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Editorial Overview

From Vitro to Vivo and Back: Forty Five Years of IVF

This week marks the 45th anniversary of the report of the first human pregnancy achieved through *in vitro* fertilisation (IVF). The milestone was accomplished by the teams of Carl Wood and John Leeton at Monash University, in Melbourne, Australia, and published in *The Lancet* on the 29th September, 1973 [1]. On this occasion, we celebrate the outstanding clinical accomplishments of IVF and reflect on the moral debates surrounding infertility, the ethics of IVF and human embryo research.

In the ancient world, fecundity was often seen as a direct correlate of a woman's worth, and as an obligatory societal contribution. Struggling with infertility in those times was challenging and even dangerous. In Timaeus, Plato states that if the womb was deprived of its desire for child-bearing, it would wander inside the woman's body like an animal and cause health problems by blocking air passages—an affliction named "uterine suffocation". However implausible such claims may now seem, they were not uncommon. Historical evidence over thousands of years indicates that childless women faced high scrutiny and pressure. Even during the Renaissance, when physicians began to understand some of the causes underlying infertility, failure to conceive was mostly attributed to the individual woman. Such 16th century sexism is well illustrated by the story of Catherine de Medici who was unable to conceive for a decade. Despite the notorious hypospadia that afflicted her husband, King Henry II of France, she was forced to resort to magicians and potions containing the most dubious and obscure ingredients, such as the urine of pregnant animals and *unicorn* horn [2].

Fast-forward to the 1970s and the attitude of most societies towards infertility had, thankfully, become much more liberal and less gendered. Nevertheless, affected individuals and couples continued to show broad-minded, remarkable willingness to engage in rather experimental procedures to deal with infertility. When Wood and Leeton informed a childless couple of their university's ongoing IVF research programme, they agreed to participate. No one knew whether the technique would work in humans, though evidence for its success in other mammalian species was well-accepted [3]. Interestingly, as mentioned in *The Lancet* article (Fig. 1), "Discussion was aided by the fact that the couple managed and owned a dairy farm and were familiar with the techniques of animal husbandry, both natural and experimental." Unfortunately, the embryo failed to implant into the wall of the uterus, but the achievement paved the way for successful IVF.

Still, it took another five years until the birth of the first baby conceived via IVF, a few kilometres Northeast of Manchester, UK, in the Oldham General Hospital. Like a proud parent, the frontpage of the hospital's website announces: "birthplace of Louise Brown, the world's first successful *in vitro* fertilised "test tube baby", on July 25, 1978 ".

The report, by British researchers Patrick Steptoe and Roberts Edwards, was published three weeks after Louise's birth as a discrete "Letters to the Editor" in *The Lancet* [4]. Steptoe and Edwards later revealed that they had relied on patients' natural hormone levels to determine the best time point for fertilization, thereby maximizing the chances for IVF success. Indisputably, the accomplishment marked a new era in reproductive biology, but Louise's birth transcended the tremendous clinical achievement behind it. It generated flashy headlines all over the world and drew unprecedented public attention. However, in stark contrast to the hope it brought to millions unable to conceive, including same-sex couples, the event unleashed a barrage of ethical, social, and legal concerns. It was the ultimate demonstration that human embryos could be generated and maintained healthy outside of the body, clearly setting the stage for human embryo experimentation, thereby prompting the need for ethical regulations and recommendations.

In 1979, the Ethics Advisory Board of the US Department of Health, Education and Welfare published a report supporting human embryo research, but limiting it to the first 14 days of development. In the UK, the 14-day limit was endorsed by The Warnock committee in the 1984 *Report of the Committee of Inquiry into Human Fertilisation and Embryology* and then enacted in the UK 1990 Human Fertilisation and Embryology Act. Since then, the 14-day rule has been embodied by other regulators and policymakers and became an inviolable research guide and an image of scientific integrity and ethical responsibility.

The 14-day timepoint is not an arbitrary one. In humans, the fifteenth day post-fertilisation represents the onset of gastrulation, marked by the appearance of the easily identifiable 'primitive streak'. The primitive streak defines the rostro-caudal and medial-lateral axes of the embryo and represents the moment after which the embryo can no longer split to form twins. According to some more philosophical and religious views, this would be the point when an embryo acquires its "individuality".

The decades that followed Louise's birth saw an explosion of remarkable technological and medical breakthroughs. These included the first birth from IVF using a cryopreserved embryo [5] and using a cryopreserved oocyte [6], and the first pregnancy after intracytoplasmic sperm injection [7]. These accomplishments were a reassurance that IVF was safe and would not lead to overpopulation, but did not alleviate ethical and moral concerns of the more conservative and religious populations. Despite the persisting climate of controversy, the Nobel Committee recognized the importance and success of IVF by awarding the Nobel Prize in Physiology or Medicine to Robert Edwards in 2010. Eight million 'test-tube' babies later, IVF clinical and laboratory methodologies continue to advance for the benefit of society.

These technological advancements are in sharp contrast to the ethical and legislative landscape of IVF, that seems to have stood rather still. Until recently, adoption of the 14-day limit was not widely questioned

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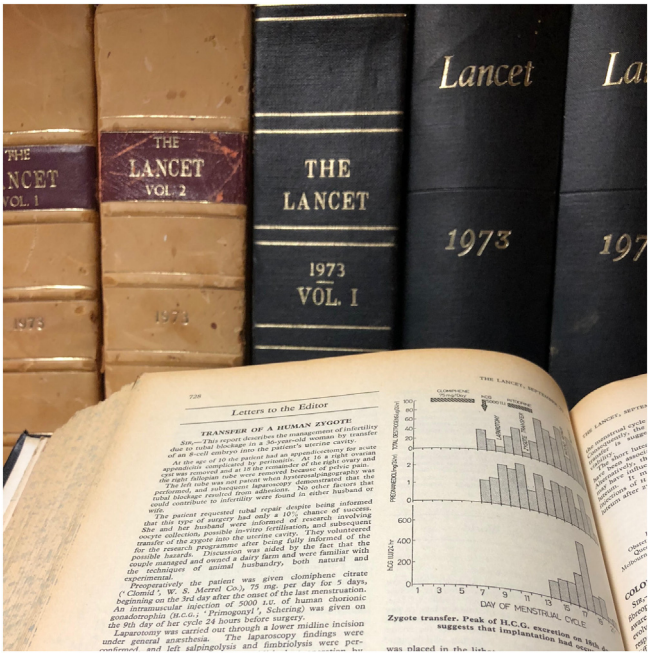

Fig. 1. The original 1973 *The Lancet* publication entitled "Transfer by a human Zygote" by Wood, Leeton and colleagues in the library of The Lancet office in London, UK.

given that technical difficulties prohibited longer culture times. However, in August 2016, two groups demonstrated that human embryos can be grown in culture for up to 13 days and, theoretically, even longer [8, 9]. Following these developments, researchers have called for a revision and extension of the 14-day rule.

Embryos that are left over from IVF treatments can be used in research to obtain precious information about very early human development. Extending this knowledge to the gastrulation period, often called the "black box" of human development, would be of great value. Beyond that, there is no question that permitting human embryos to develop *in vitro* for one or two weeks longer would likely offer unprecedented scientific knowledge that could help understand the causes of early or recurrent miscarriages, birth defects and even disease later in life. On the other hand, some fear it would provoke a backlash from opponents of embryo research or inspire a continuous time window increase for embryo research. Others are not convinced the technology is ready for accommodating older embryos and their needs for a more complex and controlled culture environment that can accurately mimic physiological conditions. There are arguments in favour of and against extension of the 14-day limit for conducting research on human embryos. This is a debate that been re-ignited several times over the past two years, but has not moved forward productively. Clearly, the 14-day cut-off represents a compromise between different views about embryo research but there is no compelling scientific reason to think that choosing a slightly later timepoint, like 21 or 28 days, would disregard that compromise. What will it take to outweigh conventions and regulations that have persisted for several decades, and that, while effective from a practical point of view, no longer seem to be relevant from a scientific perspective? Hopefully, not four more decades.

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