The early days of IVF outside the UK

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In this article the history of IVF in geographical regions outside the UK are traced by pioneers of that time. Following the birth of Louise Brown in 1978, live births after IVF occurred in Australia in 1980, in the USA in 1981 and in Sweden and France in 1982. Following the first IVF birth in Australia, the Government of Victoria established a review of IVF research and practice which led to the proclamation of the Infertility (Medical Procedures) Act 1984, the first legislation to regulate IVF and its associated human embryo research. Despite such restriction, IVF doctors and scientists from Victoria, especially those under the leadership of Carl Wood, Alan Trounson and Ian Johnston continued to initiate new treatments for infertility and new methods for delivering this treatment. In the USA IVF research began on animals as early as the 1930s, when Pincus and Enzmann at Harvard were involved in attempts at IVF in the rabbit. In the 1940s, John Rock attempted human IVF with 138 human oocytes without success. In 1965, Bob Edwards was with Georgeanna and Howard Jones at Johns Hopkins where attempts were made to fertilize oocytes in vitro. Clinical IVF began in earnest in the USA in 1980 with the first birth in 1981 achieved by the use of HMG—a first successful use with IVF. In France, two groups Frydman and Testart (Clamart) and Cohen, Mandelbaum and Plachot (Sevres) focused their research in particular directions. In 1981, the Clamart group developed a plasma assay for the initial rise in LH. The Sevres group developed a transport technique. Plachot produced a long series of cytogenetic analyses of oocytes and human embryos. Mandelbaum described the microstructures of the human oocyte. The start of IVF in France benefited from the help of animal researchers from the Institut National de la Recherche Agronomique. The first babies were born in Clamart in February 1982 and in Sévres in June 1982. Important contributions to the development of IVF from the Nordic countries include techniques for ovarian stimulation, sonographic techniques for monitoring and vaginal oocyte retrieval and also unique possibilities for monitoring IVF safety. These developments, in combination with relatively permissive laws for the practice of reproductive medicine and relatively generous reimbursement policies, as well as a general public confidence in IVF, have led to an exceptionally high availability of IVF, within international comparison.

Key words: ART/history of IVF/human embryo research/infertility treatment/legislation

Introduction

During ESHRE’s 19th annual meeting in Madrid in June 2003 Bart Fauser, the editor of Human Reproduction Update, asked me to co-ordinate a series of historical articles for the journal on the origins and early days of IVF. His idea was to ask the pioneers to tell their own stories of assisted reproduction in their own geographical regions, with each author taking responsibility for one region. These are the individuals I approached:

- Robert Edwards, the original pioneer, the model for all those who followed and the organizer of the first major meeting of IVF specialists at Bourn Hall, Cambridge, in September 1981.
- Alan Trounson for Australia.
- Howard Jones for the USA.
- Lars Hamberger for the Nordic countries.
- and myself for France!

Alongside these names and places we should remember that the first live births after IVF took place in 1978 in the UK, in 1980...
in Australia, in 1981 in the USA and in 1982 in Sweden and France.

My choice of collaborators was based solely on those first live births, and to this extent my selection was not entirely fair. In those early days of research, and within such an indifferent or even hostile environment, there were throughout the world isolated groups of enthusiastic individuals who, despite the difficulties and mistruths, had in common a sure belief in the success and worth of these new assisted techniques. But for reasons of space I was not able to call on them all—even though many of them had pioneered their own live births by 1982 and, in their work and communications, were exchanging the gifts of friendship and cooperation in the best spirit of science. I am thinking—among many—of:

- Wilfried Feichtinger and Pieter Kemeter, both active friends from the very beginning, who, after a series of natural cycle attempts, started with clomiphene in the summer of 1981. They did all their own biology. Their first twin babies were born in August 1982, and by October 1982 they reported a 23% pregnancy rate. They had problems with the Vienna University Medical School but organized in 1983 an important meeting in Vienna.
- Klaus Diedrich, who in Bonn organized ESHRE’s first annual meeting in 1985.
- André Van Steirtegem in Brussels, Pedro Barri in Barcelona, Ettore Cittadini in Palermo, Gerard Zeilmaker in Rotterdam … and many more.

They will all have stories to tell, anecdotes to recall. But space is limited …

Some of these people can be seen in the picture from the reunion meeting in Bourn Hall in 1997 (Figure 1).

In those early days of IVF enthusiasm was contagious and each group got from the next some tiny item for the recipe, some small detail which allowed this or that step of progress. At the time, of course, there were no regulations governing reproductive medicine, but Edwards had even then recognised the moral discussions which the new techniques would raise and had convened an ethics committee within the framework of the rapidly growing ESHRE. He encouraged us all not to neglect the ethical implications of what we were doing.

Edwards, with whom I formed over the years a deep bond of friendship, told me when I first approached him about this project that his own activities would not leave him the time to write his chapter on the UK. We thus agreed that in 2004 he would send me articles already published recording the history of IVF in Britain. We are still awaiting those articles, and for the present we must therefore resign ourselves to an international history of IVF without any record from Britain—or any note on the birth of Louise Brown. But this single event did indeed mark the start of IVF as it began its spread across the world, and those pioneers who embraced the technique owe everything to Jean Purdy, Patrick Steptoe and Robert Edwards.

The early days of IVF in Australia: 1970–1990

Introduction

The 1970s and 1980s saw infertility become more treatable than it ever had been. The previous limited options available to the infertile—adoption, using donor insemination or becoming reconciled to childlessness, began to proliferate rapidly. Following the advent of IVF was to come the development of an array of assisted reproduction technology (ART) techniques, each designed for treating different causes of infertility. The course of these developments in Australia is discussed here within the context of the different scientific and medical advances that occurred, the social implications of these advances and the State of Victoria Government’s responses to these rapid developments.

The beginning of IVF in Australia

Candice Reed was the first IVF baby to be born in Australia in June 1980 (Lopata et al., 1980) and the third IVF baby to be born in the world. Her birth followed the report by the Melbourne team in 1973 of two very early IVF pregnancies that had been lost after less than 1 week (De Kretser et al., 1973). These ‘chemical’ pregnancies, signified by rising levels of HCG, demonstrated that IVF embryos could develop to the blastocyst stage in vivo and probably initiate implantation. Further pregnancies occurred in the early 80’s as can be seen from Table I.

How did IVF come to be used in Melbourne, Victoria?

Successful IVF and embryo culture studies in animals had been presented and discussed at the Australian Society for Reproductive Biology Conference in 1970. This led Professor Neil Moore to suggest to Professor Carl Wood, Chairman of Obstetrics and Gynaecology at Monash University and the Queen Victoria Medical Centre (QVMC) that using a similar approach in humans might be useful as a treatment for infertility. Carl Wood and colleagues (Figure 2) had been unsuccessfully exploring the construction of artificial tubes (Wood et al., 1971) and Fallopian tube transplantation as methods to repair blocked Fallopian tubes in infertile women (Paterson and Wood, 1980).

As a consequence of these discussions and a visit to observe first hand the research of Neil Moore and his PhD student Alan Trounson at Jerildere, New South Wales, Carl Wood established a combined IVF research team in Melbourne involving the Royal Women’s Hospital (RWH), QVMC and Monash University. Drs John Leeton and J. Mackenzie Talbot were the clinical staff of

<table>
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<tr>
<th>Pregnancy outcome</th>
<th>Year pregnancy completed</th>
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<tr>
<td>Biochemical pregnancy</td>
<td>6</td>
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<td>Ectopic pregnancy</td>
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<td>Spontaneous abortion</td>
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<td>Stillbirth**</td>
<td>–</td>
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<td>All pregnancies</td>
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* Pregnancy data from Monash University IVF Program and Melbourne IVF Program.
** Includes multiple pregnancies with at least 1 stillbirth.
the QVMC team and Mr Ian Johnston (Figure 3) was the medical director of the RWH team. Alex Lopata, PhD, appointed in 1972 in the Department of Obstetrics and Gynaecology at Monash University, was the basic scientist–embryologist to both teams.

Hormonally stimulated IVF cycles were carried out in Melbourne from 1972 to 1978 using either human pituitary gonadotrophin (Talbot et al., 1976) or clomiphene and HCG (Lopata et al., 1978). Following the first successful IVF birth in England in 1978 (Steptoe and Edwards, 1978), using a natural cycle, both Melbourne IVF teams began using routine natural cycle procedures. This meant that the timing of oocyte recovery depended on the detection of a spontaneous LH surge (Kerin et al., 1980). Therefore, it was erratic and difficult for practical purposes to carry out IVF within the hospital environment. Oocyte recovery

Figure 1. Group photograph of the attendees of the 1997 Bourn Hall Reunion Meeting. Numbered key.
needed to be performed at any time during the day or night. Because of this, there was little general support for the IVF research project in some areas of the hospitals involved.

Dr Alan Trounson (Figure 4), who had been attracted by Carl Wood to return from Cambridge, UK, to join the Monash University Department of Obstetrics and Gynaecology in 1977, on a Ford Foundation Grant to Wood, Hudson, Burger and Findlay, was asked to join the QVMC IVF research team in 1979 and to share the scientific work and development of the IVF project with Alex Lopata.

Trounson began to simplify and improve the culture media used in IVF (Trounson et al., 1981). He also introduced quality control systems to select the culture medium to be used by drawing on the success of mouse IVF as an indicator (Mohr and Trounson, 1980). Perhaps the most significant change introduced by Trounson, with the encouragement of John Leeton, was the reintroduction of clomiphene–HCG hormonal stimulation cycles. With these stimulated cycles the number of mature oocytes collected could be increased and HCG administration allowed the exact timing of ovulation or oocyte collection to be identified (Trounson et al., 1981). As a result of observations by Sathananthan on the immaturity of the oocytes recovered after ovarian stimulation, Trounson also introduced a delay between oocyte collection and insemination to allow the oocytes collected to complete maturation (Trounson et al., 1982). The additional culture prior to fertilization had been shown to be important for enabling the oocytes collected to complete their meiotic maturation (Sathananthan and Trounson, 1982). Introduction of these changes led to sustained IVF pregnancies (Wood et al., 1985,
Figure 5), the training of many clinicians and scientists from around the world by the Monash group, and the establishment of repeatable and successful treatment for human infertility. From the perspective of the combined IVF research team, the birth of Candice Reed from an oocyte collected in a natural ovulatory cycle, justified the strategy of using IVF and embryo transfer to treat human infertility, despite criticism from surgeons, who at the time were repairing blocked Fallopian tubes by microsurgical techniques. The previously failed attempts of replacing women’s damaged Fallopian tubes with either artificial or transplanted tubes and the often poor results of macrosurgery and microsurgery for women with extensive tubal disease (Paterson, 1978) began to be considered to be less important approaches for the treatment of infertility due to tubal blockage.

The Melbourne IVF teams separated to conduct work in their own IVF programmes following the first successful Australian IVF birth, with Alex Lopata becoming the full-time scientific director at the RWH and Alan Trounson, the new scientific director at Monash University and QVMC. This separation was the beginning of a period of constant development of novel ARTs that would overcome many causes of infertility in both women and men.

It would have been impossible at this time to predict the rapid growth of ART that was to follow worldwide. IVF clinics were established around Australia in the early 1980s: in Sydney, under the direction of Doug Saunders; in Adelaide under the direction of Lloyd Cox, John Kerin and Warren Jones; in Brisbane with John Hennessy as director; and in Perth under the direction of John Yovich. IVF clinics also began to be established in many other countries (Gunning, 1990).

**Improving oocyte recovery and embryo transfer techniques**

Involvement with the practice of IVF had made members of the QVMC team aware that changes were needed to optimize the procedures of IVF and to broaden its applications. These changes were a priority between 1979 and 1982 and included patients with blocked Fallopian tubes and those with idiopathic infertility (Mahadevan et al., 1985).

The first change to be introduced was related to laparoscopic oocyte pick-up (EPU), which was difficult and in many cases unsuccessful because of severe tubal disease, multiple adhesions or hidden ovaries. The success rate of EPU was less than 50% per follicle, and often requiring ‘blind stabs’ as no laparoscopic operating instruments were then available (Lopata et al., 1974). Improvement in the rate of EPU to 60–80% per follicle occurred between 1979 and 1980 when a foot-controlled fixed aspiration pressure control was introduced (Wood et al., 1981) and specially designed Teflon-lined aspiration needles with bevelled points were used (Renou et al., 1981). Improved ultrasound scanning of the ovaries and systems for maturing ovarian follicles were developed too, to increase the success of EPU.

An improved technique of embryo transfer was implemented (Leeton et al., 1982). This technique also involved specially-designed Teflon-lined catheters, relied on a single clinician to perform all embryo transfers to eliminate ‘clinician bias’ and emphasized the need for more careful measurement and placement of embryos being transferred (Buttery et al., 1983).

Researchers in Adelaide introduced Tomcat catheters for successful embryo transfer based on successful methods in animals (Kerin et al., 1984).

**Development of basic methodologies in human IVF**

The gradual introduction of increased ovarian stimulation by combining clomiphene citrate with HMG (Mc Bain and Trounson, 1984) and the concomitant increase in oocytes recovered and embryos transferred (Trounson et al., 1982). The production of multiple oocytes and embryos necessitated the development of suitable oocyte (Chen, 1986) and embryo freezing techniques (Trounson and Mohr, 1983). Both of these techniques were pioneered in Australia and enabled the preservation of embryos and oocytes for subsequent use by the IVF patients.

Researchers at Monash University also confirmed the earlier studies of Steptoe et al. (1971) that the human embryos could be grown through the whole preimplantation period to blastocysts in the laboratory (Mohr and Trounson, 1982). The basic IVF procedures used successfully in Australia and then put into practice elsewhere are described in Trounson et al. (1982).

New techniques for oocyte and embryo donation were developed (Trounson et al., 1983; Lutjen et al., 1984). The establishment and maintenance of pregnancy in a patient with primary ovarian failure was based on previous observations in animals that pregnancy could be initiated by embryo transfer in ovariectomized animals (Trounson, 1992). In this case, embryo donation was used (Trounson et al., 1983). This method was adopted widely to establish pregnancy in infertile or sterile women who had no ovarian function. Oocyte or embryo donation has been integrated into ART as an additional treatment option for infertile, sterile and older women (usually > 40 years), worldwide (Lancaster et al., 1997).

While IVF was considered a potential benefit for the treatment of male and idiopathic infertility (Mahadevan and Trounson, 1984), it only became evident by the use of ICSI, pioneered by the research group in Brussels (Palermo et al., 1992) and by the demonstration of fertilization in the human by subzonal sperm injection. This development was initiated by Laws-King et al. (1987). Ng et al. (1988) in Singapore reported the first birth using subzonal sperm injection but ICSI proved to be much more efficient than subzonal sperm injection (Palermo et al., 1993) because of a block to sperm fusion at the oolemma (Sathananthan et al., 1989). Subsequently, ICSI has been adopted as the treatment of choice for all categories of male infertility, providing some sperm can be recovered from ejaculates or directly from the testes.

Research by the group at the RWH involved very early studies on gamete-intra-Fallopian transfer (GIFT) (Molloy et al., 1987) and their research findings were strongly supported by the publications of Asch et al. (1988) in the USA. GIFT became a popular method for ART in Australia, but now the number of patients using this technique has declined (Lancaster et al., 1997). This procedure has been generally replaced with IVF/ICSI and embryo transfer, as a less invasive procedure.

The GIFT technique is still used as a preference by Catholic patients at the Mercy Maternity Hospital in Melbourne. GIFT as
an outpatient procedure was pioneered in Sydney (Jansen et al., 1990). Intralupinfal transfer of embryos under ultrasound guidance was also pioneered in Sydney by Jansen and Anderson (1993), but this technique has not been retained for oocyte or embryo transfer in ART.

Society’s response to ART
The majority of Australians who have been included in polls have been in support of IVF and its related techniques since its beginning. The results of the Morgan Gallop Polls conducted in Australia between 1981 and 1994 show an average 71% of those polled agree that infertile couples should have access to IVF, 12% of people disagree with this proposition and 17% of the population is undecided. It is also of note that the proportion of people who are undecided about whether infertile couples should have access to IVF is gradually declining. In 1989 only 7% of those polled were undecided.

The support for IVF will not reach 100%. There are certain groups within the community whose religion or philosophy makes supporting IVF impossible. For instance, some feminists object to IVF, claiming that it is an exploitation of women’s bodies by a male-dominated medical profession (Rowland, 1987). The Right to Life (1990) is also a vociferous objector to IVF, claiming that the technique destroys innocent human lives, such as when embryos are discarded rather than being transferred. Devout Roman Catholics who adhere to the Vatican rulings that argues against the use of reproductive technologies. These Catholics are permitted only to use GIFT, provided that certain conditions are met during the procedure. These conditions are that the oocyte and sperm do not come into contact outside of the woman’s body and the sperm used is not obtained by masturbation (Congregation for the Doctrine of the Faith, 1987). Therefore, when the oocytes and sperm are transferred to the woman for fertilization to occur, the gametes are separated in the transfer catheter. The gametes do not come into contact until after transfer to the woman. Some other religions also show some reluctance in agreeing with IVF being practised.

The response of Governments in Australia
In Australia, legislation relating to health is essentially a matter for individual States. The only attempt to introduce Federal IVF legislation occurred unsuccessfully in the mid-1980s (Human Embryo Experimentation Bill, 1985). This proposed legislation was unsuccessful because it sought to completely outlaw all destructive human embryo research, and it contained ambiguities that brought into question whether it would have effects on areas such as prenatal diagnosis by amniocentesis and other fetal testing, such as blood sampling.

In 1984, the Australian State of Victoria became the first jurisdiction to pass legislation to regulate clinical IVF and other methods of ART and its associated human embryo research. The Act was based partly on the recommendations of an inquiry that had been established in 1982 to consider the issues raised by the new birth technologies.

The Government appointed Professor Louis Waller from Monash University to chair the ‘Committee to Consider the Social, Ethical and Legal Issues Arising from In Vitro Fertilization’. In the following 3 years this Committee had produced three reports (Committee to Consider the Social, Ethical and Legal Issues Arising from In Vitro Fertilization, 1982, 1983, 1984). In part the recommendations of these reports formed the basis of the legislation.

The Infertility (Medical Procedures) Act 1984 was not proclaimed in its entirety until 1987, before which it was amended to allow the safety of sperm microinjection to be tested [Infertility (Medical Procedures) (Amendment) Act 1987]. This amendment was a compromise of the requirements for thorough testing being sought by the IVF scientists and clinicians for the benefit of patients, that gave disproportionate acknowledgement to the groups who maintained that syngamy is an important determinant of the moral status of the human embryo.

The Infertility Treatment Act 1995 contains many more provisions to be met by IVF clinics, doctors, researchers and patients than previously. The Act also establishes the Infertility Treatment Authority (ITA), a new body to monitor adherence to its provisions, to approve counsellors, to store records relating to treatment carried out, to administer access to these records, and to grant appropriate licenses and permissions relating to clinical practice and scientific research. It also has discretion in fixing the fee to be paid for the various licenses it issues and the length of time for which this license will apply. IVF clinics, doctors and scientists can function legally only if they have obtained a license from the ITA; embryos can be stored frozen for 5 years and sperm frozen for a maximum of 10 years unless permission has been given for an extension of this time.

Apart from New South Wales, where it was decided after an inquiry by the Law Reform Commission from 1986 to 1987, not to introduce legislation relating to IVF and other new reproductive technologies, most of the other Australian States have introduced legislation to regulate certain aspects of ART. However, none of these Acts are as extensive as the Act in Victoria.

Conclusion
ART provides treatments for many types of infertility found in women and men. Its practice occurs in many countries around the world and it is now beyond doubt that this approach provides a realistic option for infertile people wishing to form a family. Australia, especially the state of Victoria, is fortunate in that it has successful and established IVF programmes that have been developed from a combination of the visionary outlook of Carl Wood and the team of IVF clinicians and scientists he attracted to begin this research. Without the continued ingenuity and tenacity of these IVF scientists, headed by Alan Trounson at Monash University, who was instrumental in reinstating and further developing the use of ovulation induction in IVF, and consequently techniques for embryo freezing, to enable patients to store their embryos for later use and so plan their families. Women lacking ovarian function also can now contemplate having their own children. Further refinements of the treatments will probably occur with ongoing use and further treatments will probably be devised. Since the start of IVF in Australia in 1970, however, it must be acknowledged that infertility has become a much more treatable condition.
The early days of IVF in USA: 1930–1990

Like many other therapeutic innovations IVF became applicable to the human only after it had been demonstrated to work in another mammalian species—in this instance, the rabbit. Furthermore, the preclinical research and early clinical efforts were international in scope. Therefore, looking at the American story is like looking only at one face of a multidimensional solid object.

There were American contributions to the preclinical investigations. Thus, in 1930, an American on leave from Harvard, Gregory Pincus, while working at the School of Agriculture in Cambridge, published a description of his first experiments on IVF in the rabbit (Pincus, 1930). These experiments were unsuccessful, as none of the ova exposed to sperm and transplanted into Fallopian tubes produced any offspring. However, Pincus was intrigued by the problem and upon returning to Harvard teamed up with Enzmann and studied IVF again. These later results were published in 1934 (Pincus and Enzmann, 1934). They thought that they had, in fact, succeeded. However, in their experiments, oocytes and sperm were mixed together and then transferred into the Fallopian tubes, following which young were born having characteristics of the genetic mother as opposed to the surrogate rabbit. We now understand that these oocytes were transferred not having been fertilized in vitro, but probably fertilized in the fallopian tubes just as they are in the procedure currently known as GIFT procedure.

In 1932, ‘Brave New World’ was published by Aldous Huxley (Huxley, 1932). In this science fiction novel, Huxley realistically described the technique of IVF as we know it. The principal difference was that in the novel the embryo was allowed to develop entirely in glass vessels by a process that Huxley labelled, ‘exogenesis’, which at the present time remains scientifically beyond our reach.


The New England Journal of Medicine 21 October 1937

Conception in a watchglass

The ‘Brave New World’ of Aldous Huxley may be nearer realization. Pincus and Enzmann have started one step earlier with the rabbit, isolating an ovum, fertilizing it in a watch glass and reimplanting it in a doe other than the one which furnished the oocyte and have thus successfully inaugurated pregnancy in the unmated animal. If such an accomplishment with rabbits were to be duplicated in the human being, we should in the words of ‘flaming youth’ be ‘going places.’

Recent efforts to document with certainty the author of this editorial was not possible from the New England Journal of Medicine as the records of this era at the office of the New England Journal of Medicine have apparently been destroyed.

However, there can be little doubt in the minds of those of us who knew John Rock that he was the author. The spirit and syntax is pure John Rock.

Time has shown that some of Huxley’s prophecies were realistic. After returning to Harvard, Gregory Pincus worked with John Rock (Figure 6), a practicing gynaecologist at Harvard, on various projects. I think there is little doubt that Rock’s reading of ‘Brave New World’, together with his discussions with Pincus about IVF, led Rock to decide that the time had come to attempt to fertilize human oocytes in vitro to overcome some of the fertility problems that he dealt with in his daily practice. In association with Miriam Menken, a fellow, Rock retrieved more than 800 oocytes from women on whom he was operating under a variety of conditions. One hundred and thirty-eight of these oocytes were exposed to spermatozoa in vitro (Menken and Rock, 1948). This was carried out long before the concept of institutional review boards. By today’s standards, the maturational state of these oocytes was crudely estimated and it is likely that they were maturationally quite heterogeneous because the timing of harvest in relation to ovulation was imprecise. Indeed, many of these oocytes were retrieved at the early part of the follicular phase of the cycle. There was no timing of the surgery in regard to the attempt to harvest the oocytes.

Menken and Rock (1948) thought that they observed cleavage in three oocytes. However, neither transfers were planned nor were any attempted. It is very likely that instead of fertilization and cleavage these oocytes exhibited fragmentation, which is relatively a common experience in this type of work. Rock finally abandoned the project as impossible. Indeed he was well ahead of his time in terms of understanding the circumstances under which oocytes could be fertilized in mammals.

As noted above, the early attempts at IVF were international and Charles Thibault in 1954, working in Paris, did obtain two pronuclei in vitro in the rabbit Dauzier et al., 1954). There was some concern in the scientific community that oocytes so fertilized might not be capable of proceeding to pregnancy.

This problem was solved in 1959 in America at the Worcester Foundation by M.C. Chang, a young Chinese investigator, who had worked at Cambridge, but in 1945 came to work at the Worcester Foundation, which Pincus was involved in starting.

Figure 6. John Rock (1890–1984), a distinguished Boston gynaecologist on the faculty at Harvard. He made a serious attempt to achieve clinical IVF in the 40s.
Chang, only to prove fertilization, transferred oocytes exhibiting two pronuclei after exposure to sperm in vitro to rabbits of a different strain and was rewarded by the birth of rabbits of the original strain, thus proving that fertilization in vitro was capable of proceeding to a birth of a live rabbit. Interestingly enough, this proof was obtained using a donor oocyte (Chang, 1959). Chang was interested in the scientific aspects of this procedure and had little interest in its clinical application. Later in life, when he would discuss this he always pointed out that there are too many people in the world anyway, and the world really did not need IVF (Figure 7). Nevertheless, Chang’s discovery was seminal, as it clearly demonstrated that oocytes fertilized in vitro were capable of developing, if transferred into the uterus and thereby produce live young.

In the 1960s, Georgeanna, my wife, and I were members of the Department of Gynecology at Johns Hopkins. There we were particularly interested in the treatment of infertility; she, the endocrinological aspects of it, and I, the surgical aspects. In the latter part of 1964, I received a phone call from Victor McKusick (Figure 8), then Director of the Division of Genetics of the Department of Medicine at Johns Hopkins. Victor asked me if it would be possible to furnish human oocytes to a friend of his, whom he described as a young, vigorous geneticist who had transferred his interest from the genetics of mice to an attempt to fertilize human oocytes in vitro. Victor McKusick said that his name was Robert Edwards (Figure 9) and asked if there was any chance that we could get him some human oocytes. I immediately responded in the affirmative because at that time the treatment in vogue for polycystic ovarian disease was wedge resection of the ovaries and we were doing two or three such operations a week. Thus, it seemed feasible that at least some of this material could be handed over for this research. It is significant that this phone call came within 5 years of the publication by Chang of the demonstration that oocytes fertilized in vitro were capable of producing young rabbits.

Bob Edwards in 1965 held that his few attempts at fertilization in the few human oocytes available to him at Cambridge had failed because the sperm had not been capacitated. Capacitation after all had recently been shown to occur as a phenomenon and to occur in the female generative tract. In IVF, the sperm, when exposed to the oocyte, have bypassed the female generative tract and therefore, according to Bob’s reasoning, capacitation could not possibly occur. The trick was to achieve capacitation by placing various parts of the female generative tract in the culture medium. Thus, as a control, we tried
culturing oocytes with sperm after what is now called a ‘swim-up,’ because, surely, no capacitation could occur with this technique, which was characterized by the absence of any exposure whatsoever to the female generative tract.

These results were compared to the results of oocytes and sperm cultured with bits of cervical mucus, bits of the cervix taken by biopsy, bits of endometrium, bits of endosalpinx, when this was available, with human oocytes and human sperm placed in the fallopian tubes of rabbits which oocytes became coated with the same gelatinous coat that characterized the rabbit oocytes during their transit to the Fallopian tube. Finally, in desperation with no success otherwise, we placed sperm and oocytes in the distal end of the fallopian tubes of the cynomolgous monkeys. In effect, we did a gift a GIFT procedure. In spite of the fact that over 50 human oocytes were used in these monkey experiments, we were never able to recover more than one or two oocytes after lapses of various intervals of time.

The details of this activity were published in 1966 (Edwards et al., 1966) and recounted in a festschrift for Bob in Human Reproduction in 1991 (Jones, 1991). In addition to the publication about attempts to fertilize human oocytes, Bob published about his continuing studies on the resumption of meiosis in mammalian oocytes liberated from follicles, this time, of course, emphasizing human oocytes. He pointed out that oocytes liberated from the follicle spontaneously resumed meiosis. This observation led to a search for what came to be known as oocyte maturation inhibitor (OMI) in several laboratories, including our own (Channing et al., 1983).

It is to be noted that in the 1965 publication, the title is, ‘Preliminary Attempts to Fertilize Human Oocytes Matured In Vitro’. Therefore, this was a negative report as far as achieving fertilization in the human in vitro. However, a few years ago, Bob Edwards and I relooked at the published photomicrographs in the paper and indeed there is at least one oocyte with two pronuclei and another with four pronuclei. Bob did not claim fertilization because the tail of the sperm was not seen in the ooplasm. Nevertheless, in retrospect it seems scarcely doubtful that human fertilization was indeed obtained at the Johns Hopkins Hospital by Bob and his associates in 1965. This might be referred to as the ‘Charles Thibault era’ of human fertilization.

Following the experience at Hopkins in 1965, Bob Edwards returned to England where 5 years later he teamed up with Patrick Steptoe and, of course, the whole world knows the rest of that story resulting in the birth of Louise Brown, the first IVF baby anywhere at almost midnight on Tuesday, 25 July 1978.

It happened that on 30 June 1978, at the end of the academic year, Georgeanna and I were required by the regulations then in force to take retirement because of age from the faculty at the Johns Hopkins. However, we had been invited by Mason Andrews (Figure 10), the Chairman of the Department of Obstetrics and Gynecology at the new Eastern Virginia Medical School, to come to that school to help it get started and specifically to initiate a division of reproductive medicine within the Department of Obstetrics and Gynecology. Thus, on the night of Tuesday, 25 July 1978, we were in a motel en route to Norfolk and it was while we were in that motel that Patrick Steptoe, just before midnight, delivered by Caesarean section the infant that changed the world of obstetrics and gynaecology. We met the movers of our newly purchased home in Norfolk on the morning of Wednesday, 26 July and were occupied in directing the movers to place furniture in various places and where to put boxes when the phone rang. It was among the first calls received in our new home. The phone call was from a reporter of the local Norfolk newspaper who asked if we had heard about the news of the birth of an in vitro baby in England and would it be possible to come and interview us. She had talked to Mason Andrews, the Chairman of the Department, who had given her some comments about the event and said that the newly arrived faculty members knew Bob Edwards and could perhaps give some more information about this momentous event.

In an hour or two, the reporter, Julia Wallace, came into our new home and interviewed us while we were sitting on the packing boxes as the movers continued to install us in our new home. After we made some very positive statements about what had been accomplished and as she was about to leave, she asked a throwaway question, ‘Could this be done in Norfolk?’ This seemed like a very flippant question and I gave her a flippant answer. I said, ‘Of course.’ She asked, ‘What would it take?’ I replied, ‘Some money.’ The next day in the article in the paper, Julia Wallace indicated that I had said IVF could be done in Norfolk and that all it would take would be some money.

The next day, we received a telephone call from a former patient living in Norfolk, who had been referred by Mason Andrews to Georgeanna in Baltimore for a fertility problem, and was rewarded by a female child, who was named Georgia. The caller expressed surprise that we were in Norfolk, extended her greetings and said that she noticed that we needed some money. Furthermore, she said she had a small family foundation and perhaps they could supply the necessary money to start a new in vitro programme. Needless to say, a meeting was held by all concerned and within 72 h of arriving in Norfolk, an in vitro programme was planned and financed, although there had been no thought of such a programme by any of the principles in making the arrangement to join the new medical school.

In planning to establish a programme of IVF in Norfolk, we were able to stand on the shoulders of Bob Edwards and Patrick Steptoe, in addition to those of Carl Wood, Ian Johnston...
and Alex Lapota, of Australia, all of whom we happen to know. Indeed, in the fall of 1979, Patrick Steptoe made a trip to Norfolk to give us the benefit of his knowledge and to help us get started.

We also benefited from visits by Carl Wood and Alex Lopata. We were advised not to try to use a stimulated cycle that had been tried unsuccessfully, but to use the natural cycle to fertilize the oocytes as promptly as possible and to transfer at about the 8-cell stage and to transfer at night. This was the basis on which we started in 1980. With 41 laparoscopic attempts to obtain oocytes, we succeeded in having cleavage in only 13 patients, all of which were transferred and with no pregnancies.

It is an important part of history to note that these procedures were carried out in the face of considerable public opposition. Before beginning, we had been required to obtain a Certificate of Need from the Health Department as this certificate was required by law for all new procedures. This resulted in a public hearing that lasted for 8 h, at which hearing opposition was expressed in an organized way by the right to life movement, which objected to an in vitro procedure on a number of grounds, including concern for abnormal children, the unnaturalness of the procedure and the fact that we were causing abortions because in the described procedure many oocytes are transferred than are expected to develop. Nevertheless, in spite of this opposition, the Certificate of Need was granted and we were authorized to start in the early part of 1980.

It needs to be noted that the public opposition continued even after the programme was underway. This opposition took the form of adverse editorials in the local newspaper, many letters to the editor expressing disapproval, and indeed groups from time to time marching on the streets with placards so that the patients in some circumstances had in effect to cross the picket line in order to receive their treatment.

Although no pregnancies were obtained, the experience of 1980 was duly recorded and among other things an accurate record was made at the time of ovulation in the normal menstrual cycle in relation to the rise of LH (Garcia et al., 1981). Also in 1981 at a conference hosted by the group at Bourn Hall of early workers from around the world (Figures 11 and 12)—a small IVF mafia type group that met several places around the world in the early days so that communication of the current state of affairs could be transmitted quickly—the group from Norfolk, because of their experience with opposition, was assigned the topic of ‘Ethics in IVF’ and this resulted in a publication about this topic very early in the history of clinical experience (Jones, 1981).

During the Christmas holidays between 1980 and 1981, Georgeanna, my wife, being the reproductive endocrinologist that she is, insisted that we go back to HMGs for stimulation to obtain more than one oocyte in the cycle, even though this procedure had been abandoned by Bob and Patrick after over 100 tries. This was not without discussion between Bob and Georgeanna because I can recall that on one occasion at a meeting in Cambridge before Bourn Hall days where Georgeanna and Bob

Figure 11. An informal meeting hosted by Bourn Hall in September 1981 with representatives from England, Australia, Switzerland, Sweden, Germany, France, Austria, and the USA—a group of 25 in all.

Figure 12. One of the groups from Bourn Hall meeting in 1981 which adjourned to the lawn. Standing: Alex Lopatal; left: Alan Trounson; right: Lars Hammerger raises arm to ask question and Howard Jones takes notes.
had a considerable and lengthy debate about the exact technique by which the stimulation could be used.

In any case, in 1981, we began using gentle doses of HMG, more or less, as Georgeanna had used this for ovulation induction in anovulatory patients. This technique resulted in a pregnancy on our 13th try. The pregnancy resulted in the birth of the first baby in the USA in December 1981. Also, this seems to be the birth of the first baby following HMG stimulation with IVF. Alex Lapota had summarized the result of stimulated cycles as of December 1980 and showed that at the end of 1980 in Oldham there had been three pregnancies and no deliveries and in Melbourne three pregnancies and no deliveries (Lopata, 1980, Figure 13).

In all of 1981 in Norfolk, 55 patients were stimulated with 31 transfers. There were seven pregnancies, all of which delivered at term (Jones et al., 1982).

The use of HMG for the production of more than the single oocyte characteristic of the normal menstrual cycle resulted in certain alterations in ovarian physiology as it was then understood. This resulted in the publication of a series of articles having to do with this altered physiology. For example, there was the recognition for the first time that with similar amounts of HMG stimulation various patients responded in general in three ways: a high response, an intermediate response and a low response. This was published in 1983 (Ferraretti et al., 1983). Furthermore, it was documented that with the use of HMG a spontaneous LH surge did not appear, even though the estradiol (E2) in the follicular phase of the cycle was well above the trigger point for the beginning of an LH surge under spontaneous conditions. This likewise was recorded and documented in 1983 (Ferraretti et al., 1983). Furthermore, the observation was pursued that Bob Edwards had made that spontaneous maturation of the oocyte resumed when liberated from the follicle. It was possible to show that OMI in the human follicular fluid declined with time (Channing et al., 1984). This finding explained the resumption of meiosis observed previously by Edwards in many species. Likewise, the follicular fluid was studied in great detail to try to understand why with stimulation the LH surge was inhibited and why with stimulation a surrogate surge, i.e., injected HCG became necessary. This resulted in identification of an LH inhibitory substance in the follicular fluid (Danforth et al., 1987) in 1984. Later studies from Norfolk dealt with the observation that basal LH, FSH and E2 levels predicted in a reasonable way the expected response, i.e., measured ovarian reserve (Muasher et al., 1988).

This seems a reasonable time to stop the early history of IVF as the practice continued in the USA with no national law covering the clinical practice of ART, contrary to the case in many other countries. However, beginning in 1986, the American Fertility Society (AFS) and its successor organization, the American Society for Reproductive Medicine, has from time to time issued guidelines covering the clinical aspects of ART and its derivatives. These guidelines cover all aspects of ART from basic IVF to such things as stem cells, cloning, donor oocytes, surrogates, etc. However, these are guidelines and there are no legally provided enforcement mechanisms for any violation that may occur. However, the Society for Assisted Reproductive Technology reserves the right to expel from membership any programme in violation of the guidelines. There seems to have been no expulsion to date under this provision (American Fertility Society Ethics Committee Report, 1994).

Nevertheless, there is a legal surveillance mechanism. This stems from the ‘Fertility Clinical Success Rate and Certification Act of 1992’ (Public law 101–403) requires that, ‘Each ART programme shall annually report to the secretary of Health and Human Services through the Centers for Disease Control and Prevention (CDC) pregnancy success rates achieved by such a programme through ART and the identity each embryo laboratory used for such programmes and whether the laboratory is certified or has applied for certification.

The beginnings of IVF in France: 1978–1984

France has a long tradition in the treatment of infertility. As early as 1940 the group of Raoul Palmer at the Hôpital Broca in Paris had perfected the application of laparoscopy and hormone therapy in infertility. In 1961, Palmer himself described the first retrieval of oocytes during laparoscopy. And the same group was the first to use on a large-scale gonadotrophins derived from the urine of menopausal women (HMG) for the induction of ovulation. To these achievements we should also add the fine record of Centre d’Etude et de Congélation du Sperme (CECOS) under the direction of Georges David. The CECOS centres, which became national institutions in 1973, pioneered the anonymous and free donation of human sperm, and set an example to the entire world. They paved the way for the development of donor insemination and oocyte donation with IVF. By 1980 there were more than 1700 live births a year in France following sperm donation.

I had first met Bob Edwards in 1968, and knew even then of the interest he had in the concept of fertilization in vitro. At
the time, at the INSERM unit of the Hôpital St Antoine, we were working with long-tailed monkeys and trying to achieve a pregnancy by IVF. However, despite some success—several follicular punctures with laparoscopy and several oocytes collected—we never did succeed in obtaining an embryo. Edwards suggested that I should start with women, because they had a better rate of success—but we never had his confidence. Nevertheless, these trials in animal models did help us to develop the first procedure for the electrical stimulation of ejaculation in the monkey, which we described in 1970 with Gabriel Arvis.

In 1977, I contacted Ondine Bomsel who at the time was directing the INSERM unit at the Hôpital Universitaire at Clamart and sent her samples of mature follicles aspirated from women who had been operated on for tubal infertility following ovarian stimulation. We were engaged in this collaboration when, in July 1978, we heard the news of Louise Brown’s birth in Oldham, UK. So we had no hesitation in proposing the application of this same IVF technique in France. However, I was at the time unsure of continuing my collaboration with the group at Clamart, and I discussed my concerns with two of them, Emile Papiernik and René Frydman. At this time Frydman himself was disappointed in results of tubal surgery and had turned to IVF as early as 1977—largely as a result of meeting Ondine Bomsel, which had sparked his interest in follicles and human oocytes. But, a few days after that meeting at Clamart, Charles Thibault, who was then professor of animal biology at the University of Paris and whom I had already approached with proposals for studies in IVF, telephoned me to recommend two young biologists who were then specializing in reproduction. One had already qualified and was working as an assistant professor in endocrinology with Professor Mauvais Jarvis at the Hôpital Necker, and the other was an INSERM scientist. They were both interested in collaborating with me, and their names were Jacqueline Mandelbaum and Michelle Plachot. So this is how the first two French groups in IVF started, the one at the Hôpital Sèvres (a communal non-university hospital) in the department of Vincent Loffredo and the other at the CHU (Centre Hospitalo Universitaire) of Clamart in the department of Professor Papiernik, with Jacques Testart heading the biology team.

In both groups oocyte retrievals were performed in natural cycles after the measurement of a urinary LH peak. This meant that we were doing laparoscopies day and night, Sundays and holidays included. But all pioneers at that time—doctors, biologists and medical staff—were fired by an enthusiasm which made such schedules acceptable. Let’s not forget that in 1978 very few doctors or biologists could predict the future of IVF in reproductive medicine. But those who were involved were motivated by a desire to succeed, innovate, understand the reasons for their failures and measure the progress of their competitors. There were indeed few forces but passion and faith in success to unite those first groups working in IVF, wherever they were in the world; and the friendships which formed at the time still persist today.

And in France too the first years of IVF began in an amicable—if competitive—atmosphere. No group achieved a live birth before 1982, despite numerous collaborative efforts. In 1980, for example, a paper signed by Testart, Gougeon, Frydman, Bomsel and Cohen described the activity of gonadotrophic hormones on human follicles in vitro Testart et al. (1980). And it was this collaboration that led to the first clinical pregnancy in France, which was derived from oocytes punctured at Sèvres, transported to Clamart for fertilization, and returned to Sèvres for transfer, but which aborted 10 weeks later.

The two French groups at Sèvres and Clamart were both working in public programmes and patients were not required to pay for their treatment. The costs of both medication and investigations were refunded by social security, and other procedures were covered by their ‘hospitalisation’.

However, each of the two groups directed their research work in particular directions. Until 1981, let me remind you, follicular punctures were performed in a natural cycle, under anaesthesia and by laparoscopy. There was thus great uncertainty in the determination of the pre-ovulatory LH peak. Edwards himself used the Higonavis assay (lyophilized sheep erythrocytes coated with antiserum against HCG), with urine collection every 4h. The cost of the process was important, and the number of collections considerable. Punctures were performed at any time of day or night and sometimes ovulation had already occurred by the time of laparoscopy. Thus, both teams very quickly benefited from their collaboration with the Fondation de Recherches en Hormonologie, which for several years had been measuring hormone levels in urine and plasma. In 1981, the Clamart group developed an LH starting initial rise in plasma assay (LH–SIR), which allowed accurate prediction of the ideal time for the retrieval of oocytes (Testart et al., 1981). The important point of this work was that ovulation could now be accurately predicted at the start of the rising LH curve and not at its peak. This would improve the efficiency of retrievals.

The early days of IVF at Hôpital Sèvres were hampered by the absence of a laboratory on the site. However, both Mandelbaum and Plachot had arranged to use the INSERM laboratory services of Professor Grouchy at Necker and, from 1981, we adopted a policy for transporting our collected oocytes by thermos flask at a steady temperature of 37°C. The actual ‘transport’ was usually accomplished by taxi in the hands of the biological father and as quickly as possible (around 90 min to Necker). The fertilized oocytes were brought back to Sèvres by the biologists in the same thermos flask, for transfer to the mother. We did have some success, despite the inconveniences; variations in the transport temperature (sometimes over 40°C) caused a decrease in pregnancy rate, and there were the occasional husbands who lost their way to the laboratory!

This transport technique, which was also used by Testart and Wilfried Feichtinger in Austria, proved very useful at the start of IVF for those groups who did not have their own laboratory facilities, but it was still not easy. In 1979, we retrieved seven oocytes at Sèvres in five natural cycles; only two fertilized. At Clamart there were 25 oocytes collected that year, with nine fertilizations. We also had to purchase from abroad the Higonavis tests to measure LH levels in urine.

Menez in 1976 had developed the world’s first B2 culture medium. This would be universally adopted by the French groups and known outside France as ‘the French medium’. This specific medium reflected the follicular, tubal and uterine environments of the sheep, rabbit and human. Indeed, the start of IVF in France benefited enormously from the help of animal researchers from the Institut National de la Recherche Agronomique. Professor Thibault himself was head of the animal
physiology unit from which Menezo, Plachot, Testart and many other younger biologists emerged. As in Australia, IVF centres in France gained greatly from the experience of biologists who had specialized in research on animals.

As early as 1979 J.P. Pez and myself began tracking the growth of follicles by ultrasound. In a study of 40 patients we showed that there was an appreciable relation between the echographic and laparoscopic observations (Pez et al., 1979). We further indicated that follicle diameter as measured by ultrasound was a better predictor of follicular maturation than hormone levels alone.

France’s first IVF baby, Amandine, was born at Clamart in February 1982, and the second, Alexia, at the Hôpital Sèvres in June. Over the next 2 years several new IVF centres opened throughout France. Jacques Salat Baroux at Tenon began a collaboration with Mandelbaum and Plachot, while in Montpellier Bernard Hédon, working in Viala’s unit with Olivier Flandres, made his first IVF attempt in 1981. They achieved a pregnancy from their third transfer, and the group’s first birth occurred in July 1983.

In September 1981 a meeting hosted by Edwards, Patrick Steptoe and Jean Purdy at Bourn Hall, Cambridge, brought together the IVF ‘pioneers’ from around the world, and especially those who had already achieved pregnancies: these included Howard and Georgeanna Jones, Feichtinger, Testart, Frydman, Plachot, Lars Hamberger, Matts Wikland, Anita Sjögren, Liselotte Mettler, Alex Lopata, Ian Johnston, Alan Trounson, John Leeton, Simon Fishel and myself (at the time Jacqueline Mandelbaum was herself pregnant in France).

One of the big discussions at this meeting was the retrieval of oocytes in a natural cycle and the problems of exact timing based on blood levels of E2, LH and progesterone. In my notes I made the following points:

- The first discussion was on how many hours after the LH peak should retrieval begin. Delays as varied as 2 and 6h were proposed, while Lopata said he used a delay of 26–36h after the start of the LH peak, with the help of ultrasound. Edwards proposed 26h after the first urine sample showed positive for LH. *In vitro* maturation was suggested by Steptoe when oocyte retrieval proved too early, which was largely in agreement with Trounson, who proposed that 12h prematurity was acceptable in animals. Frydman described Clamart’s experience with LH–SIR.

I think it is also useful to reproduce the table of successes obtained by the different groups as evident in those discussions of September 1981 (Table II).

<table>
<thead>
<tr>
<th></th>
<th>Melbourne</th>
<th>Austria</th>
<th>France</th>
<th>France</th>
<th>USA</th>
<th>UK</th>
<th>Germany</th>
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<tr>
<td>Laparoscopy</td>
<td>130</td>
<td>68</td>
<td>77</td>
<td>31</td>
<td>330</td>
<td>114</td>
<td>149</td>
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<td>Follicles</td>
<td>368</td>
<td></td>
<td></td>
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<tr>
<td>Oocytes</td>
<td>265</td>
<td>109</td>
<td>52</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Laparoscopy: at least one oocytes</td>
<td>114</td>
<td>35</td>
<td>27</td>
<td>263</td>
<td>203</td>
<td>70</td>
<td>98</td>
</tr>
<tr>
<td>Fertilization</td>
<td>154</td>
<td>24</td>
<td>59</td>
<td>16</td>
<td>16</td>
<td>203</td>
<td>70</td>
</tr>
<tr>
<td>Laparoscopy with one or more embryo</td>
<td>93</td>
<td>197</td>
<td>29</td>
<td>195</td>
<td>3</td>
<td></td>
<td></td>
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<tr>
<td>Transfers</td>
<td>78</td>
<td>19</td>
<td>24</td>
<td>5</td>
<td>12</td>
<td>195</td>
<td>3</td>
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<tr>
<td>Pregnancies</td>
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<td>4</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>44</td>
<td>0</td>
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<tr>
<td>Abortions</td>
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<td>2</td>
<td>2</td>
<td>7</td>
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<td>Clinical terminations</td>
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<td>2</td>
<td>1</td>
<td>9</td>
<td></td>
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<tr>
<td>&gt; 10 weeks ongoing</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>28</td>
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<td>28</td>
</tr>
</tbody>
</table>

The most heated discussion concerned ovulation induction. Trounson and Leeton said they used clomiphene to obtain more oocytes—and so more embryos and more pregnancies. They said a good follicle was indicated by an E2 level of 300pg, with follicle diameter adding further prognosis. Edwards and Steptoe, who had failures with clomiphene, were sceptical. Cohen described the French experience with HMG in procedures other than IVF. Howard and Georgeanna Jones said they were now using HMG and HCG in patients with normal cycles; HCG was given at 7.30 pm in all cases and oocyte collection was performed 36h later. All participants concluded that ovarian stimulation promised more oocytes and therefore more pregnancies, and that this would allow a better scheduling of oocyte collection.

Table II. Table of IVF successes in September 1981 taken from the personal notes of Jean Cohen. These data do not include the work of Wood, Leeton and Trounson

In 1984 and especially 1986, Michelle Plachot produced a long series of cytogenetic analyses of oocytes and human embryos, and additionally described the effect of abnormal fertilization on embryonic development (Cohen et al., 1983). From then on, we understood better why implantation rates were so poor in the human. Plachot also described (in 1986) the chronology of...
the first stages of human of fertilization (Plachot et al., 1986). The previous year, 1985, Jacqueline Mandelbaum with Dan Szollosi had described the microstructures of the human oocyte, which would later become fashionable as ‘oocyte dysmorphia’ (Szöllösi et al., 1986).

In time, new indications for IVF emerged: tubal stenosis, endometriosis, oligosperma, immunological infertility. Oocyte donations began. Stimulation protocols were mainly clomiphene + HMG + HCG. But throughout this time everyone was trying to understand the reasons for implantation failure. In 1982, we demonstrated the diagnostic value of the HCG growth curve after embryo transfer (Roger et al., 1983).

New centres were now opening up throughout the French provinces, and it is impossible to name them all. Alain Audebert began in Bordeaux, with their first baby born in August 1983. Jacques Montagut, who would organize ESHRE’s first meeting on the ethics of assisted reproduction in 1987, had opened a clinic in Toulouse also in 1983. Both Groupe d’Etude de la Fecondation in vitro en France and FIVNAT (the first national register of IVF results co-ordinated by unit 292 of INSERM) were formed in 1986.

If the first live births after embryo freezing occurred in Australia (Trounson and Mohr) and the Netherlands (Gerard Zeilmaker), it was Testart’s group in 1985 which published impressive results using propanediol and sucrose as cryoprotectants for embryo freezing, instead of dimethylsulphoxide (Testart et al., 1986). Today, this remains the most widely used protocol in the world. Two years later, in 1987, Mandelbaum showed that morphologically abnormal embryos were less resistant to freezing than normal embryos, and that, on thawing, blastomere loss had a deleterious effect (Mandelbaum et al., 1987). In 1988, she described her first attempts at freezing immature oocytes, a challenge which remains today (Mandelbaum et al., 1988). In 1983, Belaisch Allart and the Clamart group had explored the idea of laparoscopy and local anaesthesia for oocyte retrieval (Belaisch-Allart et al., 1983).

From 1984, with M.J. Mayeu and colleagues, I had collected data on 2342 pregnancies obtained between 1979 and 1984 at 55 IVF centres worldwide—and from these we would show, for the first time, that the rate of malformations (2.5%) appeared no higher following IVF than in the general population. However, the incidence of ectopic pregnancies in this series was 4.6%, and we concluded that this was indeed higher than in natural reproduction. We discussed several theoretical explanations, and notably the role of clomiphene, which at the time was used in combination with HMG for ovarian stimulation. Our results showed an ectopic pregnancy rate of 5.7% if clomiphene were used, but only 2.5% if HMG were used alone. Today, the incidence of ectopic pregnancies in IVF has decreased in proportion to the decline in clomiphene use.

In 1984, we described 113 cycles in 88 patients whose luteal phase was analysed after oocyte retrieval (Plachot et al., 1985). We showed that E2 levels in the same patient and with the same doses of HMG varied considerably from one cycle to another, as well as E2 and progesterone levels in the luteal phase. Nineteen endometrial biopsies analysed by J. de Brux were neither able to offer any relation of anatomical criteria and hormone levels nor to explain the implantation failures.

Early in 1984, Bob Edwards had kindly offered to come to Sèvres to help our biologists. We put him in a very modest room at the hospital and, while in Paris, he also arranged to meet the biologists at Clamart. During his stay he also came occasionally to dinner at my home and there we would often discuss the prospects for reproductive medicine in Europe. At that time the European groups had to publish their work in the American journals or at the congresses of the AFS to make their results known. Edwards and I were both agreed of the need to create a European society along the lines of the AFS. However, then support for such an idea was not universal, but Edwards and I were convinced, enthusiastic and determined. During the third World Congress of IVF and Embryo Transfer in Helsinki in May that year we stuck notices around the congress hall inviting everyone interested in a European society to join us. Thus, on Friday 18th May at 11 a.m., without any agenda, about 20 participants got together in a group which several months later would become ESHRE.

At the time, live birth rates from IVF at Sèvres had increased from 2.08% per puncture and 6.25% per transfer in 1981 to 2.52% per puncture and 9.78% per transfer in 1982; to 3.22% per puncture and 5.31% per transfer in 1983; and in 1984, a notable advance, to 9.83% per puncture and 13.83% per transfer.

During this period oocyte donation was also performed, but, because there were no laws or regulations, each group would adopt its own policy. Non-anonymous donations were performed at Clamart and Tenon, while at Sèvres we adopted a policy of voluntary anonymous oocyte donation from patients having IVF: to offer one oocyte if 7–10 were collected; and two oocytes if there were more than 10. Oocyte donation followed the same criteria of anonymity and gratuity as sperm donation (anonymous and free).

In September 1984, a symposium on assisted reproduction was organized in Carghese, Corsica, which attracted all the leading French experts in IVF, as well as basic scientists. As such, it represented the state-of-our-art, and well reflects what we knew and did not know at the time. I list below some of the presentations:

- Charles Thibault urging work in animal models first before progressing to humans. Edwards and Testart, for example, were already suggesting varied outcome from the use of clomiphene.
- Gary Hodgson on the role of the dominant follicle, and Frydman and Testart on the timing of HCG.
- Joelle Belaisch on the retrieval of oocytes with ultrasound guidance and local anaesthesia.
- Jacqueline Mandelbaum on sperm analysis.
- Michelle Plachot on the viability of oocytes.
- Y. Menezo on embryo quality.
- J.P. Renard on embryo freezing.
- Howard Jones on the luteal phase after IVF.
- Alan Trounson on oocyte donation.
- Bob Edwards on clomiphene and the premature LH surge.

The list reflects our main pre-occupations at the time—the means and consequences of ovarian stimulation, the parameters of follicle growth and the quality of the embryo.

I have chosen somewhat arbitrarily to close this historical review with the symposium in Carghese in 1984, because it brought to an end the first phase of the beginning of IVF in France. After this date we would see major legal developments.
and the creation of professional structures, including the national registry of FIVNAT. It is also certain that I have forgotten some of the landmarks of this first period, and I apologize for those omissions.

The early days of IVF in Northern Europe: 1958–1990

Introduction

Treatment of infertility has a long tradition in the Nordic Countries. As early as 1958 Carl Gemzell, Professor in Obstetrics and Gynaecology at Uppsala University, Sweden, reported together with his collaborators the first successful treatment with gonadotrophins derived from human hypophyses in infertile women suffering from anovulation dependant upon hypothalamic–hypophyseal insufficiency (Gemzell et al., 1958). Much of the basic knowledge about how follicular growth was influenced and regulated by gonadotrophins, was described in the so called the gonadotrophin two-cell types theory for estrogen formation. Also this hypothesis was put forward by the Swedish scientist Bengt Falk in his thesis in 1959 (Falck, 1959). His findings are still valid today and constitute an important basis for how gonadotrophic stimulation should be administered for optimal follicular growth.

Figure 14. Group photograph of the attendees of the 2nd Nordic IVF meeting in Geilo, Norway. Numbered key.
Ten years later another Swedish gynaecologist, Kurt Swolin, described a new microsurgical approach for re-establishing tubal patency following predominantly infections causing tubal occlusion, hydrosalpinx and peritubal adhesions (Swolin, 1967). During the following decade the microsurgical principles were developed further together with one Canadian (Dr Victor Gomel) and one British gynaecologist (Lord Robert Winston) (Gomel and Swolin, 1980). For a considerable time these three scientists were difficult to compete with when results, risks, cost-benefits, etc. were compared between the two techniques. Against this background, the report of the first test tube baby in 1978 was immediately recognized in the Nordic countries as an attractive alternative, or additional treatment option for infertile couples.

Nordic IVF clinics, their organization and communication activities

In the Nordic countries, university linked and private IVF-clinics have worked in parallel ever since the start in 1982, when the first Nordic IVF baby was born in Gothenburg, Sweden (Hamberger et al., 1982).

A friendly atmosphere has prevailed between private and university IVF units, probably due to the market being much bigger than the public availability and that all public units had and still have relatively long waiting lists. Today altogether 63 Nordic IVF Clinics are established in a population of 25 million people.

In 1981, the first Nordic IVF Conference was held in Helsinki, Denmark and around 30 delegates attended the meeting. Nordic meetings were thereafter held every 18 months and the location for these meetings varied between Denmark, Norway, Sweden, Finland and Iceland. There was a continuous growth and when the number of delegates increased to 300 in 1998, a formal Nordic Fertility Society was formed. (Membership in 2005 counts 666 members). The Nordic countries have also been hosts for international congresses on a number of occasions (Figure 14). Professor Markku Seppälä in Helsinki, Finland managed through outstanding research on ovarian and placental proteins closely related to fertility and infertility problems combined with political skill and international prestige, to get permission to organize these meetings. His work was appreciated and the society has used this opportunity and the credit gained to organize ten meetings since 1996 in the Nordic countries at an increasing scale. The number of 666 members in 2005 and the recent increase of membership to 750 would be a proof of the society's success.

During the following decade the microsurgical principles were developed further together with one Canadian (Dr Victor Gomel) and one British gynaecologist (Lord Robert Winston) (Gomel and Swolin, 1980). For a considerable time these three scientists were difficult to compete with when results, risks, cost-benefits, etc. were compared between the two techniques. Against this background, the report of the first test tube baby in 1978 was immediately recognized in the Nordic countries as an attractive alternative, or additional treatment option for infertile couples.

Legal aspects on ART in the Nordic countries

The birth of Louise Brown in 1978 opened up a new era of medical legislation for politicians around the world. Although in most countries a good deal of legislation existed concerning clinical medicine and medical laboratories, human reproduction suddenly entered these areas in a way foreign to existing legislation, making new demands on poorly informed politicians. New questions arose on issues that before were undisputed. For example: ‘who is the mother of the child?’ is such a question that suddenly needed review and reconsideration when the fertilization process was removed from the woman’s body.

Immediate reactions tended to be restrictive. ‘Better safe than sorry’, is a simplification that is the basis of earlier legislation, and this is still a stalwart of the largely restrictive legislation regulating biotechnology in Norway today.

The first law passed in the world on IVF was that of the State of Victoria in Australia in 1984. Being an early law it was an unprecedented strict law, which still makes the State of Victoria, the home of the Melbourne clinics, the most restrictive in Australia. One of the biggest problems with legislation is that laws may often be easier to pass than to repeal. This, unfortunately also applies to laws made in an atmosphere heavily laden with emotion and/or ignorance.

Norway was the first country in the world to pass a law on ART on the 12 June 1987 (Norwegian law of Artificial Reproduction of 12 June 1987). Being early legislation it was like the Victorian law extremely limiting and Norwegians working in the field of assisted reproduction are subject to its limitations to this day, when most other Nordic countries have produced less restrictive legislation, which opens the way for necessary development in the field.

Early legislation in the Nordic countries

The early Norwegian laws passed in 1987, revised in 1994, the Swedish law of 14 June 1988, in Iceland on 29 May 1996 and on 30 September 1997, and the Danish law of 10 June 1997, have many similarities. Treatment was clearly restricted to married couples or couples living together under marriage-like conditions. Same sex couples, lesbian women and single women were excluded from treatment and further surrogacy and embryo donation was not permitted. National governmental regulations were set up and detailed annual reports were required. Sperm selection is allowed only in connection with risk of serious sex-linked genetic disorders.

There were also some interesting differences between the Nordic countries. Whereas treatment may only be provided by licensed ART clinics in Norway, Sweden and Iceland, Denmark allowed the provision of donor insemination by gynaecologists without special licence. In Norway even homologous insemination was restricted to licensed centres.

Oocyte donation was allowed in Denmark but forbidden in Norway and Sweden. Contrary to Denmark, donor insemination as part of the IVF treatment was forbidden in Norway and Sweden. This was a peculiar decision as both IVF and donor insemination, as separate procedures, were permitted in these countries. The argument forwarded in support of this decision by legislators in Sweden and Norway was the curious idea that IVF with added donor insemination was manipulation of nature beyond an acceptable level, while each of these treatment modalities alone was considered within an acceptable range of manipulation. This introduced an unforeseen discrimination of women suffering from tubal infertility, who were unfortunate

Table III. IVF related international congresses hosted by the Nordic countries

<table>
<thead>
<tr>
<th>Conference name</th>
<th>Country</th>
<th>Year</th>
<th>President</th>
</tr>
</thead>
<tbody>
<tr>
<td>Third World Congress in IVF</td>
<td>Finland</td>
<td>1984</td>
<td>Markku Seppälä</td>
</tr>
<tr>
<td>5th ESHRE Annual Meeting</td>
<td>Sweden</td>
<td>1989</td>
<td>Nils-Otto Sjöberg</td>
</tr>
<tr>
<td>7th World Congress on Human Reproduction</td>
<td>Finland</td>
<td>1990</td>
<td>Markku Seppälä</td>
</tr>
<tr>
<td>15th FIGO World Congress of Obstetrics and Gynaecology</td>
<td>Denmark</td>
<td>1997</td>
<td>Jörgen Falck Larsen</td>
</tr>
<tr>
<td>14th ESHRE Annual Meeting</td>
<td>Sweden</td>
<td>1998</td>
<td>Lars Hamberger</td>
</tr>
</tbody>
</table>
enough to be married to men with infertility or subfertility problems.

Embryo research was allowed in Denmark, Iceland and Sweden for a period of up to 14 days after fertilization provided manipulated ‘research embryos’ were not used for reproductive purposes. In Sweden this was made possible by an important addition to the Swedish law in 1991 (Swedish Law number 115, 1991). This opened the way for important developments in the field of ART in these countries, including PGD and embryonic stem cell research.

This was in contrast to the situation in Norway where embryo research was totally forbidden, including research to improve the methodology. The Danish legislators poignantly pointed out that society has an obligation to improve a method once a method is considered acceptable. This solitary Norwegian restriction has had an important negative impact on the development of ART technology in that country. The Norwegian restrictive view is strongly based on giving the early embryo an exceptionally high status.

Nordic countries differed in the length of the preservation time allowed for embryo freezing. Norway initially restricted cryopreservation to 1 year, but extended the period to 3 years in 1994, Denmark allowed 2 years, Sweden and Iceland 5 years. In Norway embryo freezing was allowed but oocyte freezing was forbidden.

The initial Norwegian law of 1987 appeared to be strongly based on Swedish legislative proposals and was passed in haste as a temporary law, partly as a reaction to the unexpected appearance of a private IVF clinic in Oslo. Politicians could not agree on whether or not to allow IVF in the private sphere. This initiated a parliamentary debate. Attempts were made to disallow this development in IVF, but it became difficult to remove a legally established functioning IVF clinic. The temporary law effectively put a stop to further expansion of IVF into the private arena and no further private IVF clinics were given a licence in Norway until 1999.

An important feature of the initial Swedish law was the removal of anonymity of sperm donors in AID (Swedish law number 1140. 20.12.1984). Sweden was the first country in the world to do so through legislation. In this relation the Icelandic law was interesting. In Iceland sperm donor anonymity or non-anonymity remains a voluntary issue for couples, both possibilities being available. The Icelandic law on ART made a few years later than the Norwegian and Swedish laws was considerably more liberal and Iceland can claim to be the first Nordic country to allow oocyte donation by law. Oocyte donation was also allowed under the Danish law 3 years later. The Danish law on oocyte donation is somewhat special as it only permits donation of surplus oocytes retrieved from other IVF patients.

**The situation in Finland**

In contrast to all the legislations passed in the other Nordic countries no law on ART has as yet been passed in Finland. This makes Finland a unique example of how self-regulation can function excellently in ART. The development of Finnish ART is exemplary in the world in showing that self-regulation does not necessarily mean all loss of restraint or the up-growth of a flourishing commercialization as a result of absent legal restrictions. Practice in Finland is more liberal than in the other Nordic countries, but it is regulated through national discussions and agreements between ART centres. Single and lesbian women are not excluded from ART treatment in Finland and a non-commercial, strictly medically indicated form of surrogacy is practiced (Viveca Söderström-Antilla et al., 2002)

Oocyte donation is practiced on the basis of philanthropic oocyte donation, different from the Danish model where oocytes have to come from other infertile women.

There have been several law proposals in Finland but it is still uncertain when such proposals will effectively become law. On other issues of treatment Finish practice is very similar to that of the other Nordic countries, apart from Norway.

**Technical developments in the Nordic countries**

**Ultrasound techniques**

With the introduction, around 1975, of a new generation of ultrasound scanners with higher resolution than before, the possibility of visualizing the ovaries and follicular structures was demonstrated. Both abdominal linear array transducers and vaginal sector scanners were utilized and in certain cases it was even possible to visualize the oocyte in a pre-ovulatory follicle shortly before rupture (Hackelooer, 1977). Danish gynaecologists Susan Lenz and Jørgen GL Auritsen also demonstrated that ultrasound could be used, not only for diagnostic purposes but also operatively for puncture and aspiration of follicles. With their approach, a needle guide attached to an abdominal transducer indicated the route for the needle through a filled urinary bladder (transvesical technique) to the ovary and the antral follicles. The technique was even more effective in retrieving oocytes than laparoscopy and could be performed under short lasting general anaesthesia or under local anaesthesia on a completely outpatient basis (Lenz and Lauritsen, 1982).

A year later another Nordic Group led by gynaecologist Mats Wikland in Gothenburg, Sweden, described the possibility to use a vaginal sector scanner (transvaginal technique) for the same purpose as described above (Wikland et al., 1985). By this technique the ovaries were much better visualized than with the abdominal approach, and even smaller follicles could be successfully visualized and punctured. The procedure could also be performed in light local anaesthesia and the patient could generally leave the hospital after 1 h. The first vaginal transducer was designed and developed by the Danish ultrasound company Bruel and Kjaer in collaboration with Doctor Wikland’s Group. The importance of specific needle guides, puncture needles and other accessories for the new technique, was soon realized and a biotechnical company, SweMed Lab was formed in Gothenburg, Sweden for this purpose. The company is still a worldwide market leader in this sector. During the first couple of years, there was an initial resistance by representatives for the laparoscopic technique and it was claimed that ultrasound could be dangerous for the oocyte, which was shown not to be the case (Wikland and Hamberger, 1984). Today the new simplified vaginal ultrasound technique for oocyte retrieval is used by more than 95% of IVF clinics worldwide.

**Microfertilization techniques in the Nordic countries**

Even if IVF could be used successfully in cases of moderate male infertility, it was soon realized that poor sperm count, low
motility and or impaired morphology frequently caused failed fertilization. Zona drilling and subzonal insemination (SUZI) were techniques, that showed some success and Dr Leif Hägglund, Malmö, Sweden participated in this work together with scientists from Singapore (Ng et al., 1988). In 1992, the first successful pregnancies with ICSI were reported from Brussels, Belgium (Palermo et al., 1992). Because of a close collaboration between the IVF groups in Brussels and Gothenburg, Sweden became the second country that could report term pregnancies after ICSI (Hamberger et al., 1993). This collaboration has also resulted in a common interest in the follow-up of the ICSI children (Wennerholm et al., 1996).

**Implantation mechanisms**

One difference between natural conception and IVF, at least in the past, has been replacement of the embryos into the uterine cavity much earlier in the case of IVF (days 2–3) compared to the case of natural conception when the embryo enters the uterine cavity not until day 5–6 after conception. The reason for this difference has predominantly been due to lack of culture media and culture conditions, which could guarantee good blastocyst development. It thus seemed urgent to study the implantation mechanisms and the so called ‘implantation window’ more in detail. In the late 1980s Dr Svend Lindenberg, Copenhagen, Denmark developed in his doctoral thesis a model for studying implantation of human blastocysts in vivo on an epithelial layer derived from the uterus in connection with curettages performed in the early luteal phase. The experiments were performed in Gothenburg, Sweden since ethical permission for such experiments could not be obtained in Denmark at that time. It was then found that an oligosaccharide, lacto-N-fucopentaose on the surface of the uterine epithelium attached to specific receptors on the surface of the blastocyst (Lindenberg et al., 1990). In this non-polarized epithelial cell layer only the earliest steps, apposition and adhesion, in the implantation process could be studied.

A couple of years later another Danish scientist, Dr Ursula Bentin-Ley developed a more advanced in vitro implantation model in collaborative studies with Gothenburg University, Sweden. A polarized cell culture system was established. This three-dimensional culture system better imitates the normal endometrium and numerous important in vitro observations have been made, which has improved our understanding for promoters and inhibitors of implantation in vivo (Bentin-Ley et al., 1994, 1999).

**Culture conditions**

One of the major problems in IVF from the very start was the culture conditions and culture media. Few media fulfilled the requirements for successful blastocyst development, at least not with the right time dynamics. For such reasons short in vitro culture was recommended (1–3 days) and in the beginning most laboratories made their own media. Relatively soon biotechnical companies with a focus on IVF media appeared on the market. In the Nordic countries two companies were formed, Medicult and Vitrolife. Both companies have reached international recognition for much improved quality assurance and quality control.

In the beginning bovine or human serum was used in most media, later replaced with human serum albumin for safety reasons. Apart from traditional short-term IVF cultures Medicult has focused on IVM media and Vitrolife on blastocyst promoting media (Table IV).

**Availability and public acceptance**

In the Nordic countries, clinical IVF applications started early. Already in 1982 the first Nordic IVF baby was born in Gothenburg (Hamberger et al., 1982). Within a short period of time the IVF technique spread to the other Nordic countries. In 1984, the first private IVF clinic in the Nordic countries was established in Stockholm. Since then, a steady increase in the number of IVF cycles has been recorded and today the Nordic countries report their availability of IVF services to be the highest in the world (with the possible exception of Israel). For the year 2000, Denmark reported the highest number of cycles per million inhabitants at 1826 cycles followed by Finland at 1440 and then Sweden, Iceland and Norway around 1000 cycles per million. In comparison, the UK performed around 600 cycles per million inhabitants and the US around 250 cycles per million (Nygren and Nyboe Andersen, 2002).

These exceptionally high numbers of IVF cycles are probably due to a combination of relatively high reimbursement levels in the Nordic countries and a high public acceptance of the technique. The reimbursement policies have possibly been fuelled by a traditionally ‘socialized’ medicine in the Nordic countries. The high public acceptance may be the result of an early start of monitoring of both efficacy and safety of these procedures, so that there has been a general reassurance in the general public, that the IVF technique is reasonably safe (Nygren, 2002) for both mother and child.

**Changing clinical policies**

Already at the beginning of the 1990s, the relatively high proportion of multiple pregnancy came into focus. A voluntary process of clinical policy change was then started. The mean number or replaced embryos, traditionally around three, was then diminished, starting at the beginning of 1991 to reach a mean level of around two embryos per transfer in 1996 and onwards. This relatively dramatic change resulted in a considerable reduction in multiple pregnancies, from around 35% in year 1991 to 22% for 2001, while the efficacy remained high.

**Monitoring of efficacy, safety and quality**

In the early days, developments in IVF were mainly focused on the technical aspects. This was soon followed by an increasing

### Table IV. Nordic companies related to IVF

<table>
<thead>
<tr>
<th>Company</th>
<th>Active in IVF since</th>
<th>Business area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruel and Kjaer, Denmark</td>
<td>1982</td>
<td>Sonography, vaginal transducers</td>
</tr>
<tr>
<td>SweMed Lab</td>
<td>1984</td>
<td>Puncture needles, needle guides, equipment</td>
</tr>
<tr>
<td>K-Systems</td>
<td>1989</td>
<td>Laboratory equipment LAF benches, etc</td>
</tr>
<tr>
<td>MediCult</td>
<td>1990</td>
<td>Culture media for IVF and IVM</td>
</tr>
<tr>
<td>Vitrolife</td>
<td>1993</td>
<td>Culture media for IVF, transplantation, stem cells</td>
</tr>
</tbody>
</table>
emphasis also on a more ‘holistic view’, when patient-care and patient-counselling came into focus. A third line of development, which also started early in the Nordic countries, was a growing understanding of the importance of monitoring IVF first on efficacy, but later also on safety and quality.

The Nordic countries have had a unique possibility to follow-up medical risks for IVF children. This is due to the fact that several population-based health registers have been operating since well before the era of IVF. In Sweden, for example, it has been possible to collect safety-data through cross-linkage between IVF registers and several public health registers, like the Medical Birth Register, the Cancer Register, the Malformation Register, the Hospital Patient Register, the Cause of Death Register and the Visual Impairment Register. Cross-linkage procedures have been made possible through each citizen’s unique, personal identification number, which is the same for all registers. Not many countries around the world have this possibility for long-term follow-up.

Acknowledgement

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Danish law No 460 on Assisted Reproduction 10 June 1997.


Human Embryo Experimentation Bill (1985) (This Bill is popularly referred to as the ‘Harradine Bill’, after Senator Harradine who introduced the Bill in the Australian Senate).


Icealandic law No 55 on Assisted Reproduction of 29 May 1996.


The early days of IVF outside the UK
Swedish law No 1140 on insemination of 20 December 1984.
Swedish law No 711 on In Vitro Fertilization of 14 June 1988.

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