The wanted pregnancy
assisted conception in Australia

The world's first human IVF 'success' recently celebrated her 21st birthday and we can now say the technology has come of age. With almost 25,000 babies born in Australia as a result of IVF and related technologies, it seems appropriate to review the last two decades, examine current practice and speculate on future possibilities.

GEOFF DRISCOLL
MB BS(Syd), FRCS, FRCOG, FRANZCOG, CREI

Professor Driscoll is Medical Director of City West IVF, NSW. He is Head of the Internet Masters of Reproductive Medicine Program co-ordinated through the University of Western Sydney, and a former Chairman of the IVF Directors' Group of Australia.

In vitro fertilisation (IVF) and related technologies, collectively known as assisted reproductive technologies or ART, now result in more than 1% of births in our country. These technologies currently have – and will continue to have – very little effect on world population, their impact remaining mostly with the individuals directly involved. Nevertheless, there is immense scientific and public interest in ART. Progress to date may appear to have been rapid, but many challenges remain. The reasons couples seek assistance from ART are shown in Figure 1.

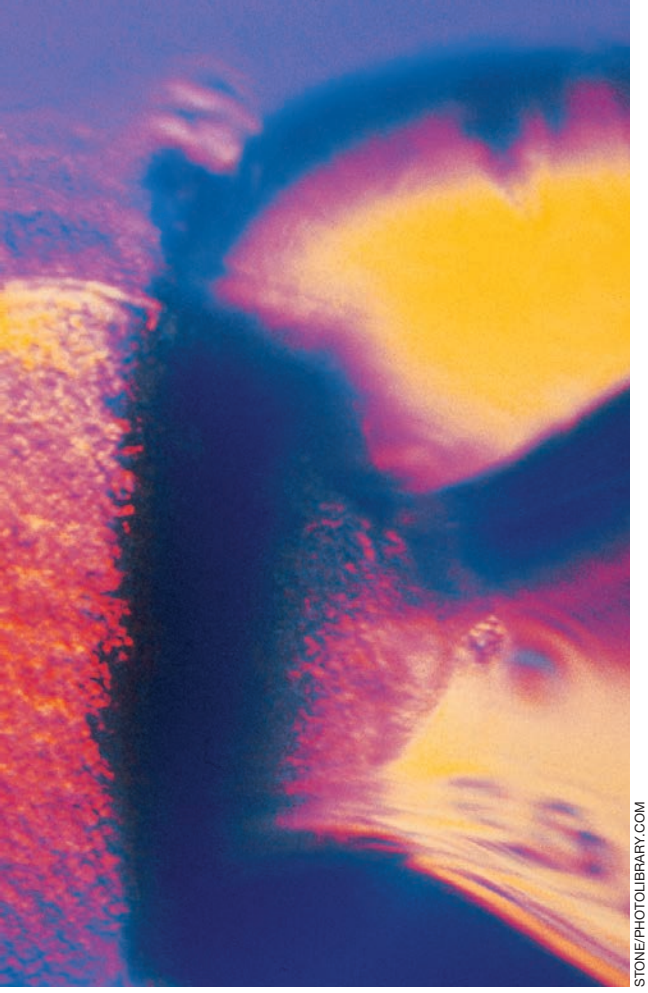
Achievements in ART to date

'Superovulation'

The first live birth in 1978 resulted from the successful collection and fertilisation of a single oocyte retrieved in a natural cycle. However, it was soon shown that by stimulating multiple follicular growth ('superovulation') to enable more

IN SUMMARY

- Assisted reproductive technology (ART) now results in more than 1% of births in Australia.
- Gamete intrafallopian transfer (GIFT) is no longer as successful as standard IVF and difficult to justify.
- There is an expanding role for preimplantation genetic diagnosis (PGD) in areas beyond simple sex selection for family balancing.
- Appropriate genetic screening and counselling are an important part of every modern assisted conception program.
- It is very important that couples have realistic expectations about success before embarking on treatment.
- There is increasing reassurance that the children resulting from intracytoplasmic sperm injection (ICSI) are no more likely to have major abnormalities than children conceived in the normal manner. However, genetic sperm problems may be transmitted.
- The treatment of infertility must address emotional and wider family and sociological aspects as well as the medical and scientific aspects. Support from a knowledgeable family physician can be crucial.



STONE/PHOTOLIBRARY.COM

oocytes to be retrieved, pregnancy rates could be markedly improved because more embryos could be developed and the healthiest embryos could be selected for transfer.

Superovulation remains the basis of current treatment, although this may change in the foreseeable future. Many different methods have been tried – the present approach is endogenous pituitary hormone suppression ('downregulation'), using GnRH analogues, followed by stimulation of multiple follicular growth using recombinant gonadotrophins. This too will soon be modified, with GnRH antagonists about to be released.

The side effects of stimulatory drugs include:

- multiple pregnancies
- ovarian hyperstimulation syndrome (mild to severe)
- nausea and headaches
- breast tenderness
- lower abdominal distension.

Multiple pregnancies. Multiple embryo replacement results in a worrying number of multiple pregnancies. Recognition of this obstetric and neonatal risk meant that embryos were often produced in excess of what was then deemed safe to transfer. The development of a successful way of cryopreserving 'surplus' embryos for later use went some way towards controlling both of these problems. However, the percentage of multiple pregnancies generated was unacceptable, with rates of over 20% for twins and up to 4% for higher order multiples.

Australian clinics have rarely returned to a patient more than four embryos at one time. Since the late 1980s, the Reproductive Technology Accreditation Committee (RTAC), established by the Fertility Society of Australia, has recommended that no more than three embryos usually be transferred. Most Australian units now prefer to transfer no more than two, with a recent trend towards single embryo transfer. However, internationally (and in the USA in particular), this conservative approach has not been followed.

Ovarian hyperstimulation syndrome. Superovulatory drugs also carry the risk of excessive response,

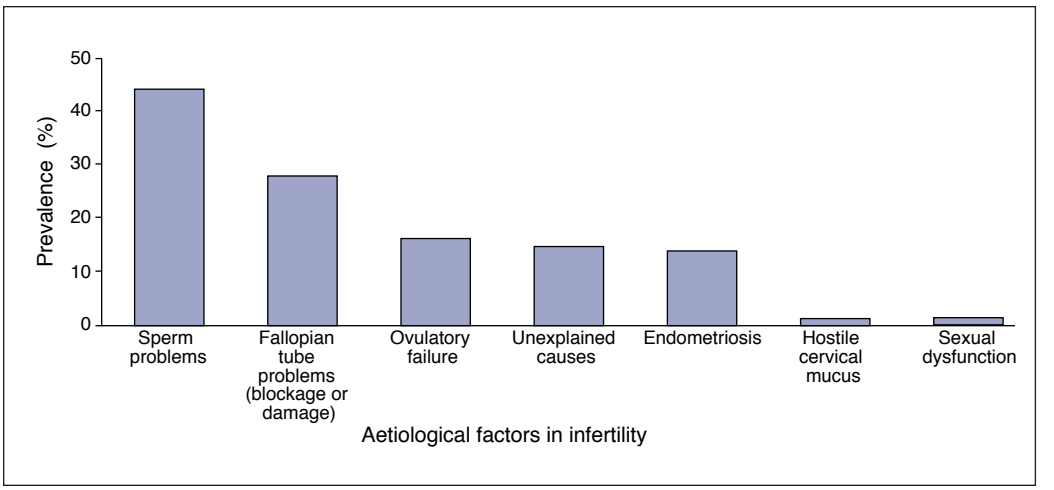


Figure 1. The prevalence of factors contributing to infertility in couples requiring ART. Note that the percentages add up to more than 100%, as many couples present with more than one factor.

the occurrence of ovarian hyperstimulation syndrome ranging from 0.25 to 1% of cases. This is a dangerous condition requiring meticulous fluid and protein control. Features include:

- nausea and vomiting
- bloatedness to extreme distension
- ascites and pleural effusion
- haemoconcentration/hypoproteinaemia
- coagulation disorders
- adult respiratory distress.

Studies reviewing long term effects of superovulation on women are reassuring, and the Fertility Society of Australia continues to encourage ongoing data collection and analysis.

Oocyte retrieval

Until the mid-1980s, all oocytes were retrieved laparoscopically. However, an extension of interventional imaging techniques, previously used only to monitor follicular growth and development, meant that oocytes could be retrieved by a much less invasive and uncomfortable procedure. Today, all oocytes are retrieved using such transvaginal ultrasound techniques under sedation or anaesthesia (local or a light general).

Intrafallopian transfer techniques

Gamete intrafallopian transfer (GIFT) was introduced in 1986, principally for couples with idiopathic infertility (laparoscopically 'normal' fallopian tubes and sufficient normal motile sperm). This technique allowed fertilisation to occur *in vivo* – the oocytes were retrieved and then the pre-agreed number were immediately returned laparoscopically into the ampulla of one or both tubes with a concentrated sample of the partner's sperm. GIFT is still used in some Australian units and has a small role if people prefer fertilisation to be *in vivo* rather than *in vitro* for ethical or religious reasons. GIFT is more invasive than standard IVF, and current rates show that it is less successful.

The concept of normal fallopian tubes being the optimal culture environment for embryos led to techniques in which embryos developed by IVF are returned to the fallopian tubes, rather than the uterus. Initially, tubal transfers attracted much interest, but they are now rarely performed.

Intracytoplasmic sperm injection

Progress in ART was slow for couples with severe spermatozoal problems (very low numbers, poor motility and/or abnormal morphology). For these people, the development of intracytoplasmic sperm injection (ICSI) in 1992 was a real breakthrough. The ICSI technique involved the isolation and capture of a single sperm and then its injection directly into the oocyte, thus bypassing the last barriers to successful fertilisation (Figure 2).

ICSI involves the use of highly sophisticated, specially developed microscope equipment and microscopic tools and was a dramatic improvement on earlier microinjection techniques. Not only did ICSI facilitate fertilisation with very poor quality sperm from the ejaculate, it also provided the opportunity to use sperm collected directly from the vas deferens, epididymides and testes by relatively simple needling techniques (Figure 3). These methods of bypassing blockages have markedly decreased the need for donor sperm, and the opportunity in such situations to have one's own biological child has obvious appeal.

There is increasing reassurance that children resulting from ICSI are no more likely to have major chromosomal abnormalities than children conceived in the normal manner. However, there is a very real likelihood that a father's spermatozoal defects – if genetic – may be passed,

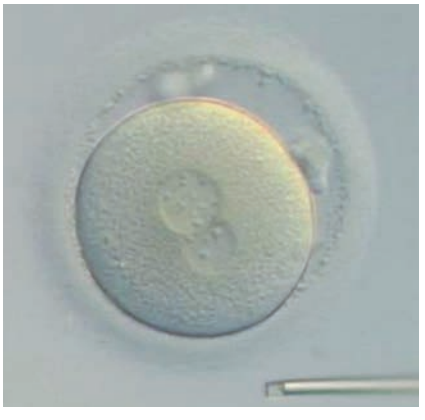


Figure 2. The pronucleus stage of an embryo formed *in vivo*.

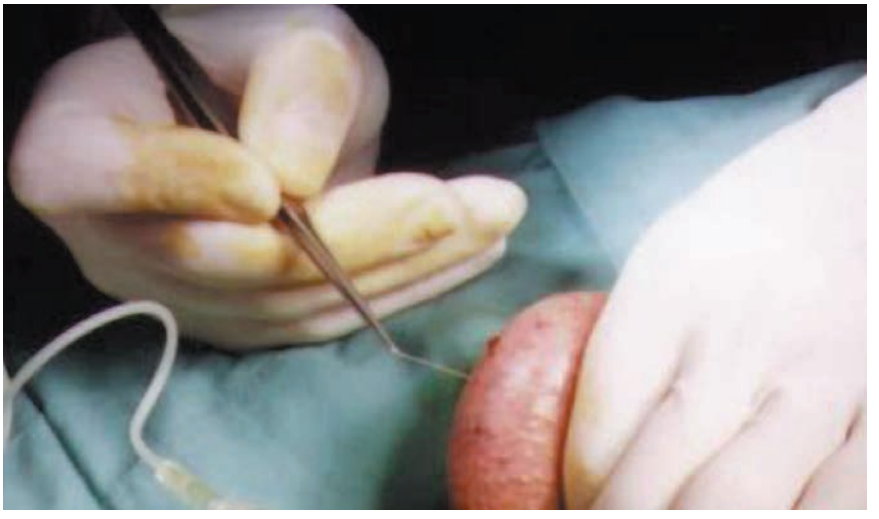


Figure 3. Surgical sperm collection. Methods of collecting sperm directly from the vas deferens, epididymides or testes to bypass blockages have markedly decreased the need for donor sperm.

Table 1. Investigations and treatment options for patients with fertility problems

Cause	Investigations	Treatments†
Ovulation failure	Hormone assessments	Ovulatory drugs (tablets or injections), ovum donation (rare)
Blockage or damage to fallopian tubes	Laparoscopy, hysterosalpinogram	Tubal microsurgery, IVF
Endometriosis	Laparoscopy	Surgical treatment, drug therapy, IVF
Fibroids	Laparoscopy, hysteroscopy, ultrasonography	Surgical removal (often laparoscopically) if treatment is needed
Hostile cervical mucus	Postcoital test, confirmation of ovulation, antisperm antibody test	Intrauterine insemination, IVF
Failure of sperm production	Initial semen analysis, hormone assessments, testicular biopsy	Surgical sperm collection, donor sperm
Blocked or absent vas deferens	Scrotal examination, cystic fibrosis screen	Microsurgical unblocking, surgical sperm collection with IVF
Low sperm numbers or poor sperm movement	Semen analysis	Intrauterine insemination, IVF
High numbers of abnormal sperm	Semen analysis	IVF
Antisperm antibodies	Antisperm antibody screen	Steroids (now rarely used), sperm preparation for intrauterine insemination, IVF

* This Table is a guide only. Every patient (or couple) will require a complete assessment and diagnosis before treatment is offered. † The IVF treatment option includes ICSI.
Reproduced courtesy of City West IVF.

with the Y chromosome, to his sons. Another notable example of potential genetic problems concerns cystic fibrosis. Mutations that may result in congenital bilateral absence of the vas and azoospermia in male carriers for cystic fibrosis (sometimes the only phenotypic expression of the defect) may be transmitted if sperm are aspirated directly from the testes of such a patient, with potentially disastrous consequences. Appropriate genetic screening and counselling are now a very important part of every modern assisted conception program, and will undoubtedly be of increasing importance in years to come.

Counselling

The importance of the team approach to ART combining the expertise of several disciplines cannot be overstated. Counselling is an integral part, and includes support counselling by the medical, scientific and nursing professionals as well as counselling about implications and therapy by the team psychologist or counsellor.

The investigations, diagnoses and treatment are all challenging for patients, who often suffer depression, anger, isolation and jealousy, together with a loss of control and self-esteem. Unlike many losses, infertility is not an event that slowly recedes into the past. It is often an ongoing, recurring loss, and for many people the dramatic roller coaster ride each month from despair to hope and back to despair again may be very difficult. The treatment of infertility, particularly treatment involving complex technology, must address the emotional and wider family and sociological aspects as well as the medical and scientific. Support from a knowledgeable family physician can be crucial.

Control

The original medicoscientific enthusiasm for ART raised understandable community concerns that seemed to focus mainly on the potential for misuse. However, there has been little to fuel any real criticism of the way the technologies have been developed and implemented in Australia. Some States have spent endless hours (and presumably dollars) deliberating, legislating, licensing, regulating and controlling assisted conception, but there is little evidence to suggest that States without

such controls have units that act in any ways that are less ethical or appropriate.

The RTAC regularly reviews the activities of all clinics, assisting where it finds any statistical divergence in the quality or the results of the service. This self-regulatory approach is unique, and works. One of the Committee's requirements is that every unit have an institutional ethics committee, constituted according to NHMRC guidelines, that reviews all of the unit's activities. The sources of gametes, how gametes are combined *in vitro*, and to whom the resultant embryos are transferred, can be complicated. These areas perhaps cause the most community concern – such areas include access by lesbians and single women to gametes and embryos, and the thorny issue of surrogacy, illegal in some States and (as yet) 'not illegal' in others. There has also been much publicity about placing embryos derived from gametes of young donors into older recipients.

Such matters will be a continuing source of public and legal debate because they impact on community acceptance and values while transgressing many legal precedents (such as sexual discrimination and other antidiscrimination Acts). It is interesting to observe community attitudes changing, albeit slowly, towards more acceptance.

Success

Success in ART is difficult to define. Some countries have 'league' tables produced by licensing authorities, but the interpretation of data in the tables is left somewhat to whim. When introduced in the United Kingdom, league tables led to changes that harmed clinical practice and created much controversy. However, proper mathematical analysis of the 1999 UK data showed only two units to be outliers, with no statistical significance between the results of all other units in the published table.

The National Perinatal Statistics Unit has been collecting and collating pregnancy data from all Australasian ART units since the early 1980s. Its findings suggest a steady increase in success rates, but do not necessarily highlight the broadened indications for the technology and the progressive decrease in the number of embryos transferred per attempt.

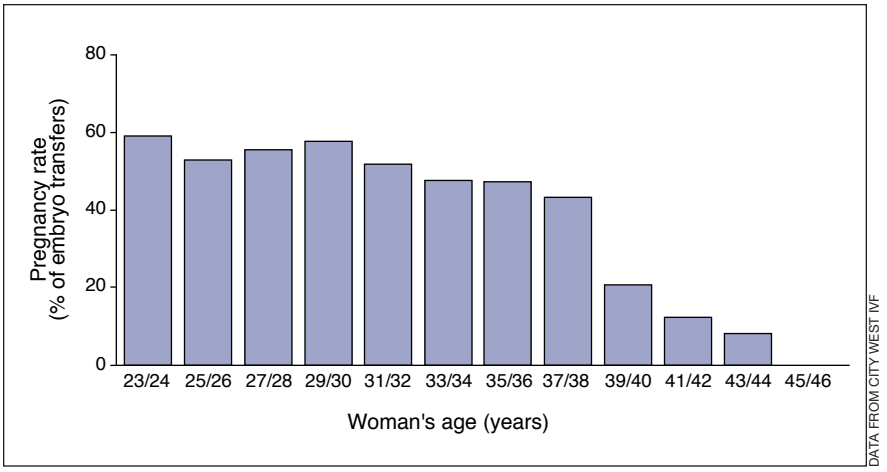


Figure 4. The effect of female age on pregnancy rate in couples who undergo ART.

An ART unit can be assessed in many ways. For example, is a unit that delivers babies to 23% of couples per treatment cycle while leaving the other 77% of couples emotionally devastated better than a unit that achieves babies for only 20% of couples but assists the other 80% so well that the latter are able to come to terms with their disappointment and attempt another treatment cycle? Intangibles maybe, but this wholly hypothetical exaggeration is used to highlight potential difficulties in assessing units and measuring success. Of course, we aim for success in all areas. Some units see a high proportion of older women and some treat more difficult patients – that is, patients who have sensibly tried everything else before resorting to ART (see Table 1). Some international units still transfer more than two embryos, and some do so few cycles that their results have no statistical power.

Even if we are to continue to accept a rather narrow definition of success, couples must be given realistic expectations. Few people seem to realise that the human species is poor at procreation. Even under optimal conditions, natural conception rarely occurs more than 25% of the time. The age of the woman is a particularly important factor (Figure 4).

Assisted conception can already lay claim to higher success than natural conception – in fact, often much higher in

Table 2. Some current applications of PGD

- Aneuploidy
  - Translocation carriers
  - Advanced maternal age
- X-linked disorders
  - Gender identification for social reasons
  - Duchenne muscular dystrophy
  - Haemophilia A
  - Fragile X syndrome
- Autosomal recessive disorders
  - Cystic fibrosis
  - Tay–Sachs disease
  - β-Thalassaemia
- Autosomal dominant disorders
  - Huntington's chorea
  - Marfan's syndrome
  - Familial adenomatous polyposis coli

the younger age groups – but obviously at a lot more cost and effort. Repeated ART attempts or the transfer of thawed cryopreserved supernumerary embryos from previous treatment cycles results in a cumulative success rate well above what is expected for 'normal' couples over a period of three to six months of unprotected coitus.

Newer developments

Improving embryo implantation

A great deal of research is seeking to improve embryo implantation. Assisted embryo hatching (somewhat like cracking the embryonic shell), whether done by laser or mechanical means, has been slow finding ubiquitous use because its ability to improve the pregnancy rate, although promising, is still somewhat controversial.

Attempts to improve implantation by culturing embryos for longer, until they reach the blastocyst stage (5 days), requires complex culture media and techniques, but it might allow more opportunity to select healthier embryos for transfer. Such techniques might improve the pregnancy rate per embryo transfer, but only time will tell if they improve the pregnancy rate per treatment cycle. Some interesting work is presently being undertaken to devise a gene expression screen for predicting potential embryo viability.

Preimplantation genetic diagnosis

Preimplantation genetic diagnosis (PGD) involves genetic analyses on a single blastomere extracted from a dividing embryo. Although the media focus on such things as sex selection for 'family balancing', PGD has other important applications, such as the avoidance of genetic disease and the appropriate selection of chromosomally normal embryos for implantation, particularly for older women.

Table 2 lists some of the disorders that can currently be tested for by PGD. Progress in human genetics is rapid and many more disorders will soon be added to the list. Inevitably, the indications will also be extended as the technology is further refined, genetics being a rapidly expanding science.

Culturing immature oocytes in vitro

An exciting and realistic prospect is a reliable method of culturing immature oocytes to maturity *in vitro* before fertilisation. This would eliminate the need for hormone stimulation of the putative mother, the immature oocytes being retrieved directly from the unstimulated ovary and then used at convenience. Oocyte culture could be repeated each cycle until a pregnancy is achieved, with the only physical inconvenience to the patient being the relatively painless embryo transfer.

Oocyte culture *in vitro* could also be used as a form of ovarian insurance for women who need radiation therapy or chemotherapy that might jeopardise their reproductive future. Whether such technology should be used for those wishing to delay childbearing for financial or career reasons is a justifiable source of community debate.

Final comments

In this short overview, I have purposely avoiding discussing such contentious issues as artificial gametes (such as somatic nuclear transfer to recipient enucleated eggs), cloning, the production of stem cell banks for tissue repair and concepts of embryo genetic 'enhancement'. However, we will inevitably hear much more about these controversial possibilities in the future.

Two decades on, advances in assisted conception continue unabated. The stakes are high for those who require such assistance; this alone should be sufficient to inspire continued research in fulfilling this most fundamental human need. MT