

# IN VITRO FERTILIZATION: A 40-Year Perspective

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“ . . . ‘And this’, said the Director opening the door, ‘is the Fertilizing Room . . . . These are the week’s supply of ova kept at blood heat; whereas the male gametes . . . they have to be kept at thirty-five instead of thirty-seven. Full blood heat sterilizes.”

– Chapter 1, *Brave New World*

## INTRODUCTION

When Aldous Huxley wrote *Brave New World* in the early 1930’s, he surmised that “bottled babies” were “technically and ideologically more than a century away.”<sup>1</sup> Yet in 1978, only forty years later, the world’s first “test-tube baby” was born. Eighty years later, in 2010, Robert G. Edwards would win the Nobel Prize in physiology for his pioneering work on In Vitro Fertilization (IVF). Since its introduction, IVF has resulted in the birth of millions of babies and made the dream of having biological children a reality for just as many couples. But reproductive technologies have advanced quickly already, futurist Ray Kurzweil predicts that during the next few decades our knowledge base will multiply thousands of times faster than it already has in the entire history of science, technology, and philosophy. With that in mind, what lies in store for human reproductive technology?

## THE HISTORY OF IVF

Shortly before Aldous Huxley wrote *Brave New World*, his geneticist friend J.B.S. Haldane described a process called “ectogenesis” where individuals were created outside the human body.<sup>2</sup> In a short editorial in the *New England Journal of Medicine* in 1937, reputed Harvard ObGyn Dr. John Rock regarded the idea as outrageous. However, before long donor insemination became a reality, and by 1950 it was being described in medical journals as an accepted practice. The world’s first sperm bank was established in 1960 in Iowa. In 1959, the first published proof of IVF in a mammalian model was provided by M.C. Chang’s work with rabbit ova.<sup>3</sup> His breakthrough came when he discovered that newly ovulated eggs could only be fertilized when placed

with capacitated sperm. Capacitation refers to the first of several membrane changes that allow the spermatozoa to eventually bind to the zona pellucida and to undergo the acrosome reaction, a prerequisite to fertilization. The next challenge was finding an adequate medium for embryo culture. Embryos would not survive long in seminal fluid, but by 1963 Ralph Brinster had developed a culture medium overlaid with oil to prevent bacterial infection. By 1970, the first infertile patients were in trials of IVF. It took over 100 transfer attempts until a sustained pregnancy finally resulted in 1977 after an 8-cell embryo transfer.<sup>4</sup> Prior to this success it was thought that the uterus would not accept an embryo “younger” than the blastocyst stage since this is the stage when the uterus receives the embryo in a natural cycle. In this first successful IVF cycle, the mature egg had been retrieved from a naturally growing follicle by laparoscopy. The easier approach of trans-vaginal ultrasound-guided oocyte aspiration that is used today had not yet been optimized.

IVF quickly became a treatment for infertility and subfertility. In the early 1990’s a technique called Intracytoplasmic Sperm Injection (ICSI) was performed successfully on human oocytes in a couple with severe male factor infertility.<sup>5</sup> This allowed men with very low concentrations of sperm to achieve fatherhood.

Today, there are more than 2000 clinics that specialize in IVF worldwide. The largest, in Tokyo, Japan, treats more than 15,000 couples a year.<sup>6</sup> Over 5 million babies have been born through assisted reproductive technologies.

A global perspective on assisted reproductive technologies (ART) is important, as different countries regulate these services uniquely. Countries such as the UK, Germany, and those in Scandinavia have laws that oversee the practice and implementation of ART. In Germany, clinicians are prohibited by law from creating more than three embryos, and all embryos created must be transferred. This renders technologies such as Preimplantation Genetic Screening (PGS) illegal, which may be an attempt

to prevent any semblance of eugenics.<sup>6</sup> In the Arab world, religious law influences practice, and the use of donor gametes or surrogates is not accepted practice, due to the cultural importance placed on genetic lineage. In Israel, the use of IVF is higher than in any other country. The government actively encourages population growth and will fund IVF for couples until they have two children.<sup>6</sup> In India, sex selection became illegal due to the widespread termination of female fetuses. With such large differences in how different countries regulate these technologies, it's not surprising that patients sometimes travel long distances for access to treatments that may be illegal or unavailable in their native country.<sup>6</sup> In the US, there are relatively few laws that dictate the implementation of ART, and for the most part ART is overseen by professional bodies, such as the American Society for Reproductive Medicine (ASRM).

#### PREVALENCE OF INFERTILITY

As the industry of IVF flourishes, it is natural to wonder whether the prevalence of infertility is increasing. Based on data collected as part of the National Survey of Family Growth, the Centers for Disease Control and Prevention issued a report on the incidence of infertility and impaired fecundity between 1982 and 2010.<sup>7</sup> Infertility was defined as lack of pregnancy in 12 months despite having unprotected intercourse on a regular basis. Impaired fecundity was defined as difficulty getting pregnant or carrying a pregnancy to term. The study showed that the percentage of married women aged 15-44 who were infertile fell from 8.5% in 1982 to 6.0% between 2006 and 2010. Male infertility remained stable at 12% between the two study periods. Infertility remains more prevalent among non-Hispanic black women compared with non-Hispanic white women.<sup>7</sup>

#### FUTURE OF INFERTILITY

Since the first successful transfer of a human embryo in 1977, numerous technologies have been developed to complement IVF.

Assisted Hatching (AH) was developed to address the problem of a thickened membrane that could prevent the embryo from "hatching" or shedding its shell and thereby prevent implantation. The technique of AH uses either an acid solution or laser to create a small defect in the zona membrane, providing a better chance for implantation. Assisted Hatching is commonly used in women above the age of 35 years, in

embryos that were previously frozen, and in women with previous repeated implantation failure.<sup>8</sup>

Preimplantation Genetic Diagnosis allows embryos to be genetically tested prior to transfer. The healthy embryos can be designated for embryo transfer, while the affected embryos are excluded. PGD is an effective alternative to prenatal diagnosis in couples at high risk for transmitting an inherited disorder, and avoids the issue of termination of an affected fetus.<sup>9</sup> There are three stages during which the embryo may be sampled and genetic material obtained: the oocyte/zygote stage via polar body biopsy on day 1; the cleavage stage via cell biopsy on day 3; and the blastocyst stage via sampling of the trophectoderm (outer layer of the embryo which later forms the placenta) portion of the embryo on day 5. Although PGD was originally intended to identify embryos carrying a severe anomaly that would otherwise indicate termination, in recent years the indications for this technology have expanded to include screening for genes associated with late-onset diseases such as BRCA1 and BRCA2, as well as HLA testing to prioritize embryos that would be a match for organ donation to a living sibling affected by a disorder requiring stem cell transplantation. This has led to intense ethical debate, and cultural and religious differences make it all the more challenging to arrive at a consensus.

Embryo and Oocyte Cryopreservation allows a couple to freeze excess good quality embryos for future use. This avoids the pressure to transfer all of the embryos during a cycle, and provides the couple with future chances to achieve a pregnancy without undergoing the stimulation process again. Human embryos have been successfully frozen and thawed since 1983. In October 2012, the ASRM removed the "experimental" designation from oocyte cryopreservation or "egg freezing" which allows women to freeze their unfertilized eggs for future use.<sup>10</sup>

In vitro maturation of oocytes (IVM) refers to the process whereby oocytes are removed from the ovaries when they are still immature, and are matured in the laboratory. This avoids the need for a woman to take stimulating drugs and is a particular benefit for women who are at high risk for ovarian hyperstimulation syndrome (OHSS). This syndrome is caused by drugs used for ovarian stimulation (Clomid, injectable gonadotropins) and is a potentially lethal condition. The central feature of clinically significant OHSS is the development of vascular hyperpermeability and the resulting

shift of fluids into the third space, with accumulation of ascites and hydrothorax accompanied by intravascular hypovolemia.

IVM also makes it possible to retrieve oocytes from prepubescent girls who are at risk for oocyte damage or loss, due to genetic disorders or the need for chemotherapy. This is a newer technique, so data about its efficacy and safety are limited, but worldwide about 400 children have been born using this technique, and results thus far are promising.

## CONCLUSION

The introduction of IVF into medical practice has not only provided the chance for otherwise infertile couples to procreate, it has advanced our understanding of human reproduction. As technologies have become more accessible, we have undoubtedly met the Huxlean future that seemed so outrageous a mere 80 years ago. How we regulate this technology will not only characterize our morals as a society, it will inevitably impact generations to come.

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