Technology in Infertility Management: Past, Present and Future

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I have to say, I truly love the specialty we are fortunate enough to practice. What other area of medicine involves the laboratory and clinic so intimately intertwined, changes so rapidly, and can bring so much joy to patients? But how are we getting there? What has the trajectory of our field been? And what role do we, as clinicians, have to play in determining outcome?
The fascinating story of human IVF spans a period of about 40 years only, but the research leading up to the final success with the birth of the first baby in 1978 was preceded by several centuries of work on many different animal species.
The History of IVF

1978  First in vitro fertilization (IVF) baby, Louise Brown, born in England

1981  First U.S. IVF baby, Elizabeth Carr, born in Virginia

1983  First pregnancy from frozen embryo

1985  First surrogate mother

1986  First pregnancy from donor egg

1989  First reported multiple pregnancy reduction of healthy fetuses, to cut a potential multiple birth down to manageable size

1990  Tennessee frozen embryo case; divorcing parents couldn’t agree on what to do with extra embryos, which were eventually destroyed

1992  First pregnancies with intracytoplasmic sperm injection (ICSI), pioneering treatment for male-factor infertility

1994  First ICSI baby born in Hawaii

1996  Doctors at University of California-Irvine donate unused embryos and eggs to women without permission of embryo/egg donors

1997  Oldest mother yet: 63-year-old California woman via donated egg

2000  First baby born in U.S. using frozen unfertilized eggs

2002  Use of preimplantation genetic diagnosis to create embryos free of genetic form of Alzheimer’s disease
Human reproduction has fascinated man since the beginning of time. This can be seen in very early cave drawings, through to Egyptian tomb inscriptions and early Greek texts. Aristotle, some 300 years BC, believed that it took “seed” from both a man and a woman to create children; but it was not for another 1200 years that any further progress was made in the understanding of procreation – animal or human.
Aristotle (384-322 BC) proposed the theory that children are a product of “the mingling of male and female seed”. This opposed the prevailing theory that children were from the male seed and women were merely the “receptacle for the child”.

Aristotle
William Harvey (1578-1657) studied the fertility of the King’s herd of deer, and wrote: “De generatione animalium” in 1651, in which occurs the well known phrase: “Ex ovo omnia” – “from the egg is everything”.
Antonj van Leeuwenhoek (1632-1723) carried out the first studies on human sperm with the newly invented microscope.
Antonj van Leeuwenhoek’s drawings of sperm

Figure 1.7. Leeuwenhoek’s drawings of spermatic animalcules. From Antoni Leeuwenhoek. “The observations of Mr. Antoni Leeuwenhoek, on animalcules engendered in the semen.” Phil. Trans. Roy. Soc., 1679.
The early work on male and female gametes, and later embryos, was carried out on a number of different animal species.

Spallanzani (1729-1799), an Italian Scientist, studied semen in mammals. He performed artificial insemination (AI) in a spaniel bitch – the first recorded instance of AI. He is also credited with the first freezing of sperm in 1776.

John Hunter in c.1790 performed the first successful human AI for a man with hypospadias.
The early history of IVF

- Walter Heape in 1890 was credited for creating the first mammalian embryos (in rabbits), but reported no pregnancies, and it was 60 years later, in 1959, that Chang was able to achieve pregnancies and births of live rabbits following IVF.

- Pincus and Enzman (1934) postulated that mammalian and human oocytes could develop normally in vitro.

- Polge in 1949 reported the first practical freezing of animal sperm using glycerol.
The early history of IVF

- Bunge and Sherman (1953) reported the first successful AI with frozen/thawed sperm in humans.
- Chang (1959) reported the first rabbit young to be born as a result of in vitro fertilized oocytes.
- Yanagimachi and Chang (1963) reported the first mammalian (hamster) IVF with sperm capacitated in vitro.
- Whittingham (1972) reported the first successful freezing of mouse embryos.
The early years of human IVF

• Once the basic research had been done in animal species, scientists and clinicians were ready to move the science on to the treatment of human infertility.

• The main problem in applying the animal research successfully to humans was the difficulty in obtaining human oocytes. Up until the introduction of laparoscopy, pioneered by both Palmer and Frangenheim, oocytes were collected by laparotomy.

• The real advances in human IVF were made due to the much simpler technique of laparoscopy. This enabled the gynecologists to see ovaries and developing follicles clearly and later to aspirate oocytes from the follicles.
The early years of human IVF

• In 1968, Patrick Steptoe, the gynecologist, and Robert Edwards, the scientist, met at the Royal Society of Medicine and started their collaboration.

• In 1973, a group from Australia, led by Professors Carl Wood and John Leeton reported the first human IVF pregnancy, but it turned out to be a “biochemical pregnancy”.

• Steptoe and Edwards in 1976 then announced the first clinical IVF pregnancy – but it was found to be an ectopic pregnancy.

• After 102 failed embryo transfers (ET), Steptoe and Edwards achieved the first ongoing human IVF pregnancy in Mrs Lesley Brown, who had severe tubal factor infertility.
The world’s first IVF baby

On 25 July 1978, Louise Brown was born by Caesarean section at Oldham General Hospital, England – the first baby to be born as a result of IVF in a human.

Patrick Steptoe, Jean Purdy and Robert Edwards with Louise Brown
The early years of human IVF

• In 1980, Candice Reed, the World’s third IVF baby is born in Melbourne, Australia, as a result of the pioneering work of Professors Carl Wood and Alex Lopata.

• Drs. Howard and Georgeanna Jones announce the delivery of the first IVF baby conceived in their pioneering program in the United States. Born 28th of December 1981. This was the first birth using hMG in a stimulated cycle.
The basic technique of IVF soon led to the development of many new ideas. These included the cryopreservation of embryos, and later of oocytes; the development of simpler ultrasound guided techniques to collect oocytes via the vagina. Gamete intra-fallopian transfer (GIFT) was developed as a variant of standard IVF.
• Arguably the most important later development was of intracytoplasmic sperm injection (ICSI), which allowed men with the most intractable infertility problems to enable pregnancies, where previously their only option was the use of donor sperm, if allowed.

• Oocyte donation program developed from about the mid-1980s, and, in a few countries, gestational surrogacy became available to treat women without an uterus.

Asch et al. developed the technique known as GIFT (gamete intrafallopian transfer).

Porter and Craft, from London, developed the use of GnRH-agonists in IVF stimulation protocols to prevent premature LH surges.
Human IVF: The last 30 years

- 1985, the first IVF baby born through gestational surrogacy was reported, born in California, as a result of the work of Utian et al.
- 1985, Prof. Wikland and his team developed the concept of vaginal ultrasound probe guided oocyte collection by the vaginal route.
- Navot et al. published the first report on preparing the endometrium of ovum recipients with estrogens and progesterone.
In 1987 the first reports on sub-zonal micro-injection of sperm to oocytes by Laws-King and Trounson in Australia were published.

In 1989, Handyside and his colleagues showed that it was possible to take a blastomere from an embryo, perform pre-implantation genetic diagnosis (PGD) and sex the embryos. This advance led to a whole new sub-specialty of diagnostic techniques including the ability to detect the sex of an embryo, and a multitude of genetic abnormalities, including single gene defects as well as to perform screening for aneuploidy.
In the clinical practice, major changes have occurred within stimulation protocols, based on the introduction of GnRH-agonists in the mid-1980s and GnRH-antagonists in the 1990s. Furthermore, the development and usage of gonadotropins for ovarian stimulation has progressed from the impure urinary, to pure urinary and later to recombinant gonadotropins.
In 1990 the first report by Verlinsky et al. of polar body biopsy, subsequent embryo transfer and pregnancy was published.

In 1991 Cha et al. developed in-vitro maturation (IVM) of oocytes and reported the first pregnancy.

1992: First pregnancies achieved using recombinant-FSH (r-FSH), reported by Germond et al., and by Devroey et al.
• 1992 First pregnancy achieved by intracytoplasmic sperm injection (ICSI) of oocytes by Palermo et al. of the Brussels group.

• 1994: First report by Silber et al. on testicular sperm extraction (TESE) combined with ICSI.
1992 First reports on the use of GnRH antagonists in ovarian stimulation protocols in IVF were published by the groups of Frydman R and Pavlou SN

1993 First patented method was reported of selection of subsets of human spermatozoa (HS) with increased motile lifetimes (MLT) by solid phase immunoadsorption (Alvarez JG and Pavlou SN)
1995 The group of Pavlou SN at Harvard showed for the first time that administration of GnRH analogs has a further direct action on the human ovary by showing GnRH receptor gene expression in the human ovary and granulosa-lutein cells.

1996 Reijo et al. published the finding that some men with severe oligoasthenospermia have deletions on the Y-chromosome.
Human IVF: The last 30 years

- 1998 Iskovitz-Eldor et al. reported the first pregnancy using GnRH-antagonist and recombinant FSH.
- 1998 Nikolaos V. Sofikitis reported the first two pregnancies achieved using ooplasmic elongating spermatid injection.
• 2000 Oktay et al. reported in the first autologous transplantation of frozen/thawed ovarian tissue.

• 2002 Wells et al. reported the use of comparative genomic hybridization and polar body testing by PGD for aneuploidy and Yoon et al. reported live births after vitrification of oocytes in an IVF programme.

• 2004 Donnez et al. published a report on the first live birth after orthotopic transfer of frozen/thawed ovarian tissue.
Upcoming technology

Recurrent IVF failure
Factors not routinely considered as part of the post-treatment analysis

Personalized prediction of live birth
Factors not routinely considered as part of the post-treatment analysis
The roles of parameters, other than age and egg quantity/quality, in determining outcome are important to consider. Such parameters include: sperm genetics/quality, embryo quality, transfer technique, and endometrial receptivity.

The future of accurate personalized prediction of ART outcomes will ultimately rely on the yet-to-be-discovered effects of these other factors.
UK scientists gain license to edit genes in human embryos

Embryo editing gets green light
UK decision sets precedent for research on editing genomes of human embryos.

BY Marcia Barinaga

The UK's Human Fertilisation and Embryology Authority (HFEA) has approved the work of researchers in the country to edit genes in human embryos, a move that sets a precedent for similar work in other countries. The decision is likely to spark a debate in the US and elsewhere about the ethics of such research.

The HFEA announced the decision on Wednesday, citing the need for further research on the safety and effectiveness of gene editing techniques. The decision is expected to have broad implications for the field of genetics, as it opens up the possibility of editing genes in human embryos to treat genetic diseases.

The UK decision sets a precedent for other countries to consider similar research, and it is likely to prompt ethical debates in other nations. The decision is not without controversy, as some argue that it could lead to unintended consequences and raise questions about the long-term effects of gene editing.

The decision comes amid a growing interest in gene editing, particularly in the field of genetics. The technology has the potential to revolutionize medicine, allowing doctors to edit genes in order to treat genetic diseases.

Science hubs win in major revamp
Research chairs emerge as the big success of Germany’s Excellence Initiative – despite its focus on elite institutes.

BY BRIAN HANSON

For many, Max-Planck’s (MPG) performance in the German Excellence Initiative has been tepid. But competition for institutional funds also has boosted the MPG’s profile, and its ability to attract top talent. The MPG’s new strategy is to focus on fostering a vibrant culture of research and innovation, and to become a hub for excellence across all disciplines.

The MPG has created 55 research chairs across all of its institutes,“In contrast to the traditional model of research, which is focused on a single discipline, the MPG’s model is more diverse and interdisciplinary,” said MPG President Matthias Stolle.

The chairs are funded by the MPG’s Strategic Research Programmes, which provide a flexible funding model for the Chairs to pursue their own research agendas.

The Chairs are also expected to attract additional funding from external sources, including government grants and private donations.

The MPG’s new strategy is expected to help the MPG compete with other excellence initiatives, such as the UK’s Research Excellence Framework (REF), and the US’s National Science Foundation (NSF). The Chairs are also expected to contribute to the MPG’s overall research portfolio, and to enhance its reputation as a leader in the international research landscape.
Next Generation Sequencing for PGD

• Reduced cost
• Enhanced detection of structural abnormalities such as chromosomes with missing or duplicate segments
• Better ability to detect when an embryo may have cells with differing results (mosaicism)
• Reduction of human errors by increasing use of automation
**Egg Repair**

**Embryo repair**

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**HOW THE IVF TECHNIQUE WORKS**

1. **Healthy nuclear DNA removed from patient’s egg cell, leaving behind faulty mitochondrial DNA**

2. **Patient’s nuclear DNA transplanted into donor egg with healthy mitochondrial DNA**

3. **‘Reconstructed’ egg cell fertilised with sperm in the lab and implanted into patient. Resulting embryo has three genetic parents**

- **Patient’s egg cell**
- **Nuclear DNA**
- **Faulty mitochondrial DNA**
- **Donor’s egg cell with nuclear DNA removed**
- **Reconstructed egg**
Responsible Integration Of New Technologies

Moving innovation to practice: a committee opinion

The introduction of new strategies, tests and procedures into clinical practice raises challenging ethical issues involving evaluation of evidence, balancing benefits and harms, supporting patient autonomy, avoiding conflict of interest, and promoting advances in health care.
Reproductive Endocrine experts must foster innovations and training in endocrinology, reproductive surgery, embryology, reproductive biology, and medical genetics.
The future of reproductive medicine centers

In the near future couples of any fertility status will visit us for genetic counseling before attempting pregnancy. In many cases, the woman will have her oocytes frozen in our center for years because she decided to preserve fertility long ago for social reasons. Once the embryos are created, they will be genetically screened before replacement in the ideal moment. Even for couples attempting natural conception after genetic screening, revolutionary tools are under development to flush the uterus, recover the embryo generated in the reproductive system, screen it genetically, and put back only the normal ones into the uterus.

Antonio Pellicer, M.D. and Daniela Galliano, M.D. Fertil Steril 2016;105:30-31
CONCLUSION

The infertility treatment using IVF and related techniques is now well established and almost universally practiced, with millions babies being born worldwide. The early pioneering days may be over, but there is a limitless amount of research still to be done in our field, particularly in genetics and stem cell research. The future of IVF and ART is built upon the past achievements of the early pioneers, and the story behind our specialty bears more study.