

## Milestones

# Patrick Steptoe, Robert Edwards and the new age of Human Reproduction

Dastur Adi E<sup>1</sup>, Tank PD<sup>2</sup>

*Honorary Professor Emeritus, Seth G S Medical College & Dean, Nowrosjee Wadia Maternity Hospital, Mumbai, India<sup>1</sup>  
Honorary Clinical Associate, Nowrosjee Wadia Maternity Hospital, Mumbai, India<sup>2</sup>*

In 1978 Louise Joy Brown was born. Normally, a birth of a baby girl in a remote English town would raise no excitement except to family and friends. But when this little girl was born, she was on the front pages of every major newspaper in the world. Her birth was marked by marvel and disbelief. For Louise Brown was the first human being in history to have been conceived outside the human body. Apart from her parents and nature, she was as much a creation of Patrick Steptoe and

Patrick Christopher Steptoe was born on June 9, 1913 in Oxfordshire, England. His father was a church organist, while his mother served as a social worker. Steptoe studied medicine at the University of London's St. George Hospital Medical School. Steptoe volunteered as a naval surgeon in World War II and on returning, he became a member of the Royal College of Obstetricians and Gynecologists in 1948. He moved to Manchester to set up a private practice. In 1951 Steptoe began working at Oldham General and District Hospital in northeast England where he pursued his interest in fertility problems. He was a pioneer of laparoscopy in England, having trained with Palmer in Paris and Frangenheim in Germany. In the early part of his career he had trouble convincing the profession about its utility. Five years passed before Steptoe published his first paper on laparoscopy. He also described laparoscopy at ovulation and the ability to collect oocytes from the ovaries<sup>1</sup>. This drew attention from all quarters of the medical profession and included Robert Edwards.

Professor Robert Geoffrey Edwards, born in Leeds on the September 27, 1925, is presently the Chief Editor of Reproductive BioMedicine Online. As a young science graduate from the University of Wales, he began his PhD at the Edinburgh University in 1951. His early work was on altering chromosomal content of mouse embryos. This gave him a strong background in embryology and reproductive physiology of mice. He teamed up with a colleague (and his future wife), Ruth Fowler to study the induction of multiple ovulation in mice with pregnant mares' serum (PMS) which was rich in gonadotropins. They were able to induce oocyte maturation and meiosis in vitro as early as 1957. Edwards



**Figure 1.** Robert Edwards (L) and Patrick Steptoe (R) receive an Honorary DSc from Hull University in 1983.

traveled to California to widen his horizons into molecular biology and genetics. He returned to London and spent two years working intensely on immunology until his curiosity returned to oocyte maturation and fertilization.

In vivo and in vitro experiments showed that rabbit, hamster and rat oocytes matured within 12 hours of administering hCG. However, oocytes from cows, sheep and monkeys showed no signs of maturity when inseminated at 12 hours. Similarly, human oocyte maturation was also thought to be impossible in vitro. Molly Rose, the gynecologist who had delivered two of Edwards' daughters, agreed to provide him with human ovarian tissue. He worked with oocytes harvested from slithers or wedges of human ovaries removed from patients with Stein-Leventhal syndrome. The results from the first two years of his work were disappointing. Having exhausted a number of options such as changing culture media, adding higher doses of hormones and sera, Edwards decided that there might be some difference in mammalian species regarding the time to oocyte maturation. This was a vital breakthrough and he was finally able to demonstrate meiosis between 24 and 48 hours. This was further refined and the time of ovulation for human oocytes was identified as 36 hours. Pig oocytes were closest to humans, requiring 37 hours<sup>2!</sup> Edwards moved to Cambridge where he further explored and optimized incubators, media and cell line cultivation.

The historic collaboration began with a phone call from Edwards to Steptoe and flourished at the Oldham and District General Hospital and later at the Kershaw's Hospital. They set up a small laboratory at Oldham. Women were stimulated with purified urinary hMG and ovulation triggered with hCG. Oocytes were aspirated 36 hours later via laparoscopy. Human embryo formation was routinely achieved. Once again, there were disappointing results in the first three years with no pregnancies. One of the mistakes that was identified was the use of Primolut depot as a form of luteal support. It was later found to be a luteolytic and abortifacient. They switched to hCG and progesterone thereafter. The pressures from critics, ethicists and colleagues were mounting. The patients, however, remained loyal and a steady stream ensured that work progressed. Much of the early work was funded by Edwards and Steptoe themselves. More bad news was

in store. Though a clinical pregnancy was established in 1976, it turned out to be an ectopic which had to be removed at about 10 weeks<sup>4</sup>. Working against the odds, Steptoe and Edwards experimented with various stimulation protocols and natural cycle IVF. Lesley and John Brown were the second entrants in the natural IVF group. Lesley had no oviducts, having lost them to ectopic pregnancies earlier. This proved to be a valuable dissuasion to critics who would later claim that the pregnancy was a fraud. After seven years of work at Oldham, the positive pregnancy test in a natural cycle was a major milestone. Louise Brown was born at 11:47 pm on July 25<sup>th</sup> 1978 at Oldham, through a planned caesarean section delivered by registrar John Webster. She weighed 5 pounds, 12 ounces (2.608 kg) at birth. Her younger sister, Natalie Brown, was also conceived through IVF, four years later, and became the world's fortieth IVF baby, and the first one to give birth herself—naturally—in 1999. Louise Brown also has a son, conceived naturally and born in 2006, with Professor Edwards in attendance. Steptoe and Edwards published their early results in 1980 with four pregnancies out of 32 embryo transfers<sup>4</sup>.

The Oldham team wound up the small laboratory and set up a private clinic at Bourn Hall. Criticism and plaudits were earned in equal measure until the late 1980s until IVF became an international phenomenon and was widely accepted in clinical practice and the public view. Patrick Steptoe died from cancer in 1988. Professor Robert Edwards continues to work on the genetic aspects controlling human reproduction and the ethics of assisted reproduction<sup>5</sup>.

## References

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