The journey of R. G. Edwards: from a single cell to Louise Joy Brown

*S. Shivaji**

This article is all about a dream 'to create a test tube baby' that came true after nearly three decades of persistence, patience and hard work. It highlights in chronological order the obstacles that R. G. Edwards had to overcome starting from procuring the oocytes, from maturing the oocyes, from fertilizing them in vitro and in transferring the developed embryos into the mother. All along Patrick C. Steptoe provided the needed support. The highlight of their effort was the birth of Louse Joy Brown, the first test tube baby, in 1978. In vitro fertilization (IVF) has helped to alleviate infertility and has brought happiness to millions of people across the globe. Thus, conferring the 2010 Nobel Prize in Physiology or Medicine to Edwards for the IVF technology would have brought happiness to many more people.

Keywords: Assisted reproductive technology, infertility, *in vitro* fertilization.

THE booming human population would convey the impression that all is well with human fertility. This is not so. Out of every ten human beings one is infertile, and while some are curable, others are not. The former group includes those with hormonal imbalance, genital diseases, low sperm count, blockage in the ejaculatory duct, blockage in the oviduct, impotence, premature ejaculation, etc. These problems can often be easily treated by assisted reproductive technologies. A simple scenario would be to administer hormones or other medicines to restore fertility. Compared to this approach, artificial insemination (AI), in which semen is directly installed in the uterus, would be a more complicated assisted reproductive technology. AI needs to be differentiated from *in vitro* fertilization (IVF), commonly referred to as 'test tube baby', the most popular of the assisted reproductive technologies (see Box 1).

How did it happen?

The road to IVF and the birth of Louise Joy Brown was indeed a bumpy road[1,2], the only solace being that Robert G. Edwards had the company of Patrick C. Steptoe at least for a good part of the journey. It all started in 1950, when Edwards started working on mouse embryos for his Ph D, but soon shifted to human oocytes and was bent upon doing IVF which was not acceptable to many. Nevertheless, he continued, overcoming several hurdles, and his persistence finally paid-off. Edwards' first hurdle was to procure human oocytes, which he managed with the help of his wife's gynaecologist. But he soon realized that conditions required for *in vitro* maturation of oocytes as well as for sperm capacitation had to be standardized and finally IVF had to be achieved. All these steps, which were already established in other mammals, took an unpredictably long time and after an intense struggle of 10 long years, Edwards demonstrated that human oocytes could be matured *in vitro*, fertilized *in vitro* and developed into blastocysts[3,4]. The *in vitro* development of blastocysts could be considered the most important and significant breakthrough in IVF research and the first step towards realization of Edwards' dream to use IVF to treat infertility. A crucial step in this process was obtaining oocytes after superovulation by laparoscopy, a technique which was invented by Steptoe. In achieving IVF, Edwards must have been physically exhausted since the oocytes were collected at Oldham and transported to Cambridge (200 miles away). Everything appeared to be simple from this step onwards, but it was not to be. Despite transferring healthy embryos into the recipients' tracts, nothing appeared to be happening even though more than 100 attempts were made. It was intriguing and may have also been frustrating. Fortunately, at this juncture it was realized that the hormonal treatment used to increase the number of oocytes in the patient was acting as an abortifacient and thus causing spontaneous abortions. These short-lived pregnancies indicated that they were close to success and the only obstacle was to provide a conducive environment for implantation and development. One approach was to cryopreserve the IVF embryos till the patient was receptive to accept the embryo. But cryopreservation attempts were not encouraging and the only

S. Shivaji is in the Centre for Cellular and Molecular Biology, Uppal Road, Hyderabad 500 007, India. *e-mail: shivas@ccmb.res.in

Box 1. What is *in vitro* fertilization (IVF)?

IVF involves retrieval of an oocyte from the mother, fertilization in a culture plate, development of an embryo, transfer of the embryo back to the uterus of the mother, implantation, further development into a foetus and birth of the young one (Figure 1). In short, it is an assisted reproductive technology involving human intervention to facilitate fertilization and early development of the embryo outside the mother, but subsequently returned to the confines of the mother for future development. On 26 July 1978, Robert G. Edwards and Patrick C. Steptoe were the first to report the birth of Louise Joy Brown, a baby girl, born by IVF using a single aspirated oocyte of her mother Lesley Brown, recovered during her natural cycle, which was fertilized and transferred at the eight-cell stage[1]. After a little more than three long decades, the 2010 Nobel Prize in Physiology or Medicine has been awarded to Edwards for the development of human IVF.

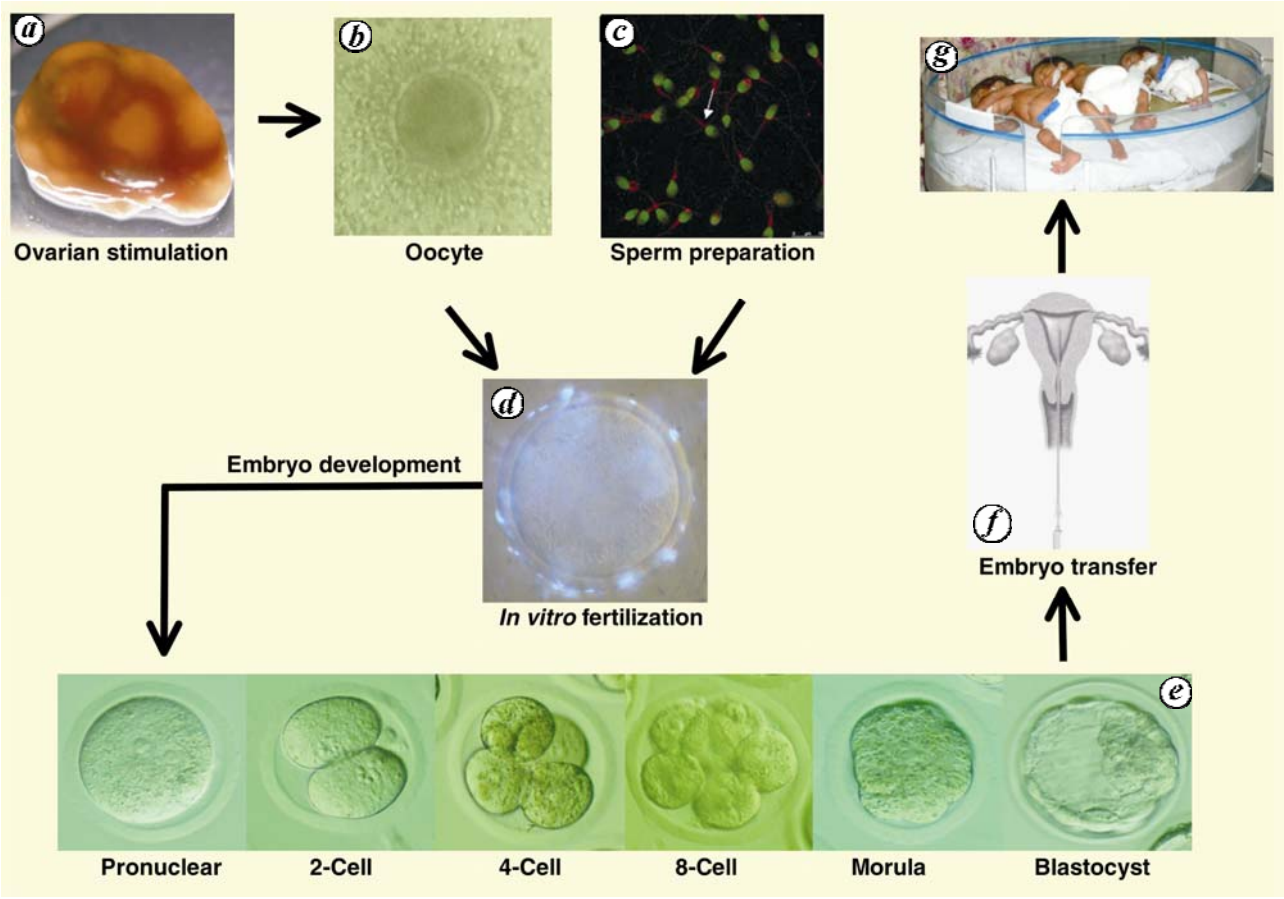

Figure 1. Steps involved in *in vitro* fertilization (IVF). Following ovarian stimulation (***a***), an oocyte is recovered (***b***) and fertilized with donor sperm (***c***) in a petri dish to obtain a zygote (***d***), which is allowed to develop to a blastocyst (***e***). The blastocyst is then transferred to the uterus (***f***), which implants and develops into a IVF baby (***g***).

option left was to retrieve the oocyte during the natural cycle just prior to ovulation – a feat that was successfully accomplished by Steptoe. This approach led to an ectopic pregnancy in 1976 in the fallopian tube and the pregnancy was terminated at 11 weeks[5]. However, success was not far behind. After two years, in 1978 Steptoe and Edwards announced the birth of Louise Joy Brown, at 11.47 p.m., on 25 July 1978 at the Oldham General Hospital, through successful IVF of a human oocyte[1]. At a later occasion, Edwards exclaimed, 'It is hard to put into words what the occasion of her birth meant to me, and to our wonderful supportive team. It was a purely routine Caesarean section, yes, but with a significance outstripping anything we had done before or were likely to achieve later'[2].

While Edwards and Steptoe were busy with human IVF, a similar activity was in progress in India. On 3 October 1978, barely two months after the birth of the world's first IVF baby, Subhash Mukhopadhyay, West Bengal, also announced India's first IVF baby – Durga

alias Kanupriya Agarwal. Recognition has eluded Mukhopadhyay both within the country and internationally. In 1997, based on Mukhopadhyay's papers and handwritten notes on his technique published in the *Indian Journal of Cryogenics* and presented in the Indian Science Congress in 1979, T. C. Anand Kumar (Institute of Research in Reproduction, Mumbai), recognized Mukhopadhyay's pioneering work in IVF and rejected all charges of 'fraud'. Further, in 2002, the Indian Council of Medical Research (ICMR) recognized Mukhopadhyay's contribution for the first time and the Government created the 'Subhas Mukherjee Professorship' in the NRS Medical College in 2005. Unfortunately, Mukhopadhyay is no more and though deprived of any recognition, he would definitely be happy for the recognition IVF has attained.

The spin-offs of IVF

After Louise Joy Brown, approximately 4 million babies have been born worldwide through IVF and many of them are now fathers and mothers. Though IVF was developed for treating women with tubal blocks, it has now become one of the most widely used assisted reproductive technologies to treat other infertile individuals with non-functional ovaries (oocyte is obtained from the donor, fertilized with the husband's semen and embryo transferred to the infertile patient), non-functional uterus (oocyte is obtained from the patient, fertilized with the husband's semen and embryo transferred to a surrogate mother), idiopathic infertility (IVF followed by embryo transfer) and males with few normal spermatozoa (intracytoplasmic sperm injection and embryo transferred to the mother). Edwards' research on IVF has also stimulated interest in embryonic stem cells, influenced the development of preimplantation genetic diagnostics and also breeding of domestic and endangered animals.

Box 2. Recent awards and honours of Dr R. G. Edwards.

Fellow of the Royal Society, 1984.
The Albert Lasker Clinical Medical Research Award, 2001.
Honorary DSC from the University of Cambridge, 2001.
Grand Hamdan Award for Clinical Science, 2002.
Pioneer in Stem Cells Award from Pittsburgh Development Center, 2004.
The Eardley Holland Gold Medal, 2005.
Honorary Doctorate of Medicine from the Karolinska Institutet, Sweden, 2006.
Chevalier dans l'Ordre National de la Legion d'Honneur, 2007.
Jacques Salat-Baroux Prize, 2007.
The Nobel Prize in Physiology or Medicine, 2010.

Never too late

The 2010 Nobel Prize in Physiology or Medicine to Edwards for the development of human IVF after a little more than three long decades, is a recognition of his scientific accomplishment and the impact it has had over the years in alleviating infertility. IVF has now exploded worldwide and brought happiness and smiles on the faces of countless infertile people the world over. It also goes to show that despite opposition based on moral issues of creating embryos, policy decisions to control fertility rather than treating infertility and scientific issues related to safety of embryos, Edwards' persistence, patience, focus and rational approach were finally rewarded. According to Edwards, 'The worm began to turn' in the early 1990s when IVF eased itself from the clutches of all the opposition and he began receiving a number of awards and honours (see Box 2).

1. Steptoe, P. C. and Edwards, R. G., Birth after the reimplantation of a human embryo. *Lancet*, 1978, **2**, 366.
2. Edwards, R. G., The bumpy road to human *in vitro* fertilization. *Nature Med.*, 2001, **7**(10), 1091–1094.
3. Edwards, R. G., Bavister, B. D. and Steptoe, P. C., Early stages of fertilization *in vitro* of human oocytes matured *in vitro*. *Nature*, 1969, **221**, 632–635.
4. Steptoe, P. C., Edwards, R. G. and Purdy, J. M., Human blastocysts grown in culture. *Nature*, 1971, **229**, 132–133.
5. Steptoe, P. C. and Edwards, R. G., Reimplantation of a human embryo with subsequent tubal pregnancy. *Lancet*, 1976, **1**, 880–882.

ACKNOWLEDGEMENT. I thank Dr B. Sambasiva Rao and Dr Sadanand Sontakke for providing technical inputs.

Received and accepted 2 December 2010