



## Review

# Founding Pioneers of IVF: Independent innovative researchers generating livebirths within 4 years of the first birth

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## ABSTRACT

In this 40th anniversary year of the first IVF live birth, it is pertinent to look at all those teams endeavouring to generate live births from this unique technology and who succeeded within 4 years of the first. There were 9 teams who achieved this and a further 3 who were successful soon after, by the end of 1982. This historical review is compiled by 2 authors who were actively engaged in the field of IVF at the time of the first birth and who have remained active in Reproductive Medicine throughout their professional lives. They bring intimate and relevant knowledge of those pioneer researchers from the early years who can be classified as the "Founding Pioneers" of IVF.

## 1. Introduction

The first "test-tube baby", Louise Joy Brown, was born at Oldham General Hospital situated in Manchester, England on 25th July 1978 [1]. She was the result of a decade of intensive research by the first pioneers, often labelled the "fathers" of in-vitro fertilisation (IVF) namely scientist Robert (Bob) Edwards who teamed with gynaecologist Patrick Steptoe in 1968. At the time of her 40<sup>th</sup> birthday, it can be appropriate to reflect on the "Founding Pioneers" of IVF – documenting a dozen ground-breaking and innovative teams in the field of reproductive medicine, 9 of whom generated live births in the 4 years following Louise Brown and a further 3 soon after leading to the explosive establishment of successful teams in 1983 [2]. This time-frame defines those IVF pioneers who relied essentially on their own resources and ideas to generate the world's first IVF-generated children (Table 1). Thereafter, numerous teams emerged who were largely reliant for training and experience from these innovative pioneers. The term IVF pioneers has sometimes been applied to those who attended the September 1981 meeting at Bourn Hall [2], Cambridge where Bob Edwards, Patrick Steptoe and Jean Purdy resumed their programme, 3 years after finishing at Dr Kershaw's Hospital where Louise Brown was actually "conceived". Kershaw Hospital is situated in Royton, Manchester and the IVF pioneers finished up there in 1978 [2] and which today has become a private nursing home. Whilst respectful of those attendees at the 1981 meeting who were keen to learn the

methodologies, several of the teams in this presentation were not present at that meeting, but achieved IVF live births by July 1982, working from independent endeavours. This was noted with surprise by John Leeton [3] who observed that several advanced facilities were not represented at this invitation-only meeting. Apart from access to the pre-1980 written articles and presentations of Edwards and Steptoe, the teams we present here independently pioneered their IVF procedures and processes. In fact, each of them developed separate ideas which have added, collectively, to the Edwards-Steptoe model and which have become the modern methods of IVF technology. We, as authors, can document their history from personal contact with these "Founding Pioneers" during the years 1976–1985 covering the scope of this review article.

## 2. The first nine successful teams

It is universally acknowledged that Robert Edwards and Patrick Steptoe were the original successful pioneers of IVF and rightfully the term "Fathers of IVF" appropriately belongs to them. Currently more than 8 million offspring have ensued from thousands of IVF Units around the world so that many countries can report that 4% or more of annual livebirths arise from IVF-related procedures. At the time when those pioneers presented the story about their amazing achievement, a number of other gynaecologists and scientists had established working facilities, also with the aim of achieving IVF births. Whilst each of them

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**Table 1**

Table depicting first IVF Teams generating livebirths. The first 9 teams achieved livebirths by the 4th birthday of the first IVF live birth Louise Joy Brown; born 25 July 1978.

First Successful IVF Teams			
Team	Country	Main Members	First Livebirth
1	Britain	Step toe, Edwards Purdy	Jul-78
2	India	Mucherjee, Muckherjee, Battacharya	Oct-78
3a	Australia	Wood, Johnston, Lopata	Jun-80
3b	Australia	Wood, Leeton, Trounson	May-81
4	USA	Howard Jones, Seeger-Jones, Veeck	Dec-81
5a	France	Frydman, Testart, Lasalle	Feb-82
5b	France	Cohen, Plachot, Mandelbaum	Jun-82
6	Britain	Craft, Yovich, Bernard	Apr-82
7	Germany	Trotnow, Kniewald, Habermann	Apr-82
8	USA	Marrs, March, Michell	Jun-82
9	Australia	Yovich, Pusey, De Atta	Jul-82
10	Sweden	Hamberger, Wikland, Enk	Sep-82
11	Austria	Feichtinger, Kemeter	Oct-82
12	Australia	Saunders, Pike, Chen	Nov-82

acknowledged that they were attempting to emulate the achievements reported by Edwards and Steptoe in 1970, those who achieved livebirths within 4 years of the birth of Louise Brown actually did so from independent positions. Several of them had sought to “stand on the shoulders” of the first pioneers, but indeed Edwards and Steptoe, although initially welcoming and advising to others up to 1975 when they faced many criticisms and setbacks to their quest, subsequently became a little reticent prior to their famous presentations at the Royal College of Obstetricians and Gynaecologists in January 1979 when all the methodological, laboratory and clinical details were revealed, and were subsequently published comprehensively during 1980 (Section 2.1). In fact, several of these independent pioneers felt (wrongly in retrospect) that Edwards and Steptoe were concealing the true details of their success. At least two of them, including ourselves, reverted to undertaking the IVF procedures within the rabbit or sheep oviduct, a process which Edwards had explored, and discarded, at an earlier stage [4,5]. Another facility, that conducted by Ian Ferguson, and which was initiated at St Thomas’ Hospital in London with the assistance of Bob Edwards, closed down in 1979 from persistent failure, despite having a state-of-the-art laboratory. We, the authors, sought advice from Ferguson over the years 1976–1979 and understood that further assistance was limited. Ferguson, also holding consultancy posts at Queen Charlotte’s and Chelsea Hospital for Women, subsequently had a more fruitful career establishing Tommy’s with obstetric colleague Anthony Kenney. With the funding support of the Hon Lucy Nelson, Tommy’s widely supports research into the problem of pregnancy complications causing intra-uterine growth retardation, pre-term and stillborn infants [6]. The IVF facility at St Thomas’ re-emerged in 1991 as the Assisted Reproduction Unit under Professor Peter Braude.

Having selected these independent IVF workers for categorisation under the title of “pioneers”, we are aware that none of them would have wished to take the main title away from Edwards and Steptoe who had the longest history and persisted against unexpected obstacles including adverse societal attitudes [7], inadequate existing knowledge concerning human reproduction, challenges from both religious and ethical viewpoints [8], and above all, rejection of their application for funding by the Medical Research Council [9]. Their spectacular success emerged after a decade of struggle and imminent closure of their programme in Manchester, UK. However, the formula for their success involving natural cycles, laparoscopic oocyte recovery, logistic difficulties for timing oocyte pickup, and lack of cover for the luteal phase, required revised methodologies in order to develop towards current practice. These problems were actually addressed by the other teams presented in this review article enabling the explosive success for IVF which is currently being witnessed.

## 2.1. The first team (British)

Edwards and Steptoe described the first human blastocyst from extracorporeal fertilisation (ECF, later to be called IVF) in 1970 [4,10] following the aspiration of oocytes from a woman’s ovary by laparoscopy, a technique which Steptoe had introduced to the United Kingdom in 1967 [11]. In fact, Edwards, from the Department of Physiology at Cambridge University, had sought out Steptoe when he heard of his pioneer work with the laparoscope. A third “silent” member of this first team was Jean Purdy, a nurse from Cambridge whom Edwards trained as the first human embryologist and who assisted his research throughout until the establishment of the Bourn Hall fertility clinic near Cambridge in the early 1980’s [12]. Purdy died aged only 39 years in 1985, Steptoe in 1988 and Edwards in 2013, three years after being awarded the Nobel prize in Physiology or Medicine (2010) and two years after his knighthood was conferred (2011). Edwards’ life has been marvellously recorded by fellow knight Sir Richard Gardner FRS in Biographical Memoirs of the Royal Society [13].

The early attempts by this team to generate pregnancies for infertile women involved ovarian stimulation by human menopausal gonadotrophins (HMG). They used Pergonal which was an extract derived from the urine of menopausal women. It enabled the stimulation of several follicles and could be scheduled with a placental-derived chorionic gonadotrophin to provide an artificial trigger for ovulation. This enabled orderly scheduling of women for laparoscopy to collect their oocytes from the follicle just prior to its rupture when the egg is released and rapidly enters the fallopian tube where it would be unavailable for retrieval. However, this process can cause major hormonal disturbance and luteal phase insufficiency, which frustrated this first IVF pioneer team. They did achieve one defined pregnancy in 1975, but it proved to be a tubal ectopic, requiring surgical removal [14]. A number of other suspected pregnancies have recently been revealed from the “Oldham Notebooks” and may be defined as probable biochemical not reaching clinical definition [5]. Following these frustrations, in 1977 Edwards and Steptoe decided to avoid ovarian stimulation with its accompanying luteal phase challenge, and to collect the single oocyte from the one follicle developing in a natural ovulation cycle. This was enabled by the recent availability of the HiGonavis kit (comprising sensitised lyophilised sheep red blood cells) to detect the natural LH surge from the urine samples of women at the peri-ovulatory stage around the middle of their menstrual cycle [15].

Having commenced their research at Oldham General Hospital but finding many logistic problems undertaking this work in the major hospital, they moved their work to the affiliated Dr Kershaw’s Cottage Hospital in 1971 thereby remaining under NHS support. There, during 1977–1978, Steptoe admitted 79 women [16,17] for ovulation tracking, detecting the LH surge in 68 who were then scheduled for laparoscopy. In 23 cases, no egg was recovered for various reasons including impossible access to the ovaries because of adhesions, misleading LH surge as no follicle detected, and no egg retrieved despite attempted aspiration of a visible follicle. In 10 cases the retrieved egg failed to fertilise after insemination and 3 cases demonstrated fertilisation by the presence of pronuclei but the zygote failed to enter the cleavage stage. At the Day-3 to Day-4 stage, 4-cell to 16-cell stage embryos were transferred to the uterus by trans-cervical cannulation, although trans-myometrial transfers at laparoscopy had also occasionally been performed. The embryo transfers were performed preferentially in the evening in 32 women, 4 of whom were subsequently diagnosed pregnant [17]. Of the four pregnancies, Louise Brown was born near term 25 July 1978 [1]. Of the other three pregnancies a miscarriage occurred in the second at gestational week 11 with a triploidy XXX fetus identified; a third male infant named Courtney Cross was born severely premature at 21 weeks on 26 November 1978 and succumbed as a post-amniocentesis loss; the fourth pregnancy proceeded to term with the first IVF male infant, Alistair MacDonald born 14 January 1979 [16,17]. The pregnancy rate was therefore 5.1% of

initiated cycles, 5.9% of laparoscopies, 8.9% of successful collections and 12.5% of transfers. The livebirth rate (not counting Courtney Cross whose life was too brief) was respectively 2.5% of initiated cycles, 2.9% of laparoscopies, 4.4% of egg retrievals and 6.3% of those reaching embryo transfers. Of relief to the pioneers, her parents and the entire scientific community, Louise Joy Brown had no fetal abnormalities, has led a normal healthy life and now delivered 2 sons, both conceived naturally – Cameron Mullinder born 20 December 2006 and Aiden Mullinder in August 2013 [18].

During those Kershaw years, Steptoe and Edwards conducted their pioneer research activities from their own financial resources, having been denied research funding from the Medical Research Council [9]. However, Edwards indicated this was supplemented with philanthropically donated funds [19]. The benefactor has recently been revealed by Edwards' colleagues, Martin Johnson and Kay Elder, as Lillian Lincoln Howell who donated the current equivalent of £500,000.00 [20].

## 2.2. The seven subsequent teams with live births by 25 July 1982

During the 1970's several other teams were working independently on the same quest to generate "test-tube" babies to resolve the problem of infertility, for which, at the time, very few medical or surgical techniques were reliably or safely successful. The following lists those teams who, whilst being inspired by the reports from Edwards and Steptoe, actually strove independently and generated livebirths over the 4 years following the birth of Louise Brown. They also deserve to be categorised among the "Founding Pioneers" of IVF, creating the platform from which the subsequent IVF teams sprang as they also spread their knowledge, which was gained from empirical studies, so widely in various ways. This history has been presented in part from a couple of sources [2,21] but is rather incomplete from the perspective of our intimate experience as the main focus was on those who attended the Bourn Hall meeting of 1981, a faulted exercise for this purpose as indicated earlier. As authors we travelled widely to meetings around the world, well supported by the newly emergent instrument, assay and culture media companies enabling us in a unique way to gain familiarity with all groups establishing during the period 1976 to 1985; hence we wish to expand the story with due perspective based on timing of live births.

### 2.2.1. The second team (Indian)

Although remaining controversial to this day, the second IVF baby was delivered in Kolkata (previously Calcutta) on 3rd October 1978 [22]. This was achieved by a team led by Medical Doctor and Scientist Subhas Mukherjee (Mukherji) [23] and which comprised cryobiologist Dr Sunit Mukherjee (Mukherji) and gynaecologist Dr Saroj Kanti Battacharya. Associated colleagues included gynaecologist Dr TC Anand Kumar who was also part of the subsequent team led by Dr Indira Hinduja, achieving India's first official IVF baby in August 1986; [24] and Dr Baidyanath Chakravarty who generated India's second official IVF baby in November 1986 [25]. Certainly, Mukherjee had the appropriate credentials with MD and PhD from the University of Calcutta, followed by a second PhD from Edinburgh University, becoming Professor of Physiology back in Kolkata. He used HMG for ovarian stimulation, then transvaginal delivery of the ovaries via posterior colpotomy to harvest the oocytes. He cryopreserved the embryos and transferred a thawed embryo in a subsequent cycle leading to the birth of Kanupriya "Durgu" Agarwal. Although a lack of clearly documented details caused scepticism about this event, Mukherjee's story has been carried into a strongly credible position by various celebrated Indian medical pioneers who worked with and learnt their techniques from him, including TC Anand Kumar [23] and Baidyanath Chakravarty [25]. Furthermore, TC Anand Kumar who was offered the crown as the pioneer of India's first official IVF baby with Dr Indira Hinduja, relegated this crown of first Indian IVF infant to Mukherjee with an

enlightened description of the events of 1977–1978 [23]. Anand also described the unfortunate reaction of the medical fraternity of Calcutta along with the naively unsupportive findings of the "alien" investigative committee set up by the Government of West Bengal which reported in February 1979. These led to severe restrictions on Mukherjee's work, reports, presentations and travel. He ended his own life in 1981 in circumstances of humiliation which Kumar believes should be redressed by a posthumous acknowledgement similar to the Nobel prize finally accorded to Robert Edwards who also faced scepticism during the decade after his pioneer achievement [3,8] and which appears to have caused the 32 year delay in conferring that prize [7,8]. Our view supports this as Dr Chakravarty spent a sabbatical period at PIVET in 1984, during which he described his training under Mukherjee and demonstrated to us his skills with posterior colpotomy exposure of the ovaries. This utilises a Sims-like vaginal speculum, only slimmer, longer and deeper enabling one or both ovaries to be spooned onto the instrument following a single 2.5 cm horizontal incision in the posterior fornix. This is similar instrumentation as that used for salpingectomy sterilizations on a large scale throughout India. It can be performed under mild sedation or local anaesthesia with procedures often conducted in 10–15 min at very low cost.

### 2.2.2. The third team (Australian)

An Australian team led by Professor of Obstetrics and Gynaecology Carl Wood reported an early biochemical-stage loss of an IVF pregnancy in 1973 from Monash University in Melbourne [26]. The 8-man team had Dr Alex Lopata as their chief scientist but remained frustrated in their attempts to achieve the world's first delivery of an IVF baby. Following the success of Edwards and Steptoe, Professor Wood divided his team into 2 groups – one based at the Royal Women's Hospital under Dr Ian Johnston with Alex Lopata as the scientist and the other at the Queen Victoria Hospital under Dr John Leeton with veterinary scientist Dr Alan Trounson [26]. Although combined as a single team, these two Melbourne units competed from the two hospitals where Johnston and Lopata followed the Edwards/Steptoe model of tracking the natural LH surge for ovulation whilst the Leeton & Trounson team pursued an ovarian stimulation model with Clomiphene assisted by an HCG injection to regulate the ovulation process [3,27]. Both teams utilised laparoscopy for the egg retrievals but the natural cycles meant laparoscopy procedures had to be arranged for irregular times, often during out-of-routine working hours whilst the regulated protocol enabled convenient surgical theatre scheduling. As it transpired, the Johnston/Lopata team achieved the first Australian IVF baby, Candice Reid born 23 June 1980 [28]. However, that team had subsequent frustration with no further pregnancies for almost 2 years, during which time the Leeton/ Trounson team achieved 14 pregnancies from 115 initiated cycles resulting in nine ongoing pregnancies proceeding to live births during 1981 and 1982. Two of these pregnancies commenced as twin gestations, one with resorption of a gestational sac, delivering as a singleton [3,29]. This heralded the first respectable pregnancy rate (12.2%) and livebirth rate (7.8%) per initiated cycle, one which continued to improve over the ensuing years, especially when gonadotrophins were added to the Clomiphene schedule for ovarian stimulation.

In his book, Carl Wood acknowledges the Edwards and Steptoe team as the first pioneers of IVF despite commencing his own efforts in Melbourne in 1971, only a couple of years after [27]. However, his team did report their mid-1970's early pregnancy losses as the first IVF pregnancies, a rather naive suggestion given that those pregnancies only reached a pre-clinical stage and we are now aware that Steptoe had many such pregnancies which he did not formally report [5] and he was critical of the Monash report. None-the-less the Wood team generated the first substantial pregnancy rate showing that ovarian stimulation with the orally active inexpensive anti-estrogen, Clomiphene, could be feasibly undertaken with its orderly scheduling system for oocyte pickup. In their books on the early history of IVF both Wood

[27] and Leeton [3] acknowledged sending Mac Talbot, one of their team to Oldham in the early seventies to learn Steptoe's laparoscopic oocyte pick-up techniques. However subsequent contributions from the "Fathers of IVF" was minimal and the Melbourne teams, described by Leeton as combined, with both under the direction of Wood, developed autonomously assisted with substantial funding from the Ford Foundation. They introduced unique ideas such as lining the aspiration needles with Teflon to reduce friction-damage to the oocyte-cumulus-complex and deferring insemination of the recovered oocytes for 4–6 h to enable further oocyte maturation. HiGonavis kits were replaced by rapid serum immuno-assay detection of the LH surge developed locally. Furthermore, Melbourne became the main demonstration centre for overseas trainees as the Kershaw facility was less available, then closed in mid-1978 with Edwards and Steptoe resuming at Bourn Hall Cambridge in 1981.

### 2.2.3. The fourth team (American)

Eminent gynaecologist Howard Jones and his wife, eminent gynaecological endocrinologist Georgianna Seeger-Jones both retired from Johns Hopkins School of Medicine in 1978. They were encouraged to start up an IVF facility in Norfolk Virginia after the birth of Louise Brown stimulated public donations to assist them and avoid the USA falling behind in this medical frontier. They assembled a team including MD's Anibal Acosta and Jairo Garcia as well as nurse Lucinda Veeck who trained up as an embryologist and subsequently produced important atlases in embryology [30]. After a year of failure with natural cycle attempts, the team utilised gonadotrophin stimulation with Pergonal, high-dose HCG Triggers, multiple embryos for transfer and high-dose progesterone (Proluton) to support the luteal phase. Their first IVF infant was Elizabeth Carr born 28 December 1981. Elizabeth subsequently delivered her own, naturally conceived son Trevor James Comeau on 5 August 2010. In an amazing medically productive life Howard Jones, born 25 December 1910, continued actively researching wide fields in reproductive medicine until just prior to his death at aged 104 years. He delivered a lecture entitled "7 roads travelled well and 7 to be travelled more" celebrating his 100th birthday and which was published in the prestigious American journal *Fertility and Sterility* in March 2011 [31]. The Norfolk contribution included the return to gonadotrophin stimulation which was enabled by the addition of high-dose parenteral progesterone therapy to cover the luteal phase.

### 2.2.4. The fifth team (British)

Whilst Steptoe and Edwards were pursuing their research quest between Oldham and Cambridge, a new team from the Royal Free Hospital School of Medicine adjacent to Hampstead Heath in London, was assembled by Professor Ian Craft in 1977. With the support of a significant donation from Pink Floyd member Roger Waters whose second wife Lady Caroline Christie was a patient with Craft and who delivered their daughter India, Craft was able to establish an IVF facility within the National Health System. Craft charged Senior Lecturer in Obstetrics and Gynaecology Dr John Yovich with the task of setting up both animal and human laboratories to develop the first IVF facility on the fifth floor within the NHS [32]. In the 2-year period prior to the birth of Louise Brown, Edwards and Steptoe had become reticent about revealing details of their methodologies as they had experienced several disappointments. Apart from the afore-mentioned ectopic pregnancy, they had received harsh medico-scientific criticism, rather than accolades, about their work and this contributed to their failure to gain Medical Research Council funding [9] whereas the Melbourne team had received substantial funding from the Ford Foundation. Without their assistance Yovich had to "start from scratch" (to coin an idiom) but was enabled to learn the embryology processes directly from the mentors and colleagues of Edwards in Cambridge at the Animal Research Station (ARS) in Huntingdon Road in the unit of Reproductive Physiology and Biochemistry. This meant an attachment during the years 1976–1979 with Chris Polge, the pioneer of bull sperm cryopreservation who was

then actively researching the challenge of pig egg cryopreservation. Through Polge at the ARS, Yovich learnt techniques from esteemed embryologists Steen Willadsen who had already achieved cloning by nuclear transfer in sheep, Cyril "Dub" Adams who demonstrated methodology for fertilising the human gametes within the rabbit oviduct (which the RFH team pursued for a period) [33,34], Bob Moore who taught tight adherence to laboratory culture systems to control pH, osmolality and temperature, Bill "Twink" Allen researching horse cloning and Ian Willmut who later achieved somatic cell cloning with Dolly the sheep. Further experience during these years was also gained directly from Professor Anne McLaren and David Whittingham based at Wolfsson House in London as well as Lynne Frazer at Chelsea House, King's College in London and John Marston researching embryo transfer techniques in Rhesus monkeys in Birmingham [35]. Craft and Yovich initially pursued IVF with Clomiphene stimulation [22] but converted to natural cycles with HiGonavis tracking after Edwards and Steptoe revealed this as their reason for success in 1978. This did indeed generate an IVF pregnancy for Craft and Yovich in 1979 in a hairdresser aged 32 years from Bristol but sadly the pregnancy miscarried at the 9th week of gestation [33,34]. Yovich returned to his home in Perth, Western Australia in December 1979 after handing over to trainee embryologist Karen Shelton, gynaecologist David Smith, ultrasonographer Bill Smith, research nurse Hillary Twigg, and laboratory technologist Albert Bernard. The team at the Royal Free Hospital soon published their first pregnancy with live birth - twins resulting from the transfer of 2-cell embryos to the uterus, delivered on 29 April 1982. These were the first documented IVF twins. Craft also described pregnancy with livebirth following the transfer of sperm and eggs, brought together in-vitro for one hour, being 6 h post oocyte recovery, then transferred into the uterine cavity where they completed fertilisation and development in a close-to-nature IVF-related process [36,37]. That birth occurred on 25 August 1982 and the *Lancet* report details 5 other advancing pregnancies including two twin gestations, following the transfer of cleavage-stage embryos [37]. In all these cases Craft had stimulated the ovaries with clomiphene citrate and triggered ovulation with HCG. Craft also later reported pregnancies and livebirths arising from pronuclear-stage zygotes being transferred to the uterine cavity, another unique IVF-related procedure [38], and his facility pioneered many other important developments documented in more than 265 Pubmed-listed publications covering the historical evolution period of IVF. Craft's contributions were wide-ranging including the demonstration that the Clomiphene/HCG stimulation schedule was feasible and that the uterus was a suitable site for gametes, pronuclear-stage oocytes and early cleavage embryos; not just blastocysts which matches the natural reproductive process. Craft's team documented ovum retention following ovulation in clomiphene cycles and postulated this as a reason for the widely discrepant difference between ovulation and pregnancy in such cycles [39]. His unit published the first description of endometrial patterns which have proven relevant for predicting receptivity [40]. Craft became the surrogate teacher for many scientists and clinicians seeking to learn the methods during the period 1977 to 1981 when Steptoe and Edwards were reticent or "between facilities". These included David Smith and Rick Porter who assisted Doug Saunders to establish his North Shore IVF facility in Sydney and which generated live births from late 1982. Craft developed his own follicle aspiration pump and catheters with Rocket Medical, a UK based company manufacturing medical devices. He was the first to successfully introduce GnRH analogues into IVF practice and published the first livebirth from PESA (percutaneous epididymal sperm aspiration) [41].

### 2.2.5. Sixth team/s (French)

Two teams evolved in Paris, France; the Clamart group led by gynaecologist Rene Frydman with scientist Jacques Testart being both competitive and collaborative with the group from Sèvres led by gynaecologist Jean Cohen and his scientists Jacqueline Mandelbaum and Michelle Plachot. The Clamart group achieved the first livebirth in

February 1982, the group from Sevres the second in June 1982 [2,21], each bringing innovative ideas to the field.

They too utilised ovarian stimulation schedules after a fruitless period with natural cycle procedures. They also developed their own needle sets for oocyte aspiration and fine embryo transfer catheters which are still popular throughout Europe today [42].

#### 2.2.6. The seventh team (German)

The first IVF child in Germany was born on April 16, 1982 in Erlangen. This achievement resulted from a team led by Dr Siegfried Trotnow with scientist Tatjana Kniewald [43]. This team was highly innovative, generating novel oocyte aspiration needles including a double-lumen needle which enabled follicle flushing in a uniquely controlled manner. His facility was highly successful and was able to report on 100 IVF pregnancies by 1985. For unclear reasons, Trotnow's wide-ranging IVF innovations went largely unsung and he was not mentioned in earlier reports of IVF pioneers [2,21] despite 46 publications listed in Pubmed to 2001. He died aged 63 years in 2004 having endured harsh criticism from many quarters for daring to undertake the “scandalous” work of IVF. (However, the authors of this article JLY and IC, admired Trotnow's endeavours and adopted much of his technologies and ideas).

#### 2.2.7. The eighth team (American)

North America comprised a number of advanced research workers in the fields of reproductive endocrinology, infertility management and gynaecological surgery, including laparoscopy and culdocentesis procedures. Prominent names included Anne Wentz with Charles Torbit (in Nashville Tennessee), Martin Quigley with Don Wolf (in Houston, Texas), Alan DeCherney with Mary Polan (in New Haven, Connecticut), Norbert Gleicher with Jan Friberg (in Chicago, Illinois) and Richard Marrs with Charles March and Daniel Mishell (in Los Angeles, California) but only the Marrs team had achieved a live birth within the 4-year time-frame. Their first infant was born on June 10, 1982 in Los Angeles [44].

#### 2.2.8. The ninth team (Australian)

Applying the skills developed under Craft, Yovich rapidly established an IVF facility at the King Edward Memorial Hospital during 1980 following his return to Perth, Western Australia (WA). This was enabled by a Bank of New South Wales grant (Aus \$11,000) along with the financial assistance from a group of local grandmothers who conducted lamington drives (Aus \$25,000) as well as benefactors who were aspiring patients (Aus \$50,000) [34]. The fledgling IVF facility generated 3 pregnancies from October 1981, one of which eventuated in the birth of Jarrad Carter on 13 July 1982 [45]. Jarrad's mother had lost both fallopian tubes from consecutive ectopic gestations. Yovich stimulated her ovaries with Clomiphene, triggered with HCG and collected the oocytes at laparoscopy. He also carried out the fertilisation and embryology procedures, assisted by a young laboratory assistant, recent high-school graduate Alison Pusey and research nurse Rosemary De Atta. Yovich utilised progesterone support in the luteal phase when it became evident that corpus luteal function was diminished. In Australia, WA was therefore the second state to achieve IVF pregnancies; after the combined teams from Melbourne in the state of Victoria. Yovich termed his clinics PIVET (an acronym for Programmed In Vitro fertilisation and Embryo Transfer) because of its commitment to ovarian stimulation and luteal support, mainly using low-dose HCG in a 4-injection schedule which remains the PIVET mainstay [46]. PIVET subsequently assisted many IVF facilities to establish in various countries including Malaysia [47], Greece [48], Japan, and Singapore, generating the first home-grown IVF infants for Malaysia and Greece. Later, Yovich introduced novel ideas to the Bourn Hallam group in 1989–1991 when he took on the role of Hallam's Medical Director, working alongside Bob Edwards, Peter Brinsden, Stuart Campbell (Ultrasound pioneer), Howard Jacobs (Endocrinology consultant), John

Pryor, Bill Hendry and Anthony Hirsch (Urology & Andrology pioneers), and supervising trainees who would soon become prominent in the field including SL Tan and Adam Balen. Yovich documented 135 IVF pregnancies by April 1985 in his PhD thesis [33] and, with Gedis Grudzinskas wrote the first comprehensive clinical and laboratory textbook on assisted reproduction [49]. Currently in Australia, PIVET, under the Medical Directorship of Yovich, operates in 3 Australian States and these have become training and research facilities for both laboratory and clinical trainees, particularly from China and Malaysia. The ovarian stimulation as well as triggering and luteal support schedules are personalised being conducted according to unique algorithms [50] which minimises risk for ovarian hyperstimulation, despite utilising HCG for luteal support in a large proportion of cases. Working with Cook Australia, PIVET developed its own aspiration needles and embryo transfer sets. The PIVET-Cook double lumen needle [49] has become one of the most popular worldwide and is especially useful for cases with few follicles as well as the small follicles for in vitro maturation (IVM).

### 3. Subsequent teams

After the afore-mentioned 9 teams, all documenting live infants during the designated 4-year period, several other prominent teams reported live births throughout the latter part of 1982. These were:

Lars Hamberger with Matts Wikland from Sweden [51] whose first IVF livebirth was in Gothenburg September 1982. This team expanded on the ideas of Bernd-Joachim Hackelöer [52,53] for ovarian follicle tracking by ultrasound and Susan Lenz for oocyte pick-up under ultrasound direction [54]. This commenced with trans-abdominal, then trans-vesical procedures before moving to trans-vaginal oocyte aspirations [55].

Wilfried Feichtinger with Pieter Kemeter from Vienna, Austria delivered their first IVF livebirth in October 1982; This team also acknowledged working on the pioneer developments of Bernd-Joachim Hackelöer and Susan Lenz to develop their very successful trans-vaginal oocyte pick-up method under ultrasound control [56]. In fact, Feichtinger came to Australia for the fourth World Congress on IVF held in Melbourne in 1985 and single-handedly converted Australian pioneers from laparoscopic to TVOA (trans-vaginal oocyte aspiration) with a series of skilful demonstrations.

Two further Australian groups – Doug Saunders with Ian Pike in Sydney and Chris Chen with Warren Jones in Adelaide deserve mention. Also, in Adelaide, Kerin and Warnes started reporting pregnancies from May 1982 but live births did not ensue until 1983. Each of these teams were well supported from the Monash facility, particularly by Leeton and Trounson.

In the United States, after Elizabeth Carr, the Norfolk group delivered numerous infants during 1982 and several other IVF facilities commenced, but to our knowledge, none of these, apart from Richard Marrs (Team 8), reported livebirths until 1983.

The highly esteemed unit of Paul Devroey with Andre Van Steirteghem from Brussels, Belgium [57] also reported their first livebirth in 1983.

Each of these IVF teams (see Table 1) were headed by a gynaecologist-scientist team similar to the First team “fathers” Steptoe and Edwards. Although we have designated the team leaders as two or three individuals, the “teams” generally comprised 6–10 individuals in the beginning, and eventually developing into structured facilities with a Medical Director, a Scientific Director, a Clinical Nurse co-ordinator, a Theatre Nurse manager, Senior and Junior Embryologists, Hormone assay technologists, Andrology technologists, and a Psycho-social counsellor.

### 4. Concluding comment

The “First Pioneers” of IVF introduced their innovative work to a

bewildered world where colleagues, politicians and the communities were uncertain how to respond to the idea of IVF or “procreation in a test tube”. Until 1978 this was considered to be a sacred process controlled by God or Nature, but definitely not by human researchers. They faced harsh criticism, resulting in various regulatory controls, until this current era where the work is universally accepted and a settled worldwide community is now seeking more advances as the broader potential is becoming clearer. Each of the “First Pioneers” presented articles examining the ethical issues which were arising and, in their respective countries, contributed to the development of a Code of Practice for assisted reproductive technologies. The leader in this area was First Pioneer, Robert Edwards, rightfully designated, along with Patrick Steptoe, as the “Father of IVF” and who, in 1984, instigated the foundation of ESHRE; the European Society for Human Reproduction and Embryology; along with four major journals covering clinical, scientific and psychosocial aspects in addition to innovations in assisted reproduction. These have become the leading vehicles world-wide for the assessment and publication of research and advances in all aspects of reproduction.

From the above “First Pioneers” of IVF, being those first independent innovative pioneers, numerous subsequent IVF facilities have evolved around the world developed on the shoulders of the first dozen. The world has now become densely populated with IVF facilities and, at the time of Louise Brown’s 40th birthday, there are estimated to be more than 8 million offspring from this amazing technology.

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