Reflections on 40 years of IVF

The past

For many practitioners of in vitro fertilisation (IVF) today, it must be hard to comprehend the disdain and disgust with which the introduction of IVF as therapy for infertility was greeted. The ethical and legal wrangling about human reproductive cloning and the current debate over trans-generational (germline) genome editing gives a small flavour of how IVF was seen then. What was regarded as an irrelevant, disruptive and unethical practice is now effectively mainstream treatment in most countries of the world.

The journey from bench to bedside was fraught with difficulty – both technical and social (1). It took almost 10 years from proof of principle of IVF in Robert Edwards' Cambridge laboratory to the first live birth 40 years ago in Oldham UK achieved by Edwards, Steptoe and Purdy. To be an IVF parent then was considered too shameful to admit, to be an IVF child was to be considered a freak, and to be an IVF practitioner or to be conducting embryo research led to you being likened to Frankenstein or Dr. Mengele. Indeed, when Edwards and Steptoe applied for a Medical Research Council (MRC) grant to fund their work in 1971, they received entirely hostile referees' reports (2), suggesting that the referees either did not believe that IVF was able to solve the problem of infertility or that it was not a problem worth solving. However, despite these funding setbacks, the hostile social environment in which they worked, and the many technical problems that they had to overcome, they pressed on undaunted, buoyed up largely by the many letters from the infertile that they received and the willing supply of patients that came to their Oldham clinic. The hostile social and professional environment was such that, even after the births of Louise Brown in 1978 and Alistair Montgomery in 1979, the situation for Edwards, Steptoe and Purdy did not improve. As Steptoe had to retire from his NHS post in Oldham, they sought support from the NHS and the University in Cambridge to continue the work there, but were unsuccessful, and were, forced to locate and adapt a private clinic at Bourn Hall, which set them back two years. During this hiatus, the Australian clinics in Melbourne took the lead, only to be hampered themselves by the same social abreaction in the form of state legislation that restricted their capacity to undertake research on human embryos. Edwards, Steptoe and Purdy started taking patients at Bourn Hall in 1982, the same year that the Government set up a committee of enquiry into IVF chaired by Mary Warnock. This committee reported in 1984, and recommended the setting up of a Human Fertilisation and Embryology Authority (HFEA) to oversee treatment and research using human embryos. The HFEA finally came into existence in 1990 after a prolonged struggle to salvage embryo research from initially very hostile houses of parliament (3).

The Present

Efficacy and safety

Despite the fact that we have much to celebrate by the introduction of IVF, it is clear that it is a technology whose efficacy, despite continuing improvement, is still limited (can you imagine any other branch of medicine or surgery accepting and working with a 70% failure rate?), and its safety is still not fully demonstrated – live born is not the same as a healthy adult. Potential epigenetic effects of superovulation, culture conditions, media constituents, and embryo or gamete manipulation have never been studied long-term (4), and only a few in the short-term. In the early days of IVF neither the MRC nor the Department of Health thought IVF important enough to consider long-term follow-up for babies and still only scant information about health follows the various registers internationally. At least ICSI was followed up strictly after its introduction in Belgium, and some preimplantation diagnosis (PGD) centres still follow the children they have helped to be born free of genetic disease.

Multiple embryo transfer

Increasing evidence has accumulated from well-designed studies about the disadvantages and risks of multiple embryo transfer not only in terms of prematurity with a multiple birth, but also the effects of vanishing twins that may accompany multiple embryo transfers (5). However, there is still a general reluctance to move wholly to single embryo transfer; the success of embryo vitrification is likely to change this, although evidence of its long-term safety is still being collected.

Oocyte cryopreservation.

Previously, this was undertaken as a last resort in the face of ageing and lack of a partner, and was thus too late to be really effective (6). However, freezing of oocytes as natural insurance against the reduction of fertility with ageing and against the increased risk of adverse genetic outcomes with age, is a recent change in practice, and the demand for this is likely to increase further, especially if the legal time limit of ten years for storage can be relaxed.

Preimplantation genetic screening and other new technologies

The debate about preimplantation genetic screening for aneuploidy (PGS/PGT-A) has raged for over nearly 25 years, with few good controlled studies, and with little prospect that well-designed trials with current genetic technologies will be undertaken, despite opportunities for doing so (7). It seems that priority is given to making a healthy profit by offering new techniques to vulnerable patients, rather than first establishing that the techniques are efficacious and safe. Indeed, the paucity of randomized studies and proper prospective follow-up when new technologies are introduced is a sad hallmark of the IVF profession today. Is it not time that our professional societies and Colleges stood firm on the need for

sound scientific rationale, together with an insistence on proper studies and follow-up, before allowing or supporting the application of new techniques? Is the absence of such careful studies a consequence of the largely private treatment of IVF in the UK and the USA? And might the lack of mandatory guidelines from NICE, leading to the postcode lottery in the provision of IVF on the NHS, be responsible for this unfortunate situation?

Role of the HFEA

There are many in the UK who still baulk at the HFE Act, through which regulation of assisted reproduction occurs, due to a perception that it has been a brake on research and innovative practice. However, it is noteworthy that the presence of such regulation has enabled the reasonably smooth public and legal acceptance of the most recent reproductive technology, mitochondrial replacement therapy (MRT) for inherited mitochondrial disease (8). The introduction of MRT here in the UK will be accompanied by mandatory long-term follow-up of offspring (with parental consent). Although not the first country to undertake MRT, the first case in the USA received significant legal and ethical criticism for its lack of transparency and lack of proper follow-up and oversight (9). Moreover, the rapid extension of MRT from avoidance of genetic disease to infertility therapy in some unregulated countries, despite the lack of any real scientific basis, gives cause for concern.

Study of the biology and role of mitochondria in development is blossoming, and improvement in culture and stem cell technology is allowing us to begin to understand the processes leading up to gastrulation, which can now be studied effectively *in vitro* for the first time (10). All of this has been done within the window of 14 days of development set out as a legal limit by the HFE Act; this limit has been followed by some other countries, but not all. Thus, up to now the Act does not seem to have been a constraint on good laboratory research, including that of genome editing of embryos (11). The need to know more about later post-implantation stages, such as gastrulation and germ cell formation, and the mechanisms governing reproductive success or failure, is likely to reopen public and legal discussion about the 14 day rule – a pragmatic red line drawn up as a compromise between public concern and scientific imperative.

The future

The future for this specialty is likely to be just as interesting and controversial as the previous 50 years because of its intimate involvement with the reproductive process and the health of future generations. Indeed, perhaps the biggest changes that the future brings will not be technological but social and ethical, with yet further challenges to our established ways of thinking about sex, gender, sexuality, reproduction, pregnancy and the family. IVF has already contributed to massive social change and promises to lead to even more! Although the use of

artificial intelligence (AI) and robotics will no doubt make its impact in ART diagnosis and the IVF laboratory, as it has in diagnostic radiology and repetitive delicate assembly tasks, it is genome editing in human reproduction that is probably going to be the most controversial topic in biology for the foreseeable future. The possibility of editing embryos to remove harmful mutations, or creating gametes *in-vitro* from cell lines that have undergone genome editing, challenges our ethical prejudices and our duties and responsibilities to future generations (12). Preimplantation Genetic Diagnosis (PGD, or PGT-M as we currently know it) may no longer be necessary once this new technology becomes efficacious and safe (13), and the number of embryos that would be available to be replaced or frozen would be significantly improved over the current use of PGD which is wholly dependent on finding the unaffected embryos amongst a small developing cohort. Genome editing in the context might therefore be regarded as more ethical than PGD, as it would result in the destruction of fewer embryos.

In the future, selection for genetic traits compatible with environmental changes that are happening to our planet may become essential for the survival of our species, although, for the time being, this remains in the world of science fiction.

Conclusions

Since its early days as a pariah of clinical and research practice, IVF has come to occupy a central place in reproductive medicine. With the award of the Nobel Prize to Bob Edwards in 2010 its important role in science and medicine has also been recognized. Despite these recognitions, IVF still retains elements of controversy in its present practice and future prospects, presaging yet more battles to be fought, both nationally and internationally.

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