



HISTORY OF DEVELOPMENT OF IVF IN INDIA AND BEYOND

DR SUDARSAN GHOSH DASTIDAR^{1,2}

1: Director, GD Institute for Fertility Research, Kolkata, West Bengal

2: Director, Centre of Excellence (in ART), Institute of Post-Graduate Medical Education and Research (IPGMER) & SSKM Hospital, Kolkata, West Bengal, India

The Evolution of IVF Technology: A Journey from Lab to Clinic

The astonishing progress in In Vitro Fertilization (IVF) technology is rooted in nearly 150 years of significant scientific and technical advancements, largely stemming from research on mammalian gametes (sperm and eggs). The success of modern IVF is essentially a testament to painstaking research in mammalian embryology. While many individuals have contributed, several pioneers deserve special recognition for their foundational work that ultimately enabled the successful incorporation of IVF into human infertility treatment in the 1970s.

Pioneering Discoveries in Mammalian Embryology

Gregory Pincus was instrumental, being the first to demonstrate that oocytes (eggs) aspirated from follicles could spontaneously begin their maturation in vitro (in a lab dish) in 1953. This finding became the fundamental basis for human IVF, which involves collecting oocytes at various stages of maturity. Independently, C. R. Austin and M. C. Chang identified that sperm capacitation—a process where sperm acquire the ability to fertilize an egg—was an essential prerequisite for successful mammalian fertilization in vitro. Further advancing the field, J. D. Biggers and colleagues in 1965 showed the crucial effect of different nutrients in culture media and osmolarity on the development of mammalian embryos. A key earlier study was published in 1952 by M. C. Chang and J. M. Bedford, detailing the fertilization of rabbit ova in vitro.

The Shift to Human IVF

Initial interest in human oocytes was limited until the publications of J. Rock and M. F. Menkin in 1944-1948, which reported on the fertilization and early embryo development of human embryos. Key to success in the lab was understanding oocyte preparation. Alan Trounson proposed that a pre-insemination incubation of 5-6 hours was required for the final maturation of the oocyte in vitro. Similarly, Dr. Subhas Mukherjee in India also suggested a 3-4 hour incubation period before insemination.

From Laboratory Research to Clinical Application

The transition of IVF from the laboratory to clinical medicine began with R. G. Edwards, B. D. Bavister, and P. C. Steptoe, who published their early work on oocyte recovery from human ovarian tissues in Nature in 1969. Between 1971 and 1972, Steptoe and Edwards attempted their first embryo transfers (ETs) using ovarian stimulation with human Chorionic Gonadotropin (hCG). After numerous unsuccessful attempts, Edwards shifted the approach in 1977 to collecting oocytes during the natural menstrual cycle by monitoring the Luteinizing Hormone (LH) surge using a high-sensitivity kit (High-Gonavis kit, Japan).

This change involved performing a laparoscopic egg retrieval (LOR) 24 to 26 hours after the urinary LH surge was recorded. Despite a low success rate of 0.8% and many failures, the dedicated efforts of R. G. Edwards, Patrick Steptoe, and Jean Purdy finally led to the birth of Louise Brown, the world's first IVF baby, on July 25, 1978, at Oldham Hospital. In a significant parallel achievement, Dr. Subhas Mukherjee in India also successfully delivered India's first IVF baby in October 1978. Following these groundbreaking successes, IVF births soon occurred globally: France (R. Frydman, 1982), Sweden, Austria, Belgium, and the Netherlands. Later, in November 1986, (B. N. Chakraborty and S. Ghosh Dastidar) India's third IVF baby was delivered (Chakraborty B.N, Ghosh Dastidar S) in Kolkata.

Major Technological Advances

In the early years, IVF laboratories had to prepare their own in-house tissue culture media (like Tyrodes or Ham's F10). The meticulous process of media preparation, quality control (QC), and filtration was time-consuming and labor-intensive, leading to significant variations in IVF outcomes between different centers globally. This challenge was addressed when J. Y. Menezo developed the first commercial embryo culture medium, "Menezo B2 Medium." A major development that simplified the IVF procedure and reduced its invasiveness was the invention of transvaginal ultrasound-guided follicular aspiration by Matts Wiklands. This technique quickly replaced the surgical laparoscopic oocyte retrieval and remains the standard method today. Another crucial advance was the development of ultrarapid cryopreservation (vitrification), which is now widely used for freezing eggs and embryos with significantly higher success rates compared to older slow-freezing methods (M. Kuwayama).

Evolution of Controlled Ovarian Stimulation (COS) Protocols

Early ovarian stimulation protocols involved using Clomiphene with hCG, and later human Menopausal Gonadotropin (hMG) and hCG, as used by the Australian group (C. Wood) and Dr. Subhas Mukherjee in India. The American group, notably Howard Jones, also favored hMG from the start.

Modern Era of Ovarian Stimulation and Safety

A crucial advance for safety emerged around 1984-1985 with the development and use of GnRH agonists to prevent a premature LH surge, finally, which could spontaneously trigger ovulation and ruin the cycle. Modern protocols, such as the widely used D-6 fixed protocol, now typically combine Follicle-Stimulating Hormone (FSH), hMG, and a GnRH antagonist (like Cetorelix or Ganirelix). This approach has virtually eliminated the problem of premature LH surge. Furthermore, safety has increased significantly for patients with Polycystic Ovary Syndrome (PCOS) through the strategic use of FSH antagonists and a GnRH agonist trigger for final egg maturation, which virtually prevents the severe complication of Ovarian Hyperstimulation Syndrome (OHSS).

Culturing Embryos to the Blastocyst Stage

Initially, embryo transfers (ETs) were performed at the 2-8 cell stage (up to 1985-1986). A significant improvement came with the development of a defined culture medium called "G2 medium" by David Gardner. This allowed for successful blastocyst culture (growing the embryo for 5-6 days) and subsequent blastocyst ET, which showed a marked increase in success rates.

Genetic Testing of Embryos

The field further advanced with the introduction of embryo biopsy for Preimplantation Genetic Testing (PGT). Alan Handyside pioneered the embryo biopsy technique in 1990. Following this, Santiago Munné developed the first Preimplantation Genetic Testing for Aneuploidy (PGT-A) in 1993, which allows for screening embryos for the correct number of chromosomes before transfer.

ICSI: A Revolutionary Advancement for Severe Male Infertility

While the text focuses on early IVF, another major revolution came with Intracytoplasmic Sperm Injection (ICSI), which solved many male infertility issues (Palermo et al., 1992).

Current Trends: AI and Robotics in IVF

The field continues to evolve, with recent focus on Artificial Intelligence (AI) and Robotics. AI is being used in embryo assessment (D3 cleaving or blastocyst stage, as studied by T. Ebner. Our group, without AI, has developed a method to identify cleaving embryos with high growth potential (S. Ghosh Dastidar, 2018). AI has proven effective in selecting the best quality embryos for transfer, thereby increasing clinical pregnancy rates. Robotics, pioneered by groups like Conceiveable Life Sciences in the USA (Ref: J. Cohen), is being developed with the potential to automate the ICSI procedure. This application of robotics is poised to standardize the ICSI process, ensuring consistent quality and output regardless of the individual human operator's skill and training.