What the future holds: a commentary on the promise of clinical embryology

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“The future will be far more surprising than most observers realize...”
Ray Kurzweil

From an anthropocentric point of view, the greatest achievement of mammalian embryology is the lending of its principles to the successful manipulation of human reproduction: at one end of the spectrum, through discovery of the contraceptive Pill (1), and at the other, through advent of in vitro fertilization and embryo transfer for alleviation of infertility (IVF/ET) (2). Over the nearly four decades since its introduction, IVF/ET has evolved into a multidisciplinary field of medicine, referred to as Assisted Reproductive Technologies (ART). ART now encompasses treatment of male and female factor infertility and sub-fertility, third party reproduction, preservation of fertility, and pre-implantation genetic diagnosis of disease.

What could be expected of ART in the next four decades?

The answer to this question is a universal answer that applies to progress in all technology, that is, improved efficiency at lower cost and a further global reach. The rate of technological progress has been a subject of study for nearly a century. Multiple hypotheses, validated by rigorous statistical examination (3), hold that this rate is predictable. One well-regarded hypothesis related to transistor efficiency is Moore’s Law (4). Gordon Moore, who became a co-founder of Intel, predicted that the number of transistors per square inch on integrated circuits would double every year and that this trend would continue for the foreseeable future, leading to exponentially increasing computational speed and power.

Moore later acknowledged that this growth would be subject to physical constraints and would eventually stop (5). The limit of his Law may have already been reached by advent of a single-atom transistor (6), but Moore’s bold prediction itself became a “self-fulfilling prophecy”, as it has been said, driving innovation and pushing researchers to confront and overcome obstacles that may have otherwise been considered intractable and left alone. The communication and information fields have come to rethink the essence of bits and Boolean states and the new field of Quantum Computing has thus emerged.

In our field, progress is evident and quantifiable. We have seen fertilization rates in cases of male infertility improve from 20% in the early 1980s to 70% in the 1990s, thanks to microsurgically-assisted fertilization (7, 8). Advances in culture media and systems have allowed culture of embryos to day 6 or 7 of development with blastocyst formation rates having improved from barely 25% in the 1980s to 60% or more 20 years later (9-11). Embryo survival rates after cryostorage have increased from 60% to nearly 100% thanks to meticulous quality control as well as improvements in cryopreservation technology, including the introduction of vitrification and new and clever cryostorage devices (12-14). Moreover, this success has been extended to oocytes (15) making fertility pre-
servation for medical and social reasons a reality for women. Clinical outcomes have also improved significantly. An analysis of data obtained from the SART national database in the United States shows that implantation rates (the number of fetuses per embryo transferred, a true measure of quality in the laboratory) have been increasing annually since 1985 at a rate of 0.3-1.5% for patients under 43 years of age (16). Implantation can be predicted to reach 100% in a not-so-distant future in some age groups (16).

So, even though the field may seem to be progressing slowly or even remaining stagnant as Vajta laments in this issue of the Journal, the actual progress has been phenomenal. Perhaps we can find an explanation for this generally pessimistic view in Kurzweil’s argument that progress can be so rapid and profound that even the most objective observer may fail to comprehend it (17).

Of course, the envelope must be pushed further: ART must enable healthy singleton live births, and future healthy adults, from transfer of a single normal embryo in one treatment cycle. To fulfill this promise, several bottlenecks in (assisted) reproduction must be resolved. One obvious such bottleneck is the paucity of normal female gametes. So derivation of oocytes from somatic cells should undoubtedly be a focus of research. Another barrier is the high frequency of chromosomal abnormalities and deleterious mutations in oocytes and embryos. So, more efficient and accurate detection of such aberrations should continue to be a goal (18, 19). On the other hand, further discoveries on the origin of aneuploidy in oocytes, particularly in the context of ART, could lead to avoidance of this problem altogether.

It is in the context of this vision of the future for assisted reproduction that recent calls to abandon embryo selection in favor of cryopreservation and “serial” transfer of all available embryos (20) are difficult to understand. If predicting the extent of future progress is a driver of innovation, setting your sights low is a sure way to discourage it! While all of medicine, and not just assisted reproductive medicine, moves decisively toward individualized treatments based on genomics, the argument against embryo selection (in essence, advocating natural selection) seems unambitious, even backward. Likewise, the declaration that genetic screening of embryos “will never work” (21), seems breathtakingly shortsighted since it is certain that the shortcomings of current screening technologies will be addressed in the future. The argument against embryo selection is also ethically dubious since it assumes that serial embryo transfer attempts are of no consequence to the patient. But this assumption is wrong. Even if one disregards the added financial burden inherent in the proposal, “serial” transfer of (mostly) abnormal embryos (until a normal embryo is found by chance) puts the patient at higher risk of (repeatedly) experiencing adverse outcomes: multiple failures which are discouraging and psychologically painful and can lead to abandonment of treatment; early pregnancy loss, in the form of biochemical pregnancy, blighted ova, and missed abortions, which are all physically and psychologically traumatic and could require further medical intervention; and abnormal pregnancy, the consequences of which need not be spelled out here.

The evolving nature of novel technologies is not synonymous with failure or a reason to reject them. We owe it to our patients and the next generation to push forward safely and responsibly, in pursuit of a “far more surprising” and successful future.

References