ART: Right to Reproduce

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ART: The Past and the Future

With the birth of Louise Brown on July 25, 1978—the first child successfully born as a result of in vitro fertilization (IVF)—came a rapid, international revolution in assisted reproductive technology (ART) unmatched by many other medical fields. Within 2 years of this milestone in the United Kingdom, the first US IVF clinic was opened in Virginia. Concurrently, the standardization of semen analyses and the early stages of preimplantation genetic diagnosis (PGD) were introduced, setting the stage for improved diagnostic techniques. Two years later, in 1982, the first babies born from frozen embryo transfer were delivered in Australia, as was the first delivery after a successful intrauterine insemination (IUI). Soon after, a woman with surgically absent ovaries underwent successful IVF using a donor oocyte, expanding the use of ART to women who would have otherwise been excluded. In 1984, the first baby conceived using a surrogate was born in California. In 1992, the process of intracytoplasmic sperm injection (ICSI) was successfully employed in Belgium and resulted in a viable pregnancy. In 2002, the first successful pregnancy after blastocyst biopsy using PGD was reported. In 2006, Louise Brown herself gave birth to a naturally conceived child, bringing full circle a whirlwind of technological advances in assisted reproduction [1].

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Advancements within each ART discipline allowed for improved treatment outcomes over time. For example, conversion in oocyte retrieval from a laparoscopic surgery to an ultrasound-guided procedure allowed this to become a primarily outpatient, same-day procedure [2]. In terms of diagnosis, PGD has undergone considerable transformation such that fewer cells can now be tested to predict hundreds of genetic disorders, improving overall diagnostic success [3]. Finally, techniques such as cryopreservation of both gametes and ovarian tissue have become pillars in fertility preservation, decreasing the pressure to transfer multiple embryos per cycle and, ultimately, the associated maternal and neonatal morbidity [4, 5].

In parallel with the fast-paced evolution of assisted reproduction came a proportional rise in public concern. The initial publication of IVF research in animal studies in the 1930s sparked ethical debate regarding the implication of reproductive freedom in humans [6]. Great concern from the government and public regarding the possibility of a "designer conception" or an "ideal race" tainted the innovative successes [7, 8]. Initially, falsified published reports claiming the use of ART for cloning caused public upheaval regarding the true intentions of ART [8]. More recently, controversial issues such as the impregnation of older women [9], the ownership over gametes or embryos [7], or sex selection via PGT [10] continue to spark debate. Even 44 years in these ethical and legal challenges add complexity to the scientific achievement.

Since 1978, more than five million births worldwide have resulted from ART [1, 2]. Studies project such exponential increase in the use of ART that, by the year 2100, nearly 167 million people will be borne by way of these interventions [11]. As a result, greater concern for societal order and ethical integrity will add important layers to the discussion and employment of assisted reproduction. The purpose of this chapter is to explore the pillars of present-day ART and the legal and ethical considerations they pose.

Pillars of Assisted Reproduction

Innovation within the field of assisted reproduction has provided previously infertile individuals and couples the opportunity to conceive in ways never before imagined [2, 12]. Before ART, diagnoses such as tubal or male factor infertility were considered insurmountable blockades. Early attempted reproductive procedures such as tubal reconstructive surgery, though promising, were largely unsuccessful and came with associated risk [12]. However, the basic science and clinical advancements in disciplines such as IVF, embryo transfer, ICSI, gamete and ovarian tissue cryopreservation, and preimplantation for genetic testing (PGT) have opened the possibility of parenthood for a wider pool of hopeful couples.

Conventional IVF involves the retrieval of oocytes from the ovaries with subsequent fertilization in a laboratory; the developing embryo is then transferred into the uterus at a later time for implantation. Even before the successful retrieval and transfer of the embryo that led to the birth of Louise Brown, the process of IVF has

undergone many modifications. In its early stages, the oocyte retrieval process required laparoscopic surgery; while minimally invasive, this technique was still quite experimental, and unstimulated cycles often yielded few mature oocytes. As a result, the discovery of medications such as human menopausal gonadotropin (hMG) and gonadotropins to help control the menstrual cycle improved oocyte yield and overall success rates [12]. In 1983, the first successful birth occurred after the use of a donor oocyte with IVF, expanding the applicability of this technology to those with premature ovarian failure or advanced maternal age [12].

The development of gamete and embryo cryopreservation was the next step in allowing for fertility preservation for medical, personal, or research-oriented reasons. Specifically for patients undergoing gonadotoxic treatments, these advancements allowed for the conservation of future fertility that was previously unimaginable. Additionally, for those individuals or couples interested in delayed childbearing, cryopreservation superseded the natural obstacle of declining female fertility. The cryopreservation of semen was the first to be actualized due to the ease of obtaining semen samples as compared with the limited quantity of excess oocytes. In fact, oocyte cryopreservation was only perfected 30 years after spermatozoan cryopreservation was developed. Most importantly, studies have shown that the freeze-thaw process required for cryopreservation does not appear to impact the embryo viability or neonatal outcomes, making this a safe and important facet of ART [5].

Cryopreservation has provided women, in particular, the independence and autonomy to pursue reproduction at a personally satisfactory time, rather than that dictated by nature. It can often be safer for the patient, allowing for the preservation of embryos from a single stimulation cycle to be used in future cycles, thereby decreasing the simultaneous transfer of multiple embryos and the number of ovarian stimulation cycles a patient may need. Additional benefits include the ability to use PGT or delay embryo transfer for other medical reasons such as ovarian hyperstimulation syndrome (OHSS) or cancer diagnoses [5].

For prepubertal patients or those with hormone-sensitive cancers who cannot undergo ovarian stimulation for gamete cryopreservation, ovarian tissue cryopreservation provides an alternative route [13]. This process involves the biopsy of ovarian cortical tissue and primordial follicles or whole ovary excision followed by autologous reimplantation after completion of treatment [12, 14]. While this option confers hope for many people, ASRM cautions against its use for benign conditions or those desiring delayed childbearing [13].

Male factor infertility such as azoospermia or poor spermatozoa motility is one of the major causes of infertility in couples. The refinement of ICSI provided a bypass mechanism for fertilization that was not previously feasible. ICSI involves isolating a single sperm and directly injecting it into an oocyte in the laboratory setting. Over the following few days, fertilization occurs and an embryo develops. In contrast with conventional IVF, ICSI more reliably guarantees insemination. It also has proven benefit in cases of transmissible viral diseases, such as HIV, as it allows for removal of seminal fluid and the selection of a single spermatozoan to reduce the risk of transmission [15].

One discipline which has undergone tremendous advancement is that of PGD. PGD involves the aspiration of embryonic cells, which are analyzed for the presence of genetic disease [3]. Eventually this led to the development of preimplantation genetic testing for aneuploidies (PGT-A), which has the ability to differentiate genetically normal and varying degrees of abnormal embryos in an effort to prioritize transfer of embryos with the greatest pregnancy potential [3]. Given that chromosomal abnormalities increase proportionally with age, this technology has been most useful in cases of advanced maternal age, as well as recurrent implantation failure, recurrent pregnancy loss, and severe male factor infertility [3].

Legal Components of ART

With the rapid advances in reproductive technologies came a need for legal regulation that could quiesce growing public skepticism [8]. Both the maternal and neonatal morbidities and mortalities associated with ART, specifically those related to the risk of multiple gestations, gave rise for concern regarding the implications of unregulated use. As a result, a combination of federal, state, and professional organizations were developed to assist in reporting and maintaining standards within the practice [16].

In 1992, Congress passed the Fertility Clinic Success Rate and Certification Act (also known as the Wyden Law), which required structured reporting of clinic and cycle data to the Centers for Disease Control and Prevention (CDC) to made public. It allowed for more accessible information to both clinics and lay people regarding the prevalence of infertility diagnoses, procedures, and clinical pregnancy and live birth rates [17]. It also prompted the development of accrediting organizations which would regulate embryology laboratories [16, 18]. Additionally, the federal government mandated other agencies, such as the Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS), to oversee various aspects of ART regulation [17].

The primary role of the FDA has been to oversee the development and use of infertility medications and devices. All new protocols or drug regimens are submitted to the FDA for approval prior to implementation [18]. The FDA also oversees the screening and storage of donor sperm or oocytes, to monitor the spread of infectious diseases and other necessary testing [17, 18].

Under the Clinical Laboratory Improvement Amendments (CLIA) of 1988, the primary role of the CMS became to ensure standardization and regulation of all laboratories which conduct testing on human specimens [17]. Responsibilities include coding and reimbursement, collection of fees, and clinic inspections [18]. This established quality assurance despite frequent use and testing of human gametes, embryos, and other tissues [17].

In the United States, individual states oversee their own clinics and physicians. Medical licenses are granted only to those who have met benchmarks and are

expected to perform at a high medical and professional level. In cases of misconduct, the states are expected to legislate [17]. Insurance coverage policies are also mandated by the states, with some providing full coverage and others offering only partial or no coverage [19]. While this allows patients in full-coverage states the opportunity to obtain services needed, it also creates a notable access-to-care disparity for patients with less financial assistance [6, 11].

The development of professional organizations also assisted in the regulation and standardized reporting of ART clinics across the country. Two of the most well-known professional societies include the American Society for Reproductive Medicine (ASRM), established in 1944, and its affiliate the Society for Assisted Reproductive Technology (SART), founded in 1987 [18]. ASRM was developed to act both as a guidepost for clinics and physicians, as well as an advocate for patients through high-quality research shared with both the science and lay communities [20]. SART was developed specifically to collect data on clinics and publish public reports through the CDC [16]. They performed audits and site visits and included site information as well as cycle characteristics [8]. Participation was and continues to be voluntary; therefore, while this data is essential, it is not always comprehensive [8].

In addition to reporting, ASRM and SART also continue to publish guidelines and committee opinions on some of the legal and ethical issues associated with assisted reproduction [17, 18]. They set minimum standards for who should be running clinics and laboratories and how ART should be most safely performed [19]. For example, in 1999, ASRM published its first set of recommendations on the minimum number of embryos to be transferred in a single cycle, taking into account a woman's diagnosis and prognosis as well as the risks of multiple gestation; while this document has been edited over the years to reflect changes in technology and practice, it serves to standardize patient safety [16, 19, 21]. However, despite these comprehensive guidelines, ultimate decisions on how to practice are left up to the clinics and physicians [21].

The lack of federal and interstate consensus on ART regulation gives rise to considerable legal debate on how certain cases are to be handled. For example, the ownership and disposition of cryopreserved embryos is an important consideration in cases of excess embryos or inability of one partner to contribute to joint decision-making [22]. Another complex issue involves the concept of legal parenthood, particularly in cases of surrogacy in which the relationship between the surrogate and the intended parents or between the intended parents themselves has dissolved. While many clinics have their own policies and contracts regarding these potential situations, multiple court cases have arisen as a result of a lack of state standards [22]. The ability for ART to provide children to same-sex couples has also led to substantial debate, including the concept of parentage, insurance coverage, and discrimination of services by individual providers [22].

Ethical Components of ART

Alongside these ongoing legal conversations arose parallel ones regarding ethical considerations. New types of parenthood for single people, same-sex couples, or older women gave rise to a multitude of concerns. Some worried how children raised by older parents or those that don't fit heteronormative roles might fare [7, 9]. Arguments have been made that younger infertile woman should be prioritized over older women and that the worthiest donor oocyte recipients should be those with the most promising outcomes [9]. However, literature exploring these topics in depth have proven no difference in medical outcomes or psychological adjustment for children born into these atypical scenarios [7, 9].

The development of PGT has allowed for more successful ART outcomes such as decreased time to pregnancy and improved pregnancy per cycle rates [23]; it has also sparked great concern regarding the implications of genetic manipulation or sex selection [10, 23]. Some question the degree to which PGT should be used to exclude genetically unfavorable embryos and which diseases should ethically be considered "unfavorable" [7]. Additionally, the possibility of sex selection by way of PGT, especially in countries where one sex may be favored over another, has been highly debated and discouraged [7, 18].

Oocyte donation has also given rise to ethical concern. Firstly, women undergoing the process of oocyte donation must understand and be extensively counseled on the risks associated with this process, including OHSS and surgical complications [10, 23]. Some argue that the routine purchase of genetic material is an unethical practice and may lead to coercion or the possibility of discounted services in exchange for donated oocytes [7, 10, 23]. The incentivization of women to donate genetic material for anything other than altruistic motive is of great concern. Conversely, the question of how to handle excess embryos—be it indefinite storage, discarding, or donation to research or to other couples—has been the source of debate across various countries, states, religions, and communities [10].

Gamete cryopreservation has massively impacted family planning, particularly for women undergoing gonadotoxic therapy. While the practice provides security, arguments arise over ownership and disposition of gametes in cases of the patient's disability or death [23]. As with all aspects of ART, cryopreservation therefore requires thorough pretreatment counseling.

Access to care continues to be a major blockade for those pursuing ART due to the high cost of care [11]. While many states offer some form of insurance coverage, the out-of-pocket cost for most patients can be burdensome. As a result, patients and physicians may be inclined to make less favorable medical decisions (such as the transfer of multiple embryos) in the hopes of optimizing the chance of conception per cycle [6]. Alternatively, if associated cost poses too great a burden, it may cause personal debt or a premature cessation of treatment [6]. Therefore, the economic barriers to infertility treatment often worsen an already difficult situation for many patients and families.

Conclusion

The revolutionary era of reproductive medicine is nowhere near completed. With every great advance made in the field over the last 44 years came a litany of social and legal debate that challenged new technology and practice. As the field inevitably continues to progress, federal and state legislatures will undoubtedly continue to confront these issues with regulation, and society will continue to contend with the legal and ethical complexities that accompany it. As a result, it will be the physicians and professional societies who will have to continue advocating for patients, improving access to care, and ensuring the safe application of practice. In time, perhaps assisted reproduction will be seen as a necessary treatment for a common disease rather than a controversial or unethical aberrance to nature.

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