Assisted reproductive technology: 25 years of progress

Robert Forman

Great strides have been made in assisted reproductive technology and nearly all forms of subfertility are now amenable to treatment. Constant advances in technology and ethical controversy ensure it has a high public profile. The impact of assisted reproductive technology will be discussed in this article.

The birth of Louise Brown in 1978 concluded a decade of work by Robert Edwards and Patrick Steptoe but introduced the possibility of a child for many women. Although assisted reproductive technology (ART) was initially developed to treat tubal infertility, its progress over the last 2 decades has meant that those involved in ART have been able to address male factor subfertility, endometriosis and idiopathic infertility. Over 1 million children worldwide owe their existence to this treatment. In the first of two articles, the author looks back on the past 25 years at the developments that have facilitated such success, the aspects of infertility that can now be treated and highlight some of the issues that need to be addressed.

MILESTONES IN THE TREATMENT OF INFERTILITY

There have been many clinical milestones in the past 25 years (*Table 1*). Embryos can now be frozen and used at a later date to complete the family. They can also be screened for certain genetic disorders to ensure that parents do not pass on disease to their offspring. Intracytoplasmic sperm injection (ICSI) has been a major breakthrough in the treatment of male infertility. This technique was initially used for men with poorly motile sperm. However, the retrieval of sperm directly from the testicle to overcome blockage or deficiency has expanded its use and significantly improved treatment outcomes in male infertility.

Not all achievements have been clinical. Social milestones include the greater (but not complete) acceptance that ART is a therapeutic intervention for a medical disorder, and there is finally a movement towards wider provision of funded fertility treatment.

TABLE 1.
Firsts in assisted reproductive technology

1978	*In-vitro* fertilization birth – Louise Brown
1983	Frozen embryo birth in the US
1985	Surrogate baby born
1989	Embryo screening
1990	Sperm microinjection
1993	Testicular sperm retrieval
1993	Chromosome screening
1997	Frozen egg birth
1998	Frozen sperm from deceased donor

THE IMPACT OF INFERTILITY

Despite these advances in the treatment of infertility, up to 1 in 6 couples in the UK still experience trouble conceiving and require medical help (Taylor, 2003). Studies of the impact of infertility on the psychological wellbeing of couples have found that they experience feelings of isolation, depression, inadequacy and even suicide (Kerr et al, 1999). While the development of counselling services alongside clinical care provides support to many couples, infertility is still a significant issue.

CAUSES OF INFERTILITY

The cause of 30% of infertility remains unknown, although 27% of all infertility is known to be caused by primary and secondary ovarian failure (Effective Healthcare, 1992). This includes polycystic ovarian disease; malfunction of the hypothalamus, pituitary or adrenal glands; and other hormonal influences such as hyperprolactinaemia, hypothyroidism and pituitary tumours. Surgery, ovarian cysts, premature

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menopause and chemotherapy all have the potential to cause damage to the ovaries, leading to secondary ovarian failure.

Physical problems account for almost 20% of infertility (Effective Healthcare, 1992). Salpingitis as a result of infection or sexually transmitted disease can cause tubal damage. Chlamydia is a major risk factor, particularly as it can remain undiagnosed in young women for many years. Previous abdominal surgery can create scar tissue or adhesions in the area of the fallopian tubes, causing them to become obstructed, and fibroids or polyps can sometimes cause distortion of the uterine cavity. Endometriosis can lead to impaired tubal patency and impaired ovulatory function in affected women.

Male subfertility affects 1 in 20 men in the UK (Hirsh, 2003) and is mostly caused by a range of factors from sperm defects, infections and sexual dysfunction to testicular injury, chemotherapy or childhood illnesses such as mumps.

RISK FACTORS FOR INFERTILITY

As the number of patients undergoing fertility treatment has increased, so has the understanding of relevant risk factors. Severe anorexia and obesity can adversely affect the ability to conceive, and alcohol intake, smoking, recreational drug use and other lifestyle factors can have an impact. Perhaps most importantly of all, one of the biggest risk factors for infertility is a woman's increasing age (*Figure 1*). For women aged 35–39 years the chance of conceiving spontaneously is about half that of women aged 19–26 years, yet most women remain acutely unaware of their declining fertility (Taylor, 2003). While procrastination has little effect on a woman in her mid 20s, it can mean the difference between having, or not having a child when she is in her mid 30s. The chance of success with *in-vitro* fertilization (IVF) and ICSI also declines with age.

TREATING INFERTILITY

More than 80% of women with ovulation problems are now successfully treated via hormonal manipulation. Oral anti-oestrogens such as clomiphene citrate and synthetic gonadotrophins such as follicle stimulating hormone (FSH) and luteinizing hormone (LH) have been successfully used to induce superovulation. In conjunction with timed intercourse or artificial insemination, these have increased the chance of successful fertilization.

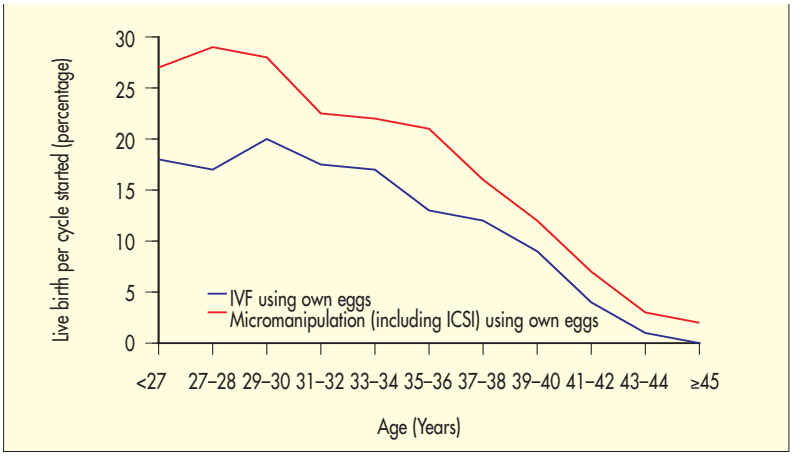
Early ART techniques such as gamete intrafallopian transfer where the egg and the sperm were placed in the fallopian tube for *in-vivo* fertilization have been superseded by intrauterine insemination, IVF and ICSI because of a greater success and the need for less invasive intervention.

Intrauterine insemination combined with ovulation induction or superovulation is a simple, relatively inexpensive procedure used successfully to treat unexplained infertility and some male factor subfertility. Pregnancy rates vary but are generally around 15% (Rowell and Braude, 2003).

IVF represents the biggest advance in the treatment of infertility. Live birth rates from IVF are just over 20% but wide differences remain because of patient variability and treatments offered (Human Fertility and Embryology Authority (HFEA), 2002). Certain clinics can reach rates of up to 46% (HFEA, 2002). It is hoped that good laboratory and clinical technique and a high degree of quality control will improve pregnancy rates by as much as 50% in the future. The Centre for Reproductive Medicine London clinic was designed specifically with environmental purity in mind, including special air filtration measures to ensure that embryos are not exposed to toxic chemicals (Hall et al, 1998). The introduction of the EU tissue directive in 2004 (EU Directive 2004/23/EC) will mean that many clinics will need to upgrade facilities to meet the new standards.

As well as improving success rates overall, the future aim will be to maximize the chance of a couple having a single healthy baby from an ART treatment cycle. Therefore the ability to select the single embryo with the greatest pregnancy potential would be of upmost significance, and the best way to achieve this will need to be evaluated.

Figure 1. How success with in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) declines with age. Human Fertilisation and Embryology Authority's (HFEA, 2000)



ICSI has been another great leap forward in ART. It has proved extremely valuable for couples who have failed fertilization, or where the quality or numbers of sperm are too low for normal IVF to succeed. The success rates in ICSI are greatly influenced by the quality of sperm preparation and by the skill of micromanipulation. When combined with IVF, ICSI is the most effective treatment for male infertility with a success rate of 20–25% of treatment cycles resulting in a live birth (HFEA, 2002).

EGG, SPERM AND EMBRYO DONATION

Donor insemination has been an accepted part of treating infertility for many years and was the only real option for certain types of male infertility before ICSI (*Table 2*). Oocyte (egg) donation is a more recent option for women with primary ovarian failure, premature menopause, genetic disorders or where there is ovarian damage following surgery, radiation or chemotherapy. However, emerging issues such as donor identity and the limited supply of eggs has prompted significant public debate.

Pressure to reduce the number of embryos transferred during IVF has led to generation of surplus embryos. Some couples have chosen to freeze these embryos to be used in further cycles of IVF, while others have donated them to other couples or to research. This raises similar issues as egg donation, coupled with an ethical dilemma about the use of embryos and when and how they should be destroyed.

ENHANCING THE SUCCESS OF TREATMENT

The current success of ART is a result of a combination of new techniques, improved laboratory procedures and the development of high quality hormone preparations. Before the commercial synthesis of the human gonadotrophins FSH, LH and human chorionic gonadotrophin (hCG), these hormones were extracted from the urine of postmenopausal women, a process which had significant drawbacks including limitations on volume and suboptimal purity of the final product. Recombinant DNA technology has allowed total control of the production process, eliminating the variations in quality seen in the older, urinary-derived hormone preparations (Loumaye et al, 1995).

TABLE 2.
Indications for intrauterine insemination, in-vitro fertilization and intracytoplasmic sperm injection

Indications for intrauterine insemination	Unexplained infertility	
	Male infertility (mild oligozoospermia, asthenozoospermia or teratozoospermia)	
	Failure to conceive after ovulation induction treatment	
	Immunological (antisperm antibodies)	
	Ejaculatory failure	
	Retrograde ejaculation	
Indications for in-vitro fertilization	Severe tubal damage	
	Bilateral salpingectomy	
	Endometriosis	
	Mild male infertility	
	Unexplained infertility	
	Immunological infertility	
Indications for intracytoplasmic sperm injection	Ejaculated sperm	Oligozoospermia, asthenozoospermia, teratozoospermia
		Antisperm antibodies
		Fertilization failure after conventional in-vitro fertilization
		Pre-implantation diagnosis using polymerase chain reaction analysis
	Epididymal sperm or testicular sperm	Congenital bilateral absence of vas deferens
		Obstruction of both ejaculatory ducts
		Azoospermia
		Failed vasovasostomy
		Failed epididymovasostomy

The consistent quality of recombinant treatments has contributed to a greater efficacy with significant improvements in pregnancy rates (Daya and Gunby, 1999). The enhanced purity of recombinant treatments has also meant that they are less likely to cause local and systemic allergic reactions, facilitating patient self-injection at home. Finally, recombinant treatments have enabled clinicians to avoid the risk of exposure of patients to plasma and urine-derived products sourced in a country with one or more cases of variant Creutzfeldt–Jacob disease. Although only a theoretical risk, the Committee on Safety of Medicines has stated that these products should be avoided given that established recombinant alternatives are now available (Breckenridge, 2003).

FUTURE ISSUES

The significant advances in treatment over the past 25 years are, unfortunately, not available to everyone in the UK. The lack of availability of NHS-funded fertility treatment has led to 80% of treatment being provided privately with the remaining 20% allocated on an inconsistent basis, a situation fairly unique in Europe. For example, in Germany, provided the woman is under 40 years of age, the couple are married and have no history of sterilization, all treatment is fully reimbursed. This divide has stood in the way of standardized care and there has been growing concern over inappropriate investigation and treatment and rise in multiple births.

The combination of replacing two or three embryos and the increasing age of women when they access IVF has generated the unprecedented increase in the number of multiple births. Of almost 10 000 twin and triplet births in the year 2000, approximately 1 in 5 were a direct result of IVF treatment (HFEA, 2000), while many others were related to ovulation stimulation for other fertility treatments. Finally, a perceived lack of cost-effectiveness, driven by poor success rates in some clinics and high costs for the neonatal management of multiple births, has both influenced provision and led to the use of less effective treatments in the NHS in an attempt to reduce costs.

CONCLUSIONS

Enormous progress has been made with ART in 25 years, with couples whose previous only hope was adoption or childlessness having achieved families of their own. As the one risk factor for infertility that is not amenable to treatment is advancing maternal age, it is important to encourage prompt referral for specialist help in primary care. However, it is also important to ensure unwilling couples are not pushed towards inappropriate treatment.

Success does not always bring just good news. It is important to address the serious quality and access issues that currently exist and reduce the incidence of multiple births.

Deciding where to draw the line between screening embryos for disability or illness and screening for desirable attributes will also have to be addressed. These are just some of the challenges facing ART the next decade. In a second article, the author will look at improving quality and safety of ART procedures and the ideal framework for their delivery.

Conflict of interest: the author is the Medical Director of an independent fertility and IVF clinic

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KEY POINTS

- Assisted reproductive technology (ART) is now very successful, providing many couples with a possibility of children.
- Infertility still affects 1 in 6 couples and has a significant psychological and emotional impact.
- The lack of NHS-funded fertility treatment in the UK has meant that the advances in ART have really only been available to those who can afford to pay but the newer, improved treatments that offer enhanced purity and safety must be made available to all patients on an equitable basis.
- There are serious inconsistencies in the current standard of care provided to patients.
- There will be growing concern about the use of ART to address social rather than clinical needs.