Bell Jar to Cloud

Since the breakthrough in the field of IVF and the birth of the first test tube baby in a “BELL JAR” in 1978, the technological advances have progressed immensely, pushing forward the frontiers of scientific innovation.

START OF THE STORY IN A BELL JAR

1978 was an incredible year when life invoked in a Bell Jar − birth of Louise Brown (Louise Brown’s embryo was taken from the jar — called a “desiccator” and transferred into her mother Lesley’s womb). This feat was achieved by the trio comprised of scientist **Robert Edwards** and his gynaecologist colleague **Patrick Steptoe** and **Jean Purdy,** the world’s first embryologist. They had been working toward it for more than a decade. Also in 1978, we witnessed the milestone achievement of the Nobel Prize being declared for the discovery of cosmic microwave background radiation—the first direct evidence of the Big Bang theory and the inception point of our universe. There is a beautiful parallel we draw between the Big Bang and life starting in a bell jar. This phenomenal declaration to the world that life could be conceived outside of a woman’s womb was the start of an amazing journey of scientific innovations and discoveries that have resulted in implantation rates ranging from <5% to the present where they touch >50%.

Fertility is considered a basic human right

As the availability of IVF services is expanding, it is being utilized increasingly. The demographic scenario, societal norms, and a greater number of women delaying child bearing due to priority given to career opportunities have contributed to a lowering of birth rates worldwide. In many nations, the fertility rates are substantially below population replacement levels, which has resulted in the governments withdrawing stringent population control policies and instead executing policies that promote population growth by way of steps like improved insurance coverage. Although the journey of treatment through IVF is an exacting one in terms of financial, emotional, and physical stress, the process of IVF has contributed to as many as 4% to 5% of births in some parts of the world. Over 2 million babies have been born by IVF in the past four decades. This technology initially was established to help couples overcome childlessness but has helped in expanding horizons in terms of medical genetics, fertility preservation, social egg freezing, and three parent embryo generation. And there are breakthrough advancements in the form of Robotics, Nanobots, artificial intelligence-machine learning, deep learning via using artificial neural network (ANN), OMICS, and stem cell advances being applied for in vitro gametogenesis (IVG).

JOURNEY TOWARDS THE FUTURE: THE CLOUD TECHNOLOGY AND AI

Various strategies intent on reducing the number of injections by utilizing long-acting gonadotropins or oral medications are already available and are becoming popular for the treatment of select patient populations.[1,2] Advances in culture media and culture systems from second generation of sequential media to third generation media simplex optimized− derived media (SOM) using micro drops and under oil culture systems. Recent advancements in imaging with portable lower-cost ultrasound devices may further simplify follicular and endometrial monitoring by way of convenient mobile facilities and potentially even self-operated endovaginal telemonitoring.[3] AI aided improved ultrasound helps with the following

(1) Assess ovarian reserve (application based on 2D or 3D ultrasound).
(2) Accuracy in assessment of endometrial receptivity demonstrating segmentation of the region of endometrium, classification of endometrial pattern, estimating peristalsis of endometrium, and assessing endometrial blood supply quantitatively.

Perhaps the most promising technological development that might revolutionize IVF access in the near term is automation and miniaturization of the IVF laboratory. Building, staffing, and manually operating an IVF laboratory account for much of the high cost, maldistribution of access, and variability of outcomes.

The novel IVF lab-on-a-chip concept has the potential to revolutionize IVF by enabling the automation of virtually all of the steps involved in a single system.[4-6]

Microfluidics is a field of study and design whereby fluid behaviors are accurately controlled and manipulated with small-scale geometric constraints that yield the dominance of surface forces over their volumetric counterparts. Integration of microfluidics into the IVF laboratory may result in: (1) precisely controlled fluidic gamete/embryo manipulations; (2) providing biomimetic environments for culture; (3) facilitating microscale genetic and molecular bioassays; and (4) enabling miniaturization and automation.[6] Current efforts are focused on integrating individualized microfluidic procedural components into a future IVF lab-on-a-chip.

Microfluidic sperm-sorting devices[7-9] and automated sperm analyzers[10] are already being introduced into routine IVF practice. Indeed, microfluidics has been used for the isolation of sperm from semen and testicular biopsies.[11-17] These novel sperm-isolating microfluidics devices providing for the collection of highly motile sperm populations replete with enriched normal morphology, most importantly, and reduced DNA fragmentation relative to conventional methods of sperm isolation.[7,15,18,19]

The future is "Automated ICSI" which will likely involve a combination of microfluidics, robotics, and refined optics.[20] As ICSI has become the dominant method of insemination in human clinical IVF, the importance of precise microfluidic push/pull cumulus-oocyte-complex cumulus cell removal has been shown to yield good visualization of the oocyte cytoplasm/orientation.[21] The fertilization step by ICSI is perhaps the most technically difficult step to achieve on a commercial scale, but the feasibility of one such system has been demonstrated.[21]

Embryo culture has already been fully automated with the use of time lapse incubators, which allow continuous monitoring of embryonic development. Data generated from time-lapse incubators can be analyzed with machine learning to aid in the selection of embryos with the highest pregnancy potential.[22-24]

Additional information about embryo viability may be gleaned from other OMICS technologies, which can either sample the embryo directly or indirectly via its culture medium. The technologies in question include genomic, transcriptomic, proteomic, and metabolomic analyses.[25]

Multiomics is the future

Multiomics is the future approach for the identification of any abnormality in an embryo. The future envisages proper homogenization of data, individual OMIC biomarkers, and data processing models that unite multiple data sets into a common platform.[26]

Another future perspective is microfluidic outlet ports connected to OMICs analyzers, which are able to assess the implantation and developmental potential of each cultured embryo without invasive assessment.

Metabolomics

Metabolomics pertaining to culture media , follicular fluid, seminal fluid and endometrial metabolomics are the potential newer techniques for ART.

Genomics

The DNA and RNA are extracted from oocytes or embryos genomes are amplified, labeled, and hybridized, and the data analyzed by FISH, CGH, SNP.

Proteomics

Analyzing proteins (differ from cell to cell) can provide a promising noninvasive tool.

(1) Single protein analysis and secretome.
(2) Embryonic secretome and protein profiling.
(3) Non-invasive proteomics.

Proteomics thus helps with endometrial profiling and predicting implantation success.

Follicular fluid proteomic markers would help to predict oocyte quality.

Although the use of preimplantation genetic testing (PGT) of trophoectoderm cells of blastocyst stage embryos is quite common in clinical practice, the use of the technique of microfluidics could be quite an advancement for PGT. Microfluidics technology has been successfully used to culture mammalian preimplantation embryos from the zygote to the blastocyst stage.[27-32] The importance of individual embryo culture in microfluidic devices can be appreciated when one considers the desire to integrate real-time imaging and morphometrics,[33] molecular,[34] and/or metabolomic[35,36] bioassays, biomechanics,[37] and non-invasive PGT of cell-free DNA in spent media.[38]

Noninvasive PGT, which utilizes cell-free DNA released into the spent embryo culture media, is likely to become the first omics technology used clinically in conjunction with a microfluidic system.[38]

Presently, cryopreservation of sperm, oocytes, and embryos has become the standard of care. Vitrification has become the dominant method for oocyte and embryo cryopreservation. While semi-automated/automated systems for oocyte/embryo vitrification have been reported, and possibly microfluidics can be used to precisely control cryoprotectant exposures (gradual vs. step-wise exposure) to oocytes/zygotes/embryos and thus reduce osmotic strain, reduce sub-lethal membrane damage, and improve subsequent development.[39-42] Integrated microfluidics for vitrification with automation is promising. Such a system/device will reduce reagent consumption, decrease labor intensity, facilitate ease of use, offer medium to high throughput, and may foster point-of-care cryopreservation and/or promote in-office cryopreservation procedures that require less in the way of technical/personnel expertise and sophisticated laboratory/equipment needs.

The growing utilization of IVF will transform the way a substantial proportion of the human species procreates. It is likely that in the near future, as many as 10% of all children will be conceived through IVF in many parts of the world. Given the rapid scientific and technological evolution of in vitro gametogenesis and reproductive genetics, it is imperative that both the public and regulatory bodies be engaged in establishing a framework for the ethical evaluation of emerging technologies. Such public engagement is critical. Premature commercialization of costly and unproven "add-ons" to IVF has been an ongoing issue in the field, ranging from procedures to medicines to laboratory techniques. Collectively, the routine application and marketing of unproven IVF add-ons may erode public trust in the reproductive medicine field. Thus, it is imperative for the field to prioritize requiring confirmation of the safety and efficacy of technologies before allowing them to be offered routinely to IVF patients. Reproductive medicine is rapidly transforming human procreation and is thus bound to remain of fundamental importance to both science and society.

The mission remains to give everyone who dreams of being a parent the opportunity to eventually hold a healthy baby in their arms but ensuring that the technology used to assist is always rooted in ethics and safety.

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Conflicts of interest

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