Development of in vitro fertilization in Australia

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In vitro fertilization (IVF) began in Melbourne in 1970 when Carl Wood founded a research group at the Queen Victoria Hospital. The group reported the first biochemical pregnancy from a transferred IVF embryo in 1973. The group included the Royal Women's Hospital Melbourne, and they were the first to report confirmation of the British group's pregnancies with the use of IVF in natural cycles in 1980. The group then split, and the Monash group pursued fertility drug–induced multiple follicle growth in controlled ovulatory cycles and demonstrated for the first time that they could achieve multiple pregnancies in 1980–1981. This became the basis of a sustainable procedure for treating infertile patients. Successful embryo freezing and thawing methods resulted in pregnancies for the first time and were adopted to cryopreserve excess embryos produced after superovulation. Embryo donation methods were devised for anovulatory patients and were the first reported use of oocyte in vitro maturation techniques (IVM) for polycystic ovarian syndrome patients. Sperm microinjection techniques were pioneered for enabling fertilization for severely infertile men, and micromanipulative techniques were published for embryo biopsy for potential use in preimplantation genetic diagnosis (PGD) for patients with inheritable genetic diseases. The latter research programs were hampered by creation of restrictive embryo research laws in the State of Victoria, handicapping their timely clinical applications. Work on cryopreservation of ovarian tissue for cancer patients enabled clinical application of this for patients at risk of loss of fertility. Vitrification was developed as an alternative to freezing for oocytes and embryos, and this has now replaced the original slow cooling methods. Blastocyst culture systems were devised and optimized to improve IVF success and PGD. (Fertil Steril® 2018;110:19–24. ©2018 by American Society for Reproductive Medicine.)

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Human in vitro fertilization (IVF) was generated as an idea by Neil W. Moore at the 1968 Australian Society of Animal Reproduction Conference as an alternative to the procedure that was being attempted by Carl ("E.C.") Wood (founding chair of Obstetrics and Gynaecology, Monash University) to correct human infertility with the use of plastic tubing engineered with micropores as a replacement for blocked fallopian tubes in infertile women (1). Wood spent some time with Moore at the McCaughy Memorial Institute's animal research laboratories in county Jerilderie, New South Wales, learning about sheep embryology and embryo transfer. Wood then established a research group at the Queen Victoria Hospital Melbourne in 1970 (Department of Obstetrics and Gynaecology, Monash University) to explore the possibility of reproducing in humans the IVF techniques that were effective in mice, rats, rabbits, and other animals. The initial members of the team included gynecologists John Leeton and J. McKenzie ("Mac") Talbot. A Ph.D. biologist, Alex Lopata, was added, and later the group expanded to include Ian Johnson, the head of Reproductive Biology Unit at the Royal Women's Hospital Melbourne, and Jim Brown, Ph.D., a noted endocrinologist also at the Royal Women's Hospital.

Wood and his team were the first to report a biochemical pregnancy in 1973 using human IVF to produce a human embryo for transplantation to an infertile patient (2). This was sufficient inducement to continue the research independent of the work being done by Edwards and Steptoe in the United Kingdom. The Australian research group concentrated on hMG stimulation for multiple follicular development and laparotomy or laparoscopy to recover oocytes (3) after hCG-induced timing of oocyte recovery (4), a strategy that Brown and Jim Evans were using for inducing ovulation in infertile women. However, there were no more pregnancies in these patients, and similarly no pregnancy outcomes were also obtained when using clomiphene citrate (Clomid) for inducing mild superovulation (5). Wood tried numerous innovations, including attempts to fertilize human oocytes in the sheep oviduct, but all of them failed to progress to successful IVF pregnancies. Talbot paid a visit to Steptoe to discuss the progress of human IVF in 1975, but

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none of the changes subsequently tried yielded pregnancies in patients. There was considerable doubt and criticism of the work from others, but Wood maintained his optimism that human IVF was indeed possible given the success in other animal species. He tried to persuade Alan Trounson, Ph.D., who was Neil Moore's postgraduate student with experience in animal IVF and embryology, to join the team in 1973, but Trounson declined and left for a Dalgety Postdoctoral Fellowship at Cambridge U.K. (1974–1976), studying reproductive biology and embryology in farm animals with L.E.A. ("Tim") Rowson, Robert Moor, and Chris Polge at the Agricultural Research Centre of Reproductive Physiology and Biochemistry. This was the world's leading center for animal reproductive biotechnology at the time. Trounson was involved in developing animal embryo freezing, oocyte maturation, embryo culture, and nonsurgical embryo transfer in cattle while in Cambridge.

DEVELOPING A SUSTAINABLE IVF PROCEDURE

News of the success for the British team of Edwards, Steptoe, and Purdy in 1978 of initiating pregnancy with the use of IVF in the natural cycle immediately motivated the Australian team to examine the natural ovulatory cycle as a way of producing babies by means of IVF. In 1977, Trounson returned to Melbourne to take up a position with Wood's team as a Ford Foundation Fellow at Monash University. Wood had been successful in attracting Ford Foundation funding for a major program in Melbourne studying human IVF and the new hormone inhibin that had been discovered by Brian Hudson, Henry Burger, David deKretser, and others at Prince Henry's Hospital Melbourne. The consortium that included John ("Jock") Findlay was awarded the Ford Foundation grant that had previously funded Robert Edwards et al. The grant included funding to return Trounson and Gordon Baker (inhibin researcher) from overseas. However, the IVF embryology work in Wood's team was handled by Lopata, so Trounson was diverted to study zona pellucida antibodies and to develop sperm-freezing technologies for artificial donor insemination. Toward the end of 1978, Wood asked Trounson to become involved fully in the IVF program and to share the embryology work with Lopata, who was working at both Queen Victoria Hospital and Royal Women's Hospital. Patrick Steptoe paid a visit to Melbourne in 1978 but declined to give details of the methods they used for achieving the first IVF baby. The account of this visit, including the competition between the Melbourne and the U.K. group and interactions and tensions between the two Melbourne hospital teams, is discussed in a book by John Leeton about the origins of IVF (6).

The assay used by Steptoe and Edwards to time the collection of oocytes, known as the Higonavis agglutination assay, which could detect LH rise in urine was basically unavailable, so Trounson abbreviated the LH radioimmunoassy to 1–2 hours to detect the onset of the LH surge in the patient's urine. He also arranged for John Buster to spend time in Melbourne to help shorten the estrogen assay to enable rapid detection of rising blood estrogen levels in spontaneously ovulating women. These tests were used to predict the time of oocyte recovery in the natural cycle.

In 1979, the Melbourne team established their first viable IVF pregnancy with the use of natural cycle monitoring (7). The decision to exclude other members of the research team from authorship on this paper caused a split in the Melbourne group, with Lopata moving full time to Melbourne University and Royal Women's Hospital and Trounson remaining with Wood at Monash University and Queen Victoria Hospital. Because of his experience in animal superovulation and embryo transfer, Trounson requested that he be allowed to work with Leeton on exploring the controlled superovulatory cycle with other modifications that would optimize fertilization rates and embryo development. These studies compared natural-cycle IVF with outcomes for patients treated with the use of clomiphene citrate (Clomid) and oocyte collection either after detection of the spontaneous LH surge, or after hCG injection to initiate follicular and oocyte maturation. These experiments from 1979–1980 demonstrated that the stimulated and controlled cycle was the preferred method for establishing pregnancies and was the beginning of a sustainable IVF procedure (8). The laboratory methods were also published soon after, showing that human embryos could be successfully grown to all preimplantation stages up to the hatching blastocyst in large numbers from superovulated women (9). Critically, the ultrastructural observations of A.H. ("Henry") Sathananthan on oocytes collected via laparoscopy indicated that they were still maturing, often with cortical granules still migrating to the plasma membrane (10). Delaying insemination allowed more oocytes to mature and to increase the cohort of apparently normal embryos produced. Trounson invited his friend Pierre Soupart, the pioneering IVF researcher from Nashville, Tennessee, who first demonstrated human fertilization in vitro with the use of electron microscopy, to visit Melbourne in 1980 a year before his death in 1981 to see the emerging successful clinical IVF procedure. It was Soupart's National Institutes of Health grant application that was scientifically approved in 1975 but rejected by the national Ethics Advisory Board, effectively preventing the continuation of his work and excluding any other research study involving human embryos from federal funding from then on. The initial success of the new superovulatory methods and culture systems developed at Monash that produced a cohort of IVF pregnancies was reported by Trounson to the World Congress of Human Reproduction in Berlin in 1981.

IVF AND ASSISTED REPRODUCTIVE TECHNOLOGIES BECOME ESTABLISHED PROCEDURES

The early success of Wood's team in Melbourne in 1979–1982 was documented in several publications (11–13), including the comparisons of natural-cycle IVF, Clomid/hCG or LH surge, Clomid + hMG/hCG or LH surge, and hMG/hCG or LH surge (14). Progressively, the methods changed to Clomid + hMG/hCG and then to hMG/hCG while maintaining pregnancy rates and birth outcomes. John McBain from Royal Women's Hospital collaborated with Trounson and Leeton