Introduction: Medical

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In vitro fertilization (IVF) and other assisted reproductive technologies (ART) have generated passionate social reactions since before their inception. These reactions derive from a number of origins. Many arise from debates about the moral status of the fertilized egg. Others derive from attitudes regarding the mystery of conception, concerns about "playing God" or manipulating the natural order, and fears about the safety of the procedures and the impact their implementation on the institution of marriage. Indeed, since IVF was initially developed to address infertility due to damaged fallopian tubes, which in may cases was the result of sexually transmitted diseases, at least some commentators may have objected to the technology out of a sense of bypassing divine justice applied in the face of promiscuity. In light of the dramatic advances in technology over the last 30 years, it is noteworthy that the moral status of the human embryo still engenders the most problematic issues in the field.

The purpose of this narrative is to provide an overview of the salient features of IVF technology from a medical and scientific viewpoint to help frame subsequent discussions. Given the relatively brief history of the technology and the profound developments that have occurred, a primarily historical approach is taken to give a sense of the cumulative aspect of progress. Assisted reproductive technology (ART) describes fertility therapies with several common features. The fundamental feature of the technology is the manipulation of both sperm and eggs in the laboratory. IN IVF, which is by far the most commonly applied ART today, conception occurs outside the body and dissociated from coitus. Early embryonic development also occurs in the laboratory. Finally, conventional ART as practiced today involves ovarian stimulation with drugs that result in the production of multiple eggs for therapy. All of these features may play a role in ethical, legal and public policy debates.

Pre-Clinical Advances

Advances in ART have been made due to technological developments in a number of scientific fields. First, observations in animals and humans yielded insights into the events of oocyte maturation and sperm capacitation, both of which are critical to the process of fertilization (1). Experience with IVF in laboratory animals provided useful information about the laboratory environment necessary for survival of eggs, sperm, and embryos outside the body (2). Concurrent advances in instrumentation for laparoscopy provided a minimally invasive method to retrieve eggs(3).

Physiology of Ovulation

An early question that had to be solved was the actual time it takes for an egg to mature to the point that it can be fertilized by sperm, and how to identify the best time to retrieve eggs for therapy. Critical to advancement in this regard was the development of rapid assays for luteinizing hormone (LH), the pituitary gland hormone that initiates the events of final egg maturation and ovulation. An outpouring of LH, the so-called "LH surge" reliably precedes ovulation, and detection of this signal became a priority to accurately time egg retrievals. Accurate assays for both urinary and serum levels were developed around 1980. Initial clinical application of these assays entailed patients providing urinary or blood samples every four hours! Because an increase in LH levels occurs sooner and more predictably in the blood than in the urine, frequent blood sampling for LH became the rule in early IVF cycles in the US. This single advance promoted the field by improving the yield of fertilizable eggs for therapy.

Early Patient Restrictions

It should be remembered that initially, treatment with IVF was restricted to women who had irreparably damaged or absent Fallopian tubes, the structures normally responsible for collecting the ovulated egg, for providing an environment for natural fertilization, and for nourishment and transport of the early embryo to the uterus. This restriction was imposed for two reasons: first, these patients clearly had no other option with which to conceive, and second, specifying this condition allowed investigators to limit the number of variables to consider in evaluating outcomes and eliminated the possibility that conception occurred coincidentally through natural means. This restriction meant that many patients had severe pelvic adhesions that restricted or prevented access to the ovaries, so many laparoscopic procedures failed to yield eggs. For example, as of September 1981 (three years after the birth of the first IVF baby by the Bourne Hall group in England) the cumulative experience of the Bourne Hall group indicated that one in five laparoscopies failed to yield an egg (1). Some programs required potential patients to undergo screening laparoscopies and/or laparotomies to evaluate and/or improve access to the ovaries before they were accepted as IVF patients. Fortunately, advances in ultrasound technology overcame this hurdle. By the mid-late 1980's vaginal ultrasound was used exclusively to guide the retrieval of eggs from patients. This development represents one of a handful of major developments in IVF with respect to reducing the burden on patients and improving the yield of eggs for therapy.

Ovarian Stimulation

Another major issue that occupied IVF pioneers for years was the question of whether ovarian stimulation could be applied successfully to IVF. Drugs to induce ovulation in women with ovulation disorders had been available and successfully employed for decades, but initial failures with these agents in the IVF setting led some (including Dr. Edwards, who was responsible for the first IVF birth in the world) to conclude that their use was incompatible with success in IVF. At the end of 1980, the cumulative experience with ovarian stimulation in England and Australia revealed a pregnancy rate of 4% (6/148 cycles) and a live birth rate of 0 (1). Nevertheless the low yield of eggs from laparoscopies in the natural cycle led the Norfolk group to initiate ovarian stimulation with gonadotropins purified from the urine of menopausal women (Pergonal®)(2). The thirteenth such cycle led to the birth of Elizabeth Carr, the first IVF baby in the US. Refinements in ovarian stimulation strategies combined with refined monitoring techniques, including measurement of ovarian follicle development by vaginal ultrasound, led to major improvements in embryo transfer rates and delivery rates. By 1985, almost 12% of egg retrievals resulted in a pregnancy in the US (4). Development and use of analogs of gonadotropin releasing hormone (GnRH) eliminated the risk of premature ovulation that had plagued up to one in six cycles of IVF and led to cancellation of numerous IVF cycles before egg retrieval. Use of these agents tended to prolong the duration of ovarian stimulation cycles, but with the benefit of promoting in most patients the development of a higher number of mature eggs and a significantly better pregnancy rate. In the 1990's antagonists of GnRH were developed, which afforded rapid protection from premature ovulation without the suppressive effects that earlier GnRH analogs had on ovarian responsiveness to stimulation in some patients, especially of advanced age.

Other Developments

Improvements in embryo culture techniques, including the development of sequential culture media designed for specific stages of embryo development also contributed to improvements in pregnancy rates, and led to the demise of GIFT and ZIFT, two reproductive technologies that required laparoscopy to deliver sperm and eggs or embryos to the fallopian tube. The cumulative effect of these developments was to promote the development of oocytes and embryos in excess of the number needed to accomplish therapy. As early as the early 1980's, when some patients began producing a large number of eggs and programs became more confident about their fertilization and embryo culture techniques, it became evident that a few patients produced far too many eggs than could be reasonable employed in therapy. The response to this was twofold. First, some investigators explored the potential for donor eggs to establish pregnancies. The first donor egg baby was born in 1983 as a result of the altruistic anonymous donation of excess eggs from an IVF patient (1). Although initially envisioned as a therapy to be limited to patients with ovarian failure as a result of a variety of medical or surgical conditions, the technology has expanded to the point where now the vast majority of donor egg recipients use the technology because of the "natural" extinction of fertility that occurs with age. The days of egg donation from IVF patients rapidly came to an end when the technology to freeze embryos was successfully established in the mid-80's. Faced with live born delivery rates of less than 20% per IVF cycle, practically all IVF patients opted to fertilize all the eggs they produced and freeze the extra embryos for future use, since frozen embryo transfer was vastly less costly and burdensome than another cycle of IVF. Nevertheless, the initial successful experiences with egg donation prompted investigators to develop programs of anonymous egg donation from healthy young women. This source remains the foundation of the technology today.

The Nineties

Two technological developments in the 90's have had additional profound impacts on the field. Intracytoplasmic sperm injection (ICSI) led to the next paradigm shift in reproductive technology. The successful microscopic insertion of a single sperm into the cytoplasm of the egg was first reported in 1992 (5). This technology revolutionized the therapy of male factor infertility, since instead of a requirement for a minimum of hundreds of thousands of sperm for in vitro fertilization, now only a single sperm for each egg was required. This profoundly expanded the application and the success of IVF for male factor infertility. In 2004, the last year for which complete data are available, ICSI was employed in 58% of IVF cycles in the US (even though the diagnosis leading to IVF involved male factor in only 35% of cases) (6).

In 1990, the first successful application of preimplatation genetic diagnosis (PGD) to couples facing the trauma of severely debilitating genetic disease was reported(7). That initial report used techniques to amplify the DNA specific to the Y-chromosome, which allowed the identification of male embryos at risk for severe, X-linked diseases (X-linked mental retardation, adrenoleukodystrophy, Lesch-Nyhan syndrome and Duchenne muscular dystrophy). This technology was recognized as an important alternative to prenatal diagnosis and therapeutic abortion n such cases. Since then, the technology has been applied to a number of genetic and chromosomal conditions, and it is estimated that thousands of healthy children have been born as a result of the technology. In 2006, the Genetics and Public Policy Center, based on a survey of all IVF programs in the US, estimated that four to six percent of all IVF cycles in 2005 involved PGD (8). Only three percent of those cycles were for the detection of X-linked disorders whereas two-thirds were for the detection of aneuploidy (an abnormal number of chromosomes), which plagues many human embryos, especially as maternal age increases.

Contemporary Therapy
To summarize, the steps involved in a state-of-the-art cycle of ART are given below:

1. Ovarian stimulation with multiple injections of fertility drugs, monitored with vaginal ultrasound and serum hormone measurements

2. Transvaginal ultrasound guided egg retrieval in an office or outpatient surgery setting

3. Collection of sperm by masturbation (or surgery in certain male factor cases)

4. In vitro fertilization with or without ICSI

5. Embryo culture in sequential media for three to five days

6. Microscopic embryo biopsy for PGD

7. Embryo transfer

8. Freezing of excess embryos for future use.

9. Hormonal supplementation to support the uterine environment after transfer

10. Serum pregnancy testing about 12 days after transfer

Future Directions
Interestingly, the profound advances in all aspect of IVF technology have led to the revival of ancient strategies, in particular the use of the natural cycle or the minimally stimulated cycle for IVF. Such an approach, although rarely employed in the US holds for the promise of several benefits, including a reduction in the risk and rate of multiple pregnancies, which is a recognized public health problem associated with conventional

IVF, a significant reduction in the cost of therapy, with a concomitant expansion of access to care, and a significant reduction in the generation of frozen embryos, which have been the source of numerous ethical and legal controversies. The degree to which application of such a strategy will change the face of IVF in the US is yet to be determined.

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