

## Early history of IVF in Australia

Zgodnji začetki zunajtelesne oploditve v Avstraliji

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### Ključne besede:

zunajtelesna oploditev;  
zgodovina medicine;  
zgodnji razvoj; Avstralija;  
Nobelova nagrada za  
medicino 2010

### Key words:

IVF; history of medicine;  
early developments;  
Australia; Nobel prize  
2010

### Citirajte kot/Cite as:

Zdrav Vestn 2014;  
83: 484–9

### Abstract

**Background:** The 1970s and 1980s represent the early era of *in vitro* fertilization (IVF) research. This article is a concise review of the early history of IVF, focusing on the contributions made by Australian pioneers.

**Objectives:** To research the history of the early days of IVF in Australia.

**Search Strategy:** 'IVF history' was used as a search criteria in PubMed.

**Selection criteria:** We selected articles that were dealing with Australian research on IVF in 1970–1980s and were also statistically sound where applicable.

**Data collection and analysis:** We collected, processed, and analyzed the data, and summed up two decades of IVF research in Australia.

**Main results:** The first ideas about introducing IVF research in Australia started in 1970. Years of trials and hard work bore success and the first baby was born in 1980. IVF procedures then spread quickly across Australia.

**Conclusions:** Australia was a leading force in the early days of IVF and with many innovative approaches contributed greatly to the development of IVF as we know it today.

### Izvleček

**Ozadje:** Sedemdeseta in osemdeseta leta 20. stoletja predstavljajo zgodnje raziskovalno obdobje *in vitro* oploditve (IVF). Ta članek je zgoščen pregled tega obdobja s poudarkom na prispevku avstralskih pionirjev IVF.

**Cilji:** Raziskati zgodnji razvoj IVF v Avstraliji.

**Strategija raziskave:** Pregled baze člankov PubMed o zgodovini IVF.

**Merila za izbor:** Izbrali smo članke, ki so se ukvarjali z avstralskimi raziskavami umetne oploditve med letoma 1970 in 1980 in so bili tudi statistično uporabni.

**Zbiranje in analiza podatkov:** Zbrali, obdelali in analizirali smo dvajsetletne podatke o raziskavah IVF v Avstraliji.

**Rezultati:** Prve zamisli o uvedbi raziskav o IVF so bile prisotne v Avstraliji že leta 1970. Leta poskusov in trdega dela so obrodili uspeh in prvi otrok iz epruvete se je rodil v letu 1980. Postopki IVF so se potem hitro širili po vsej Avstraliji.

**Sklepi:** Avstralija je bila vodilna sila v prvem obdobju IVF in je veliko prispevala s številnimi inovativnimi pristopi k razvoju metode IVF, kot jo poznamo danes.

## 1. Introduction

Dr. Robert Edwards, the father of IVF, was the recipient of the Nobel Prize for Medicine in 2010. To commemorate this occasion, we wrote an article about the history of IVF from the first ideas up to the birth of the first child born with the help of Drs Edwards and Steptoe in the United Kingdom.<sup>1</sup> When doing research we came across compelling evidence of the efforts and precious contributions of other early IVF teams across the world, especially teams from Australia and the United States. Their eagerness and enthusiasm were crucial in paving the way for IVF. We therefore felt it was more than appropriate to write an article covering the advances and struggles of those teams separately. Here, we focus on the achievements of the Australian teams. The events are listed chronologically up to the mid-1980s. Thanks to these early researchers, IVF is now a widely available method for infertile and same-sex couples and more than 4 million babies have been born worldwide with the help of IVF procedures.

## 2. A brief history

The first ideas about *in vitro* fertilization have been documented over 130 years ago. It was in 1878 that Schenk tried to fertilize rabbit eggs *in vitro* in Wien.<sup>2</sup> During the next decades, many researchers tried to fertilize eggs of different species, especially rabbit and human eggs.<sup>3</sup> Those visionary researchers were ahead of their time as knowledge of the physiology of human reproduction was scarce at the time. The first well-documented fertilization of the rabbit egg as well as embryo transfer and delivery of baby rabbits was achieved by M. C. Chang in 1959.<sup>4</sup>

Robert Edwards (1925–2013) was a British physiologist who strongly believed in the possibility of human *in vitro* fertilization. Since his early studies he had been particularly interested in oocyte maturation. In 1968, he teamed with Patrick Steptoe, a gynecologist with a special interest in infertility, who at the time was working on his technique of oocyte laparoscopic aspiration. They started working together at the *Dr*

*Kershaw's Cottage Hospital* in Royton near Oldham.<sup>5</sup>

They reported the first successful *in vitro* fertilization of oocytes they recovered after gonadotrophin stimulation. This was the first successful human IVF proved by spermatozoa penetration, emission of polar body and pronuclei formation.<sup>6–8</sup> In 1972 they started with embryo transfers (ETs) and achieved their first pregnancy in 1976, but it was an ectopic pregnancy.<sup>9</sup>

Ms Lesley Brown became pregnant after 102 unsuccessful ETs with only one embryo transferred at the stage of 8 cells. Louise Brown, the first IVF baby, was born as a normal healthy child on 25th July 1978 with a caesarian section.<sup>10</sup> Despite their success, no institution in the UK wanted to fund their activities so they did it on their own and established *Bourn Hall Clinic*, which became the first IVF centre in the world and the site of the first IVF conference in 1981 where IVF pioneers were present.<sup>5</sup>

## 3. Australia

Australia was also a leading force in the field of IVF in the years 1970–1985, and Australian researchers have achieved many world firsts: first donor egg pregnancy, first frozen embryo pregnancy, first IVF multiple pregnancy. They were also on the forefront of introducing regulations regarding IVF practices producing amongst other the first national guidelines for IVF as well as the first statute regulations concerning donor gamete pregnancies and the control of IVF procedures. They were the first to report the outcome of all IVF pregnancies in 1980.<sup>11</sup>

### Getting started

It was in 1970 that Professor Neil Moore, inspired by the Australian Society for Reproductive Biology Conference, suggested to Professor Carl Wood that human infertility could be treated using IVF. Successful IVF and embryo culture studies in animals had been the topic of the conference. Professor Wood was at the time Chairman of Obstetrics and Gynecology at Monash University (MU) and Queen Victoria Medical Centre

(QVMC). He promptly organized a combined IVF team in Melbourne. Two clinics were involved – the Royal Women’s Hospital (RWH) with Dr. Ian Johnston and QVMC with Drs. John Leeton and J. Mackenzie Talbot as well as MU. Dr. Alex Lopata was at the time a lecturer at MU and the embryologist for both groups.<sup>11</sup>

Hormonally stimulated IVF cycles were carried out in 1972–1978 using either human pituitary gonadotrophins (HPG)<sup>12</sup> or clomiphene and human chorionic gonadotrophins (HCG).<sup>13</sup> In 1973 they achieved two early IVF pregnancies as proved by a raise in HCG. Unfortunately they both ended in less than a week.<sup>14</sup> These ‘chemical pregnancies’ were an important milestone for they were proof that IVF embryos can start implantation. IVF fertilization rates remained low (10–15 %) in the early 1970s and in the next six years they recorded no IVF pregnancies in Melbourne.<sup>11</sup>

Steptoe and Edwards were experimenting with three different protocols: natural cycles, stimulated cycles and donor eggs. When Louise Brown was conceived using a natural cycle, they decided to continue with this protocol. The Melbourne group adopted this strategy as well.<sup>11</sup> By detecting LH surges they determined both the time of ovulation and egg pick-up (EPU) time.<sup>15</sup> This meant that EPU could have taken place at any time of the day or night which rendered this project even less popular within the hospital environment.<sup>11,16</sup>

### Introducing improvements

Dr. Alan Trounson joined the Monash group in 1978 and introduced a number of improvements. He simplified and improved the culture media. Encouraged by John Letton, he reintroduced ovarian stimulation with clomiphene and HCG which made it possible to predict the exact time of ovulation as well as the aspiration of more than one oocyte at a time.<sup>17</sup> He also introduced culture quality controls<sup>18</sup> and prolonged the time interval between aspiration and fertilization to allow the oocytes time to mature.<sup>19</sup> All those measures improved the success rate.

The initial rate of success of laparoscopic EPU was less than 50 % per follicle and the IVF program was often called the ‘Egg Project’ in the beginning.<sup>11</sup> The EPU was often rendered difficult by ‘frozen pelvis’, adhesions or hidden ovaries. At the time, surgical laparoscopic instruments were not yet available, so blind stabs were often performed.<sup>20</sup> The Australian IVF group also introduced a number of technical improvements and subsequently the EPU rate increased to 60–80 % per follicle. Fixed aspiration pressure (100 mm Hg) was introduced in 1979.<sup>21</sup> Dr. Peter Renou designed special Teflon-lined aspiration needles with beveled points and 1.00 mm internal diameter.<sup>22</sup> Improved ultrasound parameters were introduced to determine EPU timing further increasing the success rate.<sup>23,24</sup> Both Melbourne teams were the first to describe oocyte and embryo ultrastructure in detail<sup>25,26</sup> and to show that oocytes need three hours for maturation after recovery.<sup>11</sup> Techniques for embryo transfer were also improved in 1979–1980. Improved catheters were introduced. The researchers also stressed the need for more careful measurement and placement of embryos and that all transfers be done by one clinician in order to avoid clinicians’ bias.<sup>27,28</sup>

### The successes

The efforts, the determination and numerous innovations resulted in the birth of Candice Reed on 21st June 1980, making her the first Australian IVF baby and the third in the world. The oocyte was from a natural cycle.<sup>29</sup> Her birth was the testimony that the Melbourne teams were on the good path and that the method had potential for treating infertility. Previously, Australian doctors had tried to help women with damaged Fallopian tubes by microsurgery,<sup>30</sup> oviduct transplantation<sup>31</sup> and even artificial oviducts.<sup>32</sup> None of the methods brought the desired results, which further confirmed the important role of IVF for treating infertile women with blocked tubes.

IVF spread quickly throughout Australia, and in the early 1980s, IVF clinics were opened across the country (Sydney, Adelaide, Brisbane, Perth). Until 1982 all centers

saw the birth of IVF children, which was a major achievement on a national level. After the first birth, the two groups separated and each continued with its own IVF program.<sup>11</sup> In 1978, the QVH team investigated idiopathic infertility treated by IVF. Their results were important because previously IVF had been reserved for infertility due to tubal disease only.<sup>33</sup>

Deep-frozen sperm banks were established in the late 1970s in several Australian centers.<sup>11</sup> Frozen sperm was first used for IVF in 1983.<sup>34</sup> In 1982 the Monash group was the first in the world to report a pregnancy with a donated egg. A 38-year-old woman became pregnant in a natural cycle with an egg from a 42-year-old donor and donor sperm.<sup>35</sup> The pregnancy terminated with abortion at 10 weeks causing an international outcry of criticism regarding the age of the donor as well as the age of the recipient.<sup>36</sup> Soon followed the first pregnancy with a donated egg that resulted in the birth of a child.<sup>37</sup>

The first frozen embryo pregnancy was achieved by Alan Trounson in 1983.<sup>38</sup> He attributed the success to meticulous care as well as a change in embryo freezing timing – he froze the embryo at the stage 4–8 cells instead of the blastocyst stage. The pregnancy terminated with abortion at 22 weeks due to obstetrics reasons, but the fetus was normal. A year later, the first ET baby was born.<sup>39</sup>

Australian doctors also reported the first multiple IVF pregnancies (twins, triplets and quadruplets) as well as analyzing the pros and cons for multiple embryo transfer<sup>40</sup> and writing a report on the incidence of multiple pregnancies after IVF and ET.<sup>41</sup>

It was in 1986 that dr. Chen reported the first pregnancy following deep-freezing of oocytes.<sup>42</sup> A donor egg bank was established in Melbourne but no pregnancy with a stored egg was ever reported.<sup>11</sup>

The following years saw a significant rise in IVF pregnancies and until September 1984, 365 IVF babies had been born in Australia alone. The success rate was comparable in all seven Australian centers, which was a unique achievement on the national level at the time, pointing to very good communication and collaboration between tho-

se centers. Australia was the first country to report on birth outcomes of IVF and GIFT procedures since 1980.<sup>11</sup>

## Legislation and ethics

This article was designed to be primarily a historical review of the achievements by Australian doctors and researchers in the field of IVF in the 70s and 80s. We did not plan to concentrate either on the legislation or the ethics. However, the field of ART is controversial and was even more so in its beginnings. It is important to mention that the beginnings of IVF were met with skepticism and criticism from the scientific as well as the lay public just as was the case with other pioneer countries. However, the majority of Australians have been supportive of IVF and its related techniques since the beginning. Results from Morgan Gallop Polls showed that between 1981 and 1994, 71 % of Australians on average agreed that infertile couples should have access to IVF.<sup>16</sup>

During these decades many acts in legislation have been passed to regulate IVF practices in Australia. Listing them all would greatly exceed the scope of this article. We will therefore only mention a few important milestones. They produced amongst others the first national guidelines for IVF as well as the first statute regulations concerning donor gamete pregnancies and the first statutory legislation concerning control of IVF procedures. The first institutional ethics committee (IEC) for IVF was convened at QVH in 1980. The Fertility Society of Australia (FSA) was established in 1982 under the chairmanship of Dr. Ian Johnston. The aim of the society was to 'promote the study of the science of the human reproduction in all its disciplines with particular emphasis on the clinical application of such knowledge'.<sup>11</sup>

The field of IVF notably raised many questions and dilemmas. A lot of the opposition came from fear of the unknown. Edwards writes that the reaction was explosive. From early on, he wanted that all research in human reproduction be conducted in compliance with strict ethical rules.<sup>43</sup> The pioneers made an enormous effort to inform the

perplexed public about the new method and the possibilities it offered through news conferences, interviews, lectures and articles.

### Influences in former Yugoslavia

The work of Australian researchers had positive repercussions on the developments of IVF not only in Australia but also worldwide. Petrova Clinic in Zagreb was the first on the territory of the former Yugoslavia and the seventh center in the world to successfully complete IVF in 1983. The leader of the team was Prof. Drobňak and the Zagreb clinic also received help from their colleagues from Melbourne.<sup>44</sup>

The IVF team from RWH in Melbourne also influenced the development of IVF in Maribor. Veljko Vlajsavljević from the Slovenian IVF center in Maribor spent three months in 1987 as a clinical assistant at the Department of Reproductive Biology of the Royal Women's Hospital in Melbourne. There, he acquired knowledge about IVF laboratory techniques, which were successfully transferred to the IVF center of Maribor. In 1989, twins were born following a successful GIFT procedure, thus making Maribor the third center in the former Yugoslavia to achieve this important milestone.<sup>45</sup>

## 4. Conclusion

Since the birth of the world's first test-tube baby in 1978, more than 4 million babies have been born worldwide with the help of IVF. IVF is nowadays a widely available and accepted method for helping infertile couples. However, the path to success was long and difficult. IVF as we know it today should not be taken for granted. Many hurdles and strong opposition (mainly on moral grounds) had to be overcome. The history of IVF is a wonderful complex story about struggles, overcoming obstacles and criticism, strong will and collaboration. IVF pioneers would meet at different locations all around the world and would share experience and knowledge. It was from this great sense of camaraderie that the whole world would benefit.

### Conflict of interest

Kristina Janežič and Zvonka Zupanič Slavec wrote the manuscript. All authors approved the final version of the manuscript and declare that they have no conflicts of interest and no competing financial interests.

## References

- Janežič K, Zupanič Slavec Z, Vrtačnik Bokal E. In vitro fertilization – from concept to first child commemorating the 2010 Nobel Prize in Medicine. *Slovenian Medical Journal* 2011; 80(9): 710–8.
- Schenk SL. Mammals artificially fertilized outside of the mother. *Communications from the embryology Institute of the Imperial University of Vienna* 1878(1): 107.
- Bavister BD. Early history of in vitro fertilization. *Reproduction* 2002; 124(2): 181–96.
- Chang MC. Fertilization of rabbit ova in vitro. *Nature* 1959; 184(Suppl 7): 466–7.
- Brinsden PR. Thirty years of IVF: the legacy of Patrick Steptoe and Robert Edwards. *Hum Fertil (Camb)* 2009; 12(3): 137–43.
- Bavister BD, Edwards RG, Steptoe PC. Identification of the midpiece and tail of the spermatozoon during fertilization of human eggs in vitro. *J Reprod Fertil* 1969; 20(1): 159–60.
- Steptoe PC, Edwards RG, Purdy JM. Human blastocysts grown in culture. *Nature* 1971; 229(5280): 132–3.
- Edwards RG, Bavister BD, Steptoe PC. Early stages of fertilization in vitro of human oocytes matured in vitro. *Nature* 1969; 221(5181): 632–5.
- Steptoe PC, Edwards RG. Reimplantation of a human embryo with subsequent tubal pregnancy. *Lancet* 1976; 1(7965): 880–2.
- Steptoe PC, Edwards RG. Birth after the reimplantation of a human embryo. *Lancet* 1978; 2(8085): 366.
- Leeton J. The early history of IVF in Australia and its contribution to the world (1970–1990). *Aust N Z J Obstet Gynaecol* 2004; 44(6): 495–501.
- Talbot JM, Dooley M, Leeton J, Lopata A, McMaster R, Wood C. Gonadotrophin stimulation for oocyte recovery and in vitro fertilization in infertile women. *Aust N Z J Obstet Gynaecol* 1976; 16(2): 111–8.
- Lopata A, Brown JB, Leeton JF, Talbot JM, Wood C. In vitro fertilization of preovulatory oocytes and embryo transfer in infertile patients treated with clomiphene and human chorionic gonadotropin. *Fertil Steril* 1978; 30(1): 27–35.
- De Kretzer D, Dennis P, Hudson B, Leeton J, Lopata A, Outch K, et al. Transfer of a human zygote. *Lancet* 1973; 2(7831): 728–9.
- Kerin JF, Warnes GM, Crocker J, Broom TG, Ralph MM, Matthews CD, et al. 3-hour urinary radioimmunoassay for luteinising hormone to de-



- tect onset of preovulatory LH surge. *Lancet* 1980; 2(8191): 431–2.
16. Cohen J, Trounson A, Dawson K, Jones H, Hazekamp J, Nygren KG, et al. The early days of IVF outside the UK. *Human Reprod Update* 2005; 11(5): 439–59.
  17. Trounson AO, Leeton JF, Wood C, Webb J, Wood J. Pregnancies in humans by fertilization in vitro and embryo transfer in the controlled ovulatory cycle. *Science* 1981; 212(4495): 681–2.
  18. Mohr LR, Trounson AO. The use of fluorescein diacetate to assess embryo viability in the mouse. *J Reprod Fertil* 1980; 58(1): 189–96.
  19. Trounson AO, Mohr LR, Wood C, Leeton JF. Effect of delayed insemination on in-vitro fertilization, culture and transfer of human embryos. *J Reprod Fertil* 1982; 64(2): 285–94.
  20. Lopata A, Johnston IW, Leeton JF, Muchnicki D, Talbot JM, Wood C. Collection of human oocytes at laparoscopy and laparotomy. *Fertil Steril* 1974; 25(12): 1030–8.
  21. Wood C, Leeton J, Talbot JM, Trounson AO. Technique for collecting mature human oocytes for in vitro fertilization. *Br J Obstet Gynaecol* 1981; 88(7): 756–60.
  22. Renou P, Trounson AO, Wood C, Leeton JF. The collection of human oocytes for in vitro fertilization. I. An instrument for maximizing oocyte recovery rate. *Fertil Steril* 1981; 35(4): 409–12.
  23. Buttery B, Trounson A, McMaster R, Wood C. Evaluation of diagnostic ultrasound as a parameter of follicular development in an in vitro fertilization program. *Fertil Steril* 1983; 39(4): 458–63.
  24. Hoult IJ, de Crespigny LC, O’Herlihy C, Speirs AL, Lopata A, Kellow G, et al. Ultrasound control of clomiphene/human chorionic gonadotropin stimulated cycles for oocyte recovery and in vitro fertilization. *Fertil Steril* 1981; 36(3): 316–9.
  25. Lopata A, Sathananthan AH, McBain JC, Johnston WI, Speirs AL. The ultrastructure of the preovulatory human egg fertilized in vitro. *Fertil Steril* 1980; 33(1): 12–20.
  26. Sathananthan AH, Wood C, Leeton J. Ultrastructure evaluation of 8–16 cell human embryos cultured in vitro. *Micron* 1982; 13: 193–203.
  27. Kerin JF, Jeffrey R, Warnes GM, Cox LW, Broom TJ. A simple technique for human embryo transfer into the uterus. *Lancet* 1981; 2(8249): 726–7.
  28. Leeton J, Trounson A, Jessup D, Wood C. The technique for human embryo transfer. *Fertil Steril* 1982; 38(2): 156–61.
  29. Lopata A, Johnston IW, Hoult IJ, Speirs AI. Pregnancy following intrauterine implantation of an embryo obtained by in vitro fertilization of a preovulatory egg. *Fertil Steril* 1980; 33(2): 117–20.
  30. Paterson P. Tubal microsurgery—a review. *Aust N Z J Obstet Gynaecol* 1978; 18(3): 182–4.
  31. Paterson P, Wood C, editor. Microvascular transplantation of the human fallopian tube. Proceedings of the First International Meeting on the Transplantation of the Fallopian Tube; 1980. Glenbole.
  32. Wood C, Leeton J, Taylor R. A preliminary design and trial of an artificial human tube. *Fertil Steril* 1971; 22(7): 446–50.
  33. Trounson AO, Leeton JF, Wood C, Webb J, Kovacs G. The investigation of idiopathic infertility by in vitro fertilization. *Fertil Steril* 1980; 34(5): 431–8.
  34. Mahadevan MM, Trounson AO, Leeton JF. Successful use of human semen cryobanking for in vitro fertilization. *Fertil Steril* 1983; 40(3): 340–3.
  35. Trounson A, Leeton J, Besanko M, Wood C, Conti A. Pregnancy established in an infertile patient after transfer of a donated embryo fertilised in vitro. *Br Med J (Clin Res Ed)* 1983; 286(6368): 835–8.
  36. Steptoe P, Edwards R. Pregnancy in an infertile patient after transfer of an embryo fertilised in vitro. *Br Med J (Clin Res Ed)* 1983; 286(6374): 1351–2.
  37. Lutjen P, Trounson A, Leeton J, Findlay J, Wood C, Renou P. The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure. *Nature* 1984; 307(5947): 174–5.
  38. Trounson A, Mohr L. Human pregnancy following cryopreservation, thawing and transfer of an eight-cell embryo. *Nature* 1983; 305(5936): 707–9.
  39. Downing BG, Mohr LR, Trounson AO, Freemann LE, Wood C. Birth after transfer of cryopreserved embryos. *Med J Aust* 1985; 142(7): 409–11.
  40. Speirs AL, Lopata A, Gronow MJ, Kellow GN, Johnston WI. Analysis of the benefits and risks of multiple embryo transfer. *Fertil Steril* 1983; 39(4): 468–71.
  41. Kerin JF, Warnes GM, Quinn PJ, Jeffrey R, Kirby C, Matthews CD, et al. Incidence of multiple pregnancy after in-vitro fertilisation and embryo transfer. *Lancet* 1983; 2(8349): 537–40.
  42. Chen C. Pregnancy after human oocyte cryopreservation. *Lancet* 1986; 1(8486): 884–6.
  43. Edwards RG, Sharpe DJ. Social values and research in human embryology. *Nature* 1971; 231(5298): 87–91.
  44. Drobnyak P, Grizelj V, Mačič E, Puharić I, Suchanek E, Šimunić V. Initial Results of the in Vitro Fertilization Program: January 31–June 15, 1983. *J Vitro Fertil Embr Transf* 1984; 1: 83–4.
  45. Borko E, Breznik R, Vlaisavljevic V. Zaetki programa zunajtelesne oploditve in prenosa zarodka (IVF-ET) v Sloveniji. *Zdrav Vestn* 2011; 80: Supl 201.1: 11–19