate them to "look" at their data and publish observations and findings?***

Assisted reproduction labs are a gold mines of information if the data is kept meticulously and if embryologists are encouraged to do so and thereby delve into the various research activities and collaborations. Various workshops being organised by fertility societies in India on research methodologies are a welcome move. When the regulator comes with stringent codes of practice, it becomes a mandatory practice to maintain the data. Hence with the new ART regulations in India, we may see an upsurge and interest for a culture by fertility clinics to have an electronic medical record (EMR) keeping. This in turn may naturally evolve in establishing the fertility clinics in India a hub of robust data provided the guidance on quality data management is imbibed from now itself. Hence, ART Societies have an important role to play in this regard by organizing regional, interactive one-to-one workshops on data management. So, the door is open now for embryologists as fertility clinics can't get away from registering clinical data in an organised format like EMR. Grab the opportunity, get the best softwares for medical records, accumulate the data, mine the data, make collaborations with research institutes, publish your findings, show how well you perform compared to your peers...the list goes on. I would like to conclude again with a quote from Deming- "Without data you are just another person with an opinion" and we are moving into an era of data driven decision making (especially with the artificial intelligence platforms) not by the "opinion of an authority figure around us".



**Dr. Varsha Samson Roy**

***What is your view on the scientific contributions of Indian embryologists?***

From an era of no clear definition of an embryologist to accepting them as an important contributor in the field of ART, describing his/her roles & responsibilities ... Indian embryologists have come a long way. The earlier decades made learning the techniques/skill aspect very challenging, most were self trained by merely observing embryologists abroad . Inspite of

those many challenges, they continued to grow in knowledge & skill by sheer perseverance, contributing to making IVF accessible. The free lancing embryologists travelled to far inaccessible areas on very regular basis to perform the IVF procedures. However I must admit that we failed in keeping a scientific data/audit of our work. Whether it was due to lack of time or environment lacking research , we failed in documenting, auditing & publishing our vast experiences.

But the last couple of years we observe a sea change in this aspect with lot of embryologists presenting their original work at not only national level but internationally too. I am confident the future belongs to them.

### ***What do you think are the reservations?***

Today most of the IVF chains have a well defined hierarchical structure for embryologists . The reservations or insecurities related to this profession are probably few & less compared to the earlier times. This is a profession that requires both knowledge & skill. There is a learning curve to most of the procedures which may slightly vary from person to person. This requires practice, patience, good observational skills & attention to details. Though the Indian IVF scenario is bound to increase exponentially and this will fuel an increase in the professionals as well .However this growth may not be directly proportional to the financial aspirations of the individual. it will require more than just skill & knowledge for professional growth... empathy towards the patient, team building abilities, drive to keep oneself updated with the recent advances, acceptance and use of technology to its fullest will surely go a long way.

How can ACE assist or train our embryologists to contribute more to science and the subject of embryology?

The recently passed ART bill mandates a basic qualification for an embryologist which is a welcome change. But there are those vast majority, already practising embryology for many years without this qualification, hence ACE can play a major role by introducing a structured method for licensing the Clinical embryologists into different categories like many other organisations like ESHRE, ABB e tc. Thus being a certifying body for both those with the required qualifications & for those without it but practising embryology for many years.



**Dr. D. Swaminathan**

### ***Do you think ACE should do some programmes on the welfare of embryologists?***

Probably, YES! Since we completed 10 years of existence, as one among the largest professional societies ( Clinical Embryologists) in south east Asia, I think we have to come up with some programmes or schemes. In fact, I have done a personal survey recently , among our fraternity.

The out come was, as expected. After the new ART ACT 2021, we need some kind of legal shield so that the mind and hands which does a noble profession on earth, can be assured and carry out their responsibilities without fear with full confidence and pride.

Do they need some kind of support system considering an emergencies of calamities that they may face?

I am not sure, because the work and social environment may differ, an uniform support system may not work, as we assume. As I mentioned in my previous question, a supportive system, in general may be helpful. More over, we should initiate a recognizing or certification program from ACE , or by a separate independent forum to take things further, constructively. For example, embryologist's who wish to go out of india for job, he/she do not have any proof, of certification, from a registered professional society. This is must, and must be done at any cost. ESHRE certification is not government approved, yet it holds a value. I think we INDIANS should have a stringent certification process.

### ***What can be done beyond academics for embryologists?***

Intiate Research Attitude. We have huge data, we should make use of it. A well structured Continuous Skill Acquisition ( CSAP) Program could be a possibility. "Take care of YOU" (TCoY) , a must holistic health wellness program, could be introduced.

Yoga, Wellness programs along with Like minded organizations, on membership basis can be introduced, since, anything free, may not give any value. Now a days, everyone is health conscious, our fraternity lives in a controlled, closed environments ( most of time) would benefit from such specific wellness programs.

I will that all of you work with great zeal and pride.

**HAPPY EMBRYOLOGY,  
HAPPIEST EMBRYOLOGIST.**

## The Evolving World of IVF

- Dr. Charulata Chatterjee

Infertility is the failure to conceive after 12 months of regular and unprotected sexual intercourse and is estimated to affect around 8–12% of couples with reproductive age worldwide.[1] It has been estimated that 56% of couples have sought medical care including fertility related issues and treatment.[2] During 1978, the world witnessed the first major scientific breakthrough in the field of ART (Assisted Reproductive Technology) – the IVF, which stands for In Vitro Fertilization. On 25th July, renowned gynecologists Patrick Steptoe and Robert Edwards were successful in giving birth to the world's first test tube baby after an arduous journey of 102 iterative cycles– Louise Joy Brown, a healthy daughter to the proud couple – Lesley and Peter Brown.[3] The Second IVF and first from frozen-thawed-embryo baby, Durga alias Kanupriya Agarwal, was born in India on 3rd October 1978, by the legendary and visionary Dr Subhash Mukhopadhyay.[4] The first IVF baby was born as a result of cleavage stage fresh embryo transfer, now embryos are culture till day 5 and 6 at blastocyst stage and preferred for frozen embryo transfer to avoid the risk of OHSS- Ovarian Hyper Stimulation Syndrome.[5] The advanced method of cryo-preservation called vitrification has made the task easy for technologist to freeze the embryos.[6]

IVF had transformed itself from an alien concept to a widely acceptable and easily accessible one. With the help of state-of-the-art instruments, brilliant specialists driven by passion and powered by immaculate knowledge, this has helped couples to improve the probability of success to become parents. Despite these milestone developments, implantation failure still grapples our many researchers and out of many other reasons, chromosomal abnormalities is a matter of grave concern.[7] It is estimated that more than 50% of miscarriages are due to aneuploidy. [8] Recent studies have revealed that transfer of euploid embryos assessed through such advanced techniques as array comparative genomic hybridization (aCGH), next-generation sequencing (NGS) or qPCR based comprehensive chromosomal screening of trophoctoderm (TE) biopsies of blastocysts, [9] significantly improves implantation and ongoing pregnancy rates, and decreases miscarriage rates. Such methods are also successfully applied for couple having any history of genetic disorder.

Again, a non-invasive method like genetic analysis from the spent media of embryo culture dish can help to identify a chromosomally normal embryo. [10] Advances have also been made in gamete and embryo culture as well as embryo transfer media.[11]

Andrological techniques have been upgraded from simple sperm preparation to advanced sperm preparation like Magnetic Activated Cell Sorting – MACS and Microfluidics. Many other Sperm Function Test are either ready to use in lab or under research for checking the fertility potential of the sperm. [12]

Conventional morphological selection of embryos has been found to have limited value in predicting the developmental competency of embryos. Hence all the milestone of developing embryos plays a major role in embryo selection.[13]

Time lapse technology can analyze embryos based on its developmental stages.

Many ancillary treatments to improve the outcomes have been applied for specific indications. Few of them are cumulus aided transfer, Artificial oocyte activation, polar body biopsy and co culture.[14]

Another significant achievement was intra cytoplasmic morphological sperm injection (IMSI) where sperm is visualized at 6600x magnification. [15] Advancements have also been made in case of instruments what we use in an IVF lab like triple gas incubators, spindle view, Laser, electronic witness system etc. [16]

Improvements to maintain Total Quality Management System has also come long way like HVAC - Heating, ventilation, and air conditioning for quality air for quality air, Digital temperature meter, VOC – Volatile Organic Compound meter, PH meter, alarm system and list is so on. [17]

Along with the advancements in technology, the importance of holistic fertility care can't be cornered. People now are inclined to go back to basics of learning a healthy lifestyle. A healthy body and stress-free mind definitely help in improving the success rate of the treatments.

Covid – A global pandemic changed everyone's lives and vision to see the fertility care. In this scenario, "Digitalization" outshined everything and became the blessing in disguise for everyone. As far as ART is concerned, the focus shifted majorly on patient's comfort. With so many options into mobile health apps, hospital digitalization, doctor-patient video consultations, fairly transparent protocols and systematic

procedures – this new “Virtual Care” became an overnight hit and are now a trend. Not only for patients it has now become mandatory for reproductive scientist as it made life easy in the lab, days are not far when ‘Lab on chip’ will be the fact. Considering its popularity among the patients, doctors and embryologists - we are sure that it is definitely here to stay for long!

### New ART bill - A revolution

Supporting this trend is the new ART Bill that promises high quality, regulation & transparency of fertility treatments to increase the effectiveness and health outcomes of ART treatments in India. ART rules has been made keeping in mind a patient’s perspective for emotional wellbeing, transparency of protocol and centralized data under the government of India.[20]

IVF has increased phenomenally in the recent years, mostly due to delayed childbearing, professional commitments and hectic lifestyle. With all these in place, there is little reason to believe that this trend will halt. And with all these positive improvements in technologies & policies of IVF industry, one can truly hope that the future of ART technologies in India will be promising!

### Article editor : Mr Ahwaan

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## Sperm Aneuploidy Testing (SAT)

**Dr. Pankaj Kaingade, Amar Nikam, D. Swaminathan, Gorakh Mandrupkar, Sachin Kulkarni**

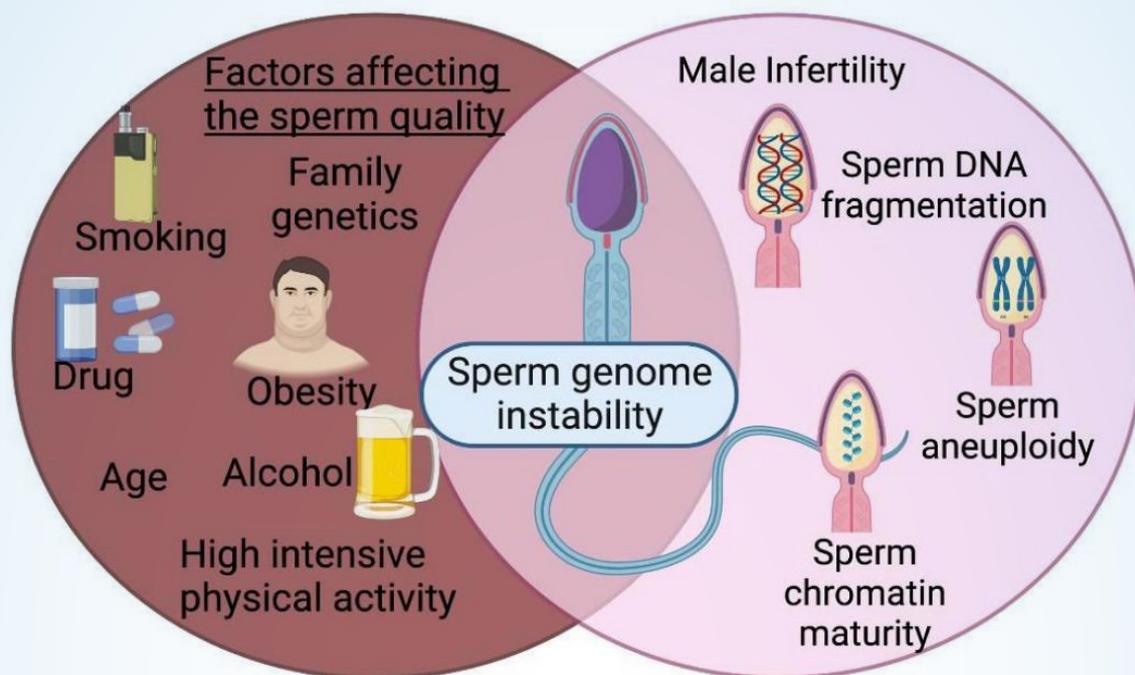
Since the 1970s, when human sperm was injected into hamster and mouse oocytes a developed system was used for karyotyping, where sperm aneuploidy screening has been performed to diagnose and determine treatment options for male factor infertility. Later, men with oligozoospermia, teratozoospermia, or translocations have been identified as a result of these studies and subsequent work with interphase chromosome analysis.

Sperm function deficiencies are frequently the result of spermatogenic defects. Spermatogenesis is a biologically complex and necessary process in which spermatogonia undergo meiotic recombination, genome reduction to a haploid state, and extensive cellular modifications, resulting in a motile cell competent for traversing the female reproductive tract, surviving various potential viability threats, and successfully fertilising a mature oocyte to give rise to an embryo. Defects in any stage of spermatogenesis can lead to male infertility, which affects about 5-7% of the population. An identification of infertility issues is frequently difficult for patients, leaving them with few treatment options, a large percentage of which rely on costly and emotionally exhausting assisted reproduction (ART). Male factors, alone or in conjunction with female factors, are responsible for about 50% of cases. In some cases, abnormalities in the male partner's sperm parameters are discovered. In many cases, the cause of decreased sperm parameters is unknown. Current male partner testing can only determine the underlying cause of infertility in about 20% of cases, leaving approximately 80% of male factor infertility unresolved. Semen parameter evaluation provides some basic information and may indicate the need for additional genetic testing (e.g., karyotyping, CFTR mutation analysis, and/or Y chromosome microdeletion analysis).

Fluorescence in situ hybridization is commonly used to detect sperm aneuploidy. The majority of studies have found similar results, namely: (1) all men produce aneuploid sperm; certain chromosomes are more prone to chromosome nondisjunction; (2) infertile men typically have significantly higher levels of sperm aneuploidy than controls; and (3) the level of aneuploidy is frequently correlated with the severity of infertility. Despite this, screening for sperm aneuploidy is rarely performed in an infertility clinic. There appears to be renewed interest in the clinical significance of sperm aneuploidy in recent years. It is very essential to investigate the gender differences in meiosis and why less emphasis is placed on the paternal contribution to aneuploidy. Immunofluorescence staining is commonly used in studies of chromosome pairing and meiotic recombination in males and females during the prophase I stage of meiosis. Fluorescent antibodies against SCP1 and SCP3 of the synaptonemal complex are typically used to detect proteins involved in homologous chromosome pairing, antibodies against MLH1 detect meiotic recombination sites, and CREST antibodies detect chromosome centromeres. FISH is a critical cytogenetic tool for detecting genetic abnormalities that have been used for decades by scientists and clinical diagnostic labs all over the world. If appropriate probes are chosen and implemented to relevant target cells or tissues, FISH has a high specificity and sensitivity. FISH has several key advantages: (1) it is relatively quick to perform, (2) it can be performed in interphase cells, eliminating the need for metaphase chromosomes, and (3) it can be multiplexed by using multiple fluorochromes up to five (or more when fluorochromes are used in combination), and (4) robust high-throughput automated systems exist for some FISH applications, allowing automated slide loading, image capture, and analysis with minimal user intervention. Because of these benefits, this immensely useful molecular cytogenetic tool is now widely used for a wide range of scientific and health diagnostic applications.

Furthermore, several studies have found a link between environmental factors and enhanced sperm aneuploidy frequencies. Smoking, benzene, air pollution, parabens, chemotherapy, polychlorinated biphenyl, and scrotal heating are just a few of the associations that have been reported. It is crucial to remember that such human studies are incredibly difficult to design, compare, and reproduce, and proving causation is extremely difficult given the vast number of confounding factors that occur in such studies. Furthermore, while the raises in sperm aneuploidy identified in the above-said studies are significant, they infrequently reach the levels seen in infertile patients. Nonetheless, mounting evidence points to a link between advanced paternal age and a higher likelihood of single-gene and multifaceted abnormalities (e.g., achondroplasia, down syndrome, apert syndrome, autism, and schizophrenia amongst others).

Despite the need for new procedures and strategies for male factor infertility, the field must proceed with caution before implementing new tests. Any new test or medical approaches must be thoroughly validated, with special consideration given to patient phenotypes. The greater standard of heterogeneity in male infertility phenotypes is frequently overlooked, but it is critical in determining which patients will benefit, not only from new tests and therapeutic interventions. The clinically effective implementation of any tests will also necessitate a shift in attitude among many clinicians and embryologists, away from the belief that “you just need any sperm” and toward the realisation that the paternal genome contributes more to early embryogenesis and IVF outcomes than is currently recognised through the vast majority of the scientific community.



**Fig- The factors influencing the sperm genome instability**

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# Artificial Intelligence in Human Embryo Selection:

## The Use, The Misuse & The Disuse!

- Dr Bindu Chimote

Application of Technology to our knowledge of science, offers us with a wide variety of alternatives to further enhance our understanding and to promote innovation in science. However, while doing so, we must bear in mind that technology should not become an overpowering tool to increase the gap between our emotional intelligence and the intellectual intelligence.

- Kevin Kelly,

Excerpt from 'What Technology Wants'

### Introduction

Use of technology in reproductive biology, especially in the field of in vitro fertilization (IVF), has been such a boon that the procedure itself is called Assisted Reproductive 'Technology'. The sophisticated treatment regimens now available using IVF technique has helped countless childless couples realize their dream of parenthood; in the process, not only imparting hope and happiness, but also consolidating their social and psychological bearing.

The current focus of investigation in IVF revolves around evaluation and selection of morphologically and genetically the best embryo for transfer leading to birth of a healthy baby. Conventionally, morphological evaluation methods are used to select the best embryo for transfer. However, these static, fixed time frame evaluation methods are plagued by bias, subjectivism, intra/inter- observer inconsistency as well as inter-centre disparity. Consequently, newer technological devices like time-lapse monitoring systems were introduced to assess the morphokinetic behaviour of embryos in real time. The dynamic morphokinetic system is still being explored as there can be infinite number of predictive parameters. These methods are often coupled with the OMICS approach whereby the proteome, genome, transcriptome, metabolome, secretome profile of embryos is examined in culture fluids or the micro-environmental milieu. The ocular, kinetic and metrical methods can be used in conjunction to effectively facilitate selection of that single embryo with the highest implantation potential. To further polish the selection process and obviate any ambiguity, latest techno-tools using computer based algorithms are being marketed to allow automated embryo selection. These systems employ artificial intelligence, whereby the natural human intelligence is simulated by using computer software. The entire effort is driven towards designing of an unbiased, universal and reproducible prediction model.

Human Intelligence (HI) and Artificial Intelligence (AI)

HI is a quality that helps humans in learning, understanding and solving problems with brilliant ideas by using content memory and thinking. This is because humans have thought, intuition, perception, logic and reason. Their analytical, assimilative and cognitive power helps humans draw inference. Most importantly, humans have the communicative skills that make them realize and rectify their mistakes. AI is something that mimics human beings by the information that is received, using built-in instructions, designed by scientists. AI, as the name suggests, is artificial, little and temporary, created by humans. This man-made machine has no heart and mind of its own to learn from or rectify any errors. Eventually, behind each such AI software is a powerful human mind. Nevertheless, in the 21st century, AI is evolving to be superior to humans in many tasks, which makes it seem that we are ready to outsource our intelligence to technology. The question of whether AI will replace human workers assumes that AI and humans have the same qualities and abilities, an answer only time will tell!

### AI in Human Embryo selection: The Use

Artificial Intelligence Algorithm does away with human derived subjectivity and variability. It offers an unbiased, automated embryo assessment/grading by compiling a huge amount of data generated after processing a neural network of a plethora of embryo images. Most softwares ascribe a score to each of the evaluated parameters and give a Known Implantation Data KIDScore. The advantages of AI include instant evaluation and accurate and consistent predictions for e.g. it can assess how many cells were actually used to form the inner cell mass (ICM). Among the best Predictive softwares is STORK framework based on Google's inception model.

It is necessary to understand exactly how researchers test their algorithms before drawing conclusions from headline statistics. Jørgen Berntsen et al 2022 (1) retrospectively evaluated a huge data set generated from transfer of 14,644 KID embryos across 18 IVF centres. Their fully automated, deep learning prediction model iDAScore v1.0 correlated positively with blastocyst grades (AUC 0.63-0.69), ruled out any inter-/intra-observer prejudices since it did not involve assessment by Embryologist and performed at par with any hi-tech up-to-date manual method of embryo selection.

In an earlier study, Khosravi et al 2019 (2) retrospectively applied AI algorithm to embryos that had been graded manually by embryologists into good, fair and poor quality. Their algorithm could differentiate the good from poor quality embryos with 96.94% efficiency. Although it performed better than the individual embryologist scoring, it could not effectively distinguish between the 'fair' and good or poor. This AI system thus has limited application if the goal is to select the best from a whole cohort of similarly graded embryos. Similarly, Tran et al 2019 (3) used IVY model to evaluate the likelihood of an embryo to cause a fetal heart (FH) pregnancy on a scale of 0-10. Although their AUC was a promising 0.93; the embryos on which their system was tested were of such poor quality that they would have been easily discarded by embryologists. Thus the clinical usability of such an algorithm is not feasible. Furthermore, it is an uphill task to leverage the enormous amount of information generated, to make predictions. For e.g. the AI system may predict whether an embryo has a potential to produce live birth or not. However, it may not be able to comprehend and assimilate non-embryonic factors like age, health of mother etc. that can influence a live birth.

Many AI studies for embryo selection use uninterpretable "black-box" machine learning (ML) models. These models are either too complicated for any human to understand or they are proprietary; each explanation may lead to varied interpretations. Clinicians therefore may find it cumbersome to juggle through data containing unfamiliar technical jargon. It would also be necessary to segregate the data and identify patient populations for whom the model might be applicable. Additionally, relevance of ML models is dependent not only on predictive parameters but also on the risks, advantages and consequences associated with embryo evaluation. So, pertinently, are we AI literate enough to comprehend such models?

## **Ethical Concerns**

The foremost deterrent to use of AI is that improper assimilation and comprehension of data may lead to misinterpretations that may potentially harm the patient interests. Skewed sex ratio or racial/ethical biases and effect on health and well being of the child thus born, cannot be ruled out. Most importantly, since AI rather than clinician/embryologist is the entity that decides which embryo has to be selected; it is not clear who would be held responsible and accountable in case of any legal dispute that may arise.

The primary question remains, does AI really interpret the reported results from scientific and practical perspectives? Major drawbacks associated with studies till date are small sample size, imbalanced data sets, limited performance metrics and lack of robust, prospective, published clinical trials affirming clinical effectiveness, thereby limiting widespread implementation of these systems (4,5). Long term follow-up and validation of the AI system used is necessary to maintain equipoise with other manual evaluation methods.

### **AI: The Misuse**

Lack of conclusive evidence-based research in the field leaves it wide open for marketing gimmickry as an 'add-on' option to IVF treatment. Since each prediction model has its own way of data interpretation (or the lack of it) depending on the subsidiary information apart from embryo images fed into the system; it leaves a lot of room for manipulation especially by pharmaceutical companies. They may propose an ecosystem where only a specific combination of incubators or specific drugs for stimulation or culture media may provide desired results. This may not only cause interference with standard clinical protocols, but also impart a lot of economic power to the pharma industry.

### **AI: The Disuse**

Using such models would force the embryologist to abrogate decision-making to programs they themselves do not understand. Since the reasoning power of these applications cannot yet be evaluated, laying trust in AI may lead to faulty decision making. Qualified embryologists, who are otherwise adept at real time troubleshooting, may feel helpless and reduced to mute spectators, due to lack of error checking mechanism in AI.

## Conclusion

Technology has undoubtedly helped us immensely in understanding several life processes. Technology has tremendous power and is here to stay. But while we have to constantly upgrade ourselves with the latest gadgetry, we cannot let technology overpower us. We have to be discreet in our use of technological tools. Eventually, we have to bear in mind, that we are dealing with and helping create human life! Artificial Intelligence can indeed be an additional tool for embryo assessment and selection, but it should not be a replacement to man. To conclude, in the words of Elbert Hubbard “One machine can do the work of 50 ordinary men, but no machine can ever do the work of one extraordinary man”.

## References

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## Journal Club

### Human Eggs stay healthy for decades by putting their ‘batteries on standby mode.’

- Sanketh Dhumal Satya

Human primordial oocytes are formed during fetal development and remain dormant in the ovary for up to 50 years. Like all the eukaryotic cells, oocytes have thousands of mitochondria which act as batteries that generate the energy for the needs of the cell. Despite a long period of dormancy, oocytes retain the ability to give rise to a new organism after fertilization, so what could be a reason for this long-term survival of the oocytes without undergoing a wear and tear?

A while ago, researchers discovered a landmark paradigm of how the reproductive cells have adapted throughout an evolution. “Humans are born with a predetermined supply of egg/ovum cells they have for a lifetime. As humans are also one of the longest-lived terrestrial mammals, egg cells must maintain unaltered conditions while avoiding decades of wear-and-tear. This condition is well attained by skipping a fundamental metabolic reaction which is also the primary source of damage to the cell. It is like putting batteries on standby mode as a long-term maintenance strategy.

This rare and unconventional behaviour of early-stage oocytes is achieved by turning off the activity of the complex protein and the enzyme known as “COMPLEX 1.” which acts as a gatekeeper that initiates the reactions to generate the energy in the mitochondria. Complex I is the first of five mitochondrial complexes that carry out a multi-step process called oxidative phosphorylation, through which cells derive much of their energy.

One of the fundamental reasons for shutting down the activity of complex 1 is to keep away from the production of Reactive Oxygen Species (ROS). As we know, excess cellular levels of ROS cause damage to proteins, nucleic acids, lipids, membranes and organelles, which can lead to activation of cell death processes such as apoptosis.

They have shown that dormancy involves survival with an inactive mitochondrial complex I. By shutting down complex-I and keeping the rest of the OXPHOS system active, early oocytes keep their mitochondria polarized enough to support the synthesis of haem, essential amino acids and nucleotides, while at the same time keeping their activity low to avoid ROS. Other quiescent cells, such as neuronal and haematopoietic stem cells, exhibit similarly low ROS levels, and reduced ETC activity, raising the possibility that other cell types might utilize this regulatory mechanism.

These findings also clarify why patients with complex-I-related hereditary mitochondrial diseases do not experience subfertility. Complex-I suppression represents an evolutionarily conserved strategy that allows longevity while maintaining biological activity in long-lived oocytes and thus paving the path for extended reproductive age of the female in particular and the species in general.

Rodríguez-Nuevo *et al.* Oocytes maintain ROS-free mitochondrial metabolism by suppressing complex I. *Nature* 607, 756–761 (2022). <https://doi.org/10.1038/s41586-022-04979-5>

## News to Ponder About:

### **ICSI vs conventional IVF cIVF in patients with non-male factor infertility.**

Iwamoto et al., *Fertil Steril*, July 2022. <https://doi.org/10.1016/j.fertnstert.2022.06.009>

The cumulative live birth rates (CLBRs) and cost effectiveness of ICSI and cIVF for non-male factor infertility was compared in a total of 46,967 patients with non-male factor infertility with autologous oocyte retrieval cycle between January 2014 and December 2015.

Among cycles without PGT-A in patients with non-male factor infertility, the CLBR was 60.9% for ICSI cycles vs. 64.3% for cIVF cycles, a difference that was not significantly different after adjustment for covariates (adjusted risk ratio, 0.99; 95% confidence interval, 0.99–1.00). With PGT-A, no difference in CLBR was found between ICSI and cIVF cases after adjustment (64.7% vs. 69.0%, respectively; adjusted risk ratio, 0.97; 95% confidence interval, 0.93–1.01)

**Editors note: Is it time to stop “ICSI for All.”**

### **Synthetic embryos complete gastrulation to neurulation and organogenesis**

Amadei et al., *Nature* (2022). <https://doi.org/10.1038/s41586-022-05246-3>

The authors have created embryos from embryonic stem cells by their interaction with extraembryonic stem cells, including trophoblast stem cells (TSCs), extraembryonic endoderm stem cells (XEN), and inducible-XEN cells (iXEN). They showed that they could recapitulate whole natural mouse embryo development in utero to day 8.5. The embryonic model displayed head-folds with defined forebrain and midbrain regions and develops a beating heart-like structure, a trunk comprising a neural tube and somites, a tail bud containing neuromesodermal progenitors, a gut tube, and primordial germ cells. This complete embryo model develops within an extra-embryonic yolk sac that initiated blood island development. The study demonstrates the self-organization ability of embryonic and two types of extra-embryonic stem cells to reconstitute mammalian development through and beyond gastrulation to neurulation and early organogenesis.

## TIMELINE FOR ART & SURROGACY (REGULATION) ACT, 2021

ART (REGULATION) BILL, 2020 FIRST INTRODUCED IN LOK SABHA	<b>14<sup>TH</sup> SEPTEMBER, 2020</b>
STANDING COMMITTEE REPORT PREPARED BY FAMILY & HEALTH WELFARE, NEW DELHI	<b>19<sup>TH</sup> MARCH, 2021</b>
ART (REGULATION) BILL, 2020 PASSED BY LOK SABHA	<b>01<sup>ST</sup> DECEMBER, 2021</b>
ART (REGULATION) BILL, 2020 PASSED BY RAJYA SABHA	<b>08<sup>TH</sup> DECEMBER, 2021</b>
ART (REGULATION) BILL, 2020 RECEIVED ASSENT FROM THE PRESIDENT OF INDIA	<b>18<sup>TH</sup> DECEMBER, 2021</b>
ART (REGULATION) ACT 2021 PUBLISHED BY THE AUTHORITY ON THE GAZETTE OF INDIA	<b>20<sup>TH</sup> DECEMBER, 2021</b>
SURROGACY (REGULATION) BILL RECEIVED ASSENT FROM THE PRESIDENT OF INDIA	<b>25<sup>TH</sup> DECEMBER, 2021</b>
ART & SURROGACY (REGULATION) ACT 2021 NOTIFIED ON THE GAZETTE OF INDIA BY DEPARTMENT OF HEALTH & RESEARCH (act came into force)	<b>25<sup>TH</sup> JANUARY, 2022</b>
NOTIFICATION BY THE CENTRAL GOVERNMENT FOR THE NATIONAL ART & SURROGACY REGISTRY (with operational effects from)	<b>22<sup>ND</sup> APRIL, 2022</b>
NOTIFICATION BY THE CENTRAL GOVERNMENT FOR THE COMPOSITION OF NATIONAL & STATE BOARDS FOR BOTH ACTS	<b>04<sup>TH</sup> MAY, 2022</b>
MODIFICATIONS RECEIVED FROM MINISTRY OF HEALTH & FAMILY WELFARE ON SURROGACY (REGULATION) ACT 2021, PUBLISHED BY AUTHORITY ON GAZETTE OF INDIA	<b>17<sup>TH</sup> JUNE, 2022</b>
MODIFICATIONS RECEIVED FROM MINISTRY OF HEALTH & FAMILY WELFARE ON ART (REGULATION) ACT 2021, PUBLISHED BY AUTHORITY ON GAZETTE OF INDIA	<b>21<sup>ST</sup> JUNE, 2022</b>

## ART & SURROGACY (REGULATION) ACT 2021 APPROPRIATE AUTHORITY AND BOARD IN INDIA

### List of Boards & Appropriate Authority Formed (as of 20th September)

Division/ states	Board	Appropriate authority	Date of formation
NATIONAL	YES	-NA-	04.05.2022
RAJASTHAN	-NA-	YES	08.08.2022
HARYANA	-NA-	YES	23.07.2022
MANIPUR	YES	YES	14.07.2022
GOA	-NA-	YES	05.08.2022
MAHARASTRA	YES	YES	13.07.2022
ANDHRA PRADESH	YES	YES	11.07.2022
WEST BENGAL	YES	YES	06.07.2022
MIZORAM	YES	YES	10.03.2022
KERALA	-NA-	YES	20.06.2022
ARUNACHAL PRADESH	YES	YES	01.07.2022
TAMIL NADU	-NA-	YES	07.06.2022
ODISHA	YES	YES	04.06.2022
TELANGANA	YES	YES	15.06.2022
MADHYA PRADESH	YES	YES	26.05.2022
PUNJAB	YES	YES	12.05.2022
CHATTISGARH	YES	-NA-	18.04.2022
KARNATKA	YES	YES	08.08.2022
NAGALAND	YES	-NA-	27.07.2022
HIMACHAL PRADESH	YES	YES	14.09.2022
MEGHALAYA	YES	YES	31.08.2022
CHANDIGARH	-NA-	YES	3.8.2022
ANDAMAN & NICOBAR ISLANDS	-NA-	YES	9.9.2022
GUJARAT	-NA-	YES	25.08.2022
JHARKHAND	YES	YES	25.8.2022

Compiled by - DR RAHUL SEN

## INDIANS at ESHRE

### Eshre certified Embryologists

#### Senior Category

Doel Bose  
Bharat Harpude

#### Clinical Category

Mateshwari Govindarajan  
Raj Priya Pandian  
Prashant Patil

### ESHRE Mentorship Program 2022

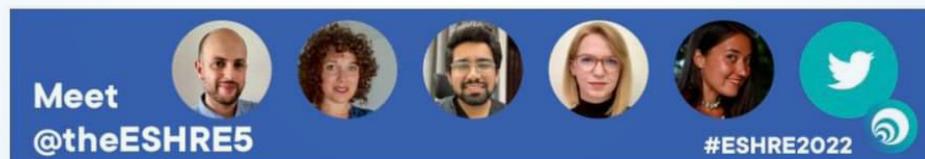


Congratulations DR RAHUL SEN for being accepted into the ESHRE MENTORSHIP PROGRAM 2022.

ESHRE has developed a mentoring programme with the aim to support young scientists and/or clinicians working in the field of infertility and looking for support in ways to expand their expertise, by connecting them with mid-career/senior scientists or clinicians to bridge the gap. To facilitate individual 1:1 virtual or in-person (when possible) mentoring sessions.

### ESHRE 5 Young Ambassador

## Meet the ESHRE 2022 Young Ambassadors



- @theESHRE5 >
- Attilio  
<https://twitter.com/AttilioDGM7> >
- Irene  
<https://twitter.com/iraini> >

#### Prateek Makwana



Consultant Embryologist at Vasundhara Hospital Ltd.,  
Director, Vasundhara IVF  
Educator & Influencer: @fertility\_scribbles

## Embryologists Creativity

What's Edwards without Steptoe and the reverse is also true

What are you without us and what are we without you?

Louise is turning forty four

And after her so many more

Are there just because of you

So grateful for all that you do.

You start the process with so much prep

Impeccable in every step

In the egg retrieval your voice

Calls the eggs and we rejoice

And sometimes after the seventh flush

And an eternal anxious hush

We call on you and truly beg

For you to somehow find an egg

Even an M1 would be fine

But a polar body is divine

And then later you close the door

And this is when you do much more.

Do the sperm know as you break their "leg"

That they need this to meet the egg?

And as you grow embryos for five days

When they make blasts you earn our praise

You biopsy them all not a bit frazzled

With a skill that leaves us all dazzle

Then you freeze each in a straw

And retrieve them when it's time to thaw

You load the catheter with so much grace

That the embryo falls right into place

And you do all this behind your mask

Unpretentious in every task

And no one there to give you cheer

But we appreciate all you do from "egg number one " to " the catheter is clear "

**Dr. Amin Milki**

Infertility specialist at Stanford Medicine, Sunnyvale, CA

*A clinicians gesture of gratitude towards fellow embryologists expressed beautifully in this poetry.*

## Embryo's Voice

Began the debut as a single cell  
Into the journey of gifted life.

Unlike the rest, in a dish  
Test-tube baby fondly called.

Caressed, nurtured, graded and sort,  
With warmth, love, toil and rapport.

By the Embryologist near and dear  
Forever it is with a mighty cheer.

In an Incubator, round the clock  
Until the timing crucial knocked.

To be transferred securely bound  
Gently loaded safe and sound.

The fortnight's wait and delightful shout,  
Elated joy and spreading throughout.

The prayers are a sigh  
When emotions run high.

Throughout the wait  
Day in and day out.

And here arrives the little one  
Unfurling rejoice a million ton.

Yes - it's worth all the time and shots  
As endless bliss is all that counts.

~ Sandhya ~

## Knitting Life

- Harshitha Raj



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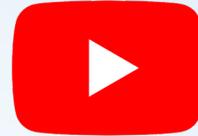


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# Briogyn

Follitropin ALFA, with Auto-Pen

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# ZyhMG

Menotrophin

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# Naturogest

Natural Micronised Progesterone

  
Dedicated To Life