An Opinion on Regulating the Assisted Reproductive Technologies

Don P. Wolf¹

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The assisted reproductive technologies (ARTs) have made spectacular progress since their inception in the late 1970s with the birth of Louise Brown. Originated for the treatment of absolute tubal infertility, these technologies have since been expanded to include the routine treatment of male factors, even azoospermia, with intracytoplasmic sperm injection of testicular sperm, maternal age related conditions with donor egg, and certain genetic predispositions with preimplantation genetic diagnosis (PGD). In two decades, our ability to cope with infertility has improved to the degree that few conditions remain outside the realm of treatment. These accomplishments have been realized without substantial investment in preclinical trials or translational research in animal models. Indeed, from the perspective of ARTs in nonhuman primates, the human is the model for the monkey!

Of course, there are also many activities that have been attempted or applied without reaching clinical, state-of-the-art status including embryo deselection, cytoplasmic transfer, and germinal vesicle transfer, along with "experiments" that never reached the light of day perhaps even including somatic cell nuclear transfer and the first cloned human (1). The latter all are good examples of the ARTs at their unregulated best or worst depending on your perspective, driven by what I will call a Wild West, anything goes, mentality! And while the motive of the health care professionals, or are they "cowboys," may often be

pure, the bottom line is unregulated experimentation on human gametes and embryos. Moreover, market forces make the selling of human eggs or the renting of a womb from surrogate mothers, an increasingly lucrative venture.

Consequently, to say that we have reasoned, consensus-driven regulation in force is simply not possible given, on the one hand, the absence of Federal restrictions on the ethically sensitive issue of cloning and, on the other, the preposterous limitations imposed by administrative fiat on human embryonic stem cell research (2). In my opinion, we need, if not more, better regulation.

What should we expect from regulation of the ARTs? First and foremost, consumer protection, addressing safety, efficacy and quality of care issues. Secondly, creation of a level playing field for not only consumers who need equal access at a reasonable cost but also for practitioners of the ARTs, for remember that beside the admirable desire to treat infertility patients, there is a financial incentive here and competition between clinics can impact the decision making process. Regulation should also be proactive as well as reactive and it could and should address the ARTs and embryo research in broad strokes including somatic cell and therapeutic cloning, embryonic stem cells as well as the genetic implications of PGD and the like.

At the outset, it is appropriate to recognize that numerous layers of oversight and regulation already exist involving federal, state and private entities as summarized recently by Adamson (3), a practitioner of the ARTs, who makes a compelling case for oversight as opposed to regulation. He subdivides these efforts into mandatory regulations affecting medicine in

¹ Oregon National Primate Research Center, Oregon Health and Sciences University, 505 NW 185th, Beaverton, Oregon 97006; e-mail: wolfd@ohsu.edu.

general, clinical, ART-specific regulations such as the Fertility Clinic Success Rate and Certification Act of 1992 and nonmedical regulations concerning truth in advertising and marketing. A multitude of oversight activities includes laboratory accreditation and certification programs, Professional Society Guidelines and Practice Standards and ethical guidelines.

It is important to realize that for the most part these regulations and oversight activities were established only after the technologies had become widespread and accepted as the standard of practice. Also, in the case of oversight, there is no provision for non-compliance apart from membership revocation. Perhaps inevitably, critical issues are not regulated in this format. Take as a specific example, the Clinical Laboratory Improvement Act or the College of American Pathology/American Society of Reproductive Medicine sponsored laboratory accreditation programs. Laboratory inspections can readily document the existence of credentialed personnel, appropriate quality control and quality assurance activities, record keeping and detailed protocol preparation. However, outcome measures and what is done with eggs and embryos in the guise of advancing the state of the ARTs is beyond the pale.

What then are the specific loopholes that need to be addressed in considering further regulation of the ARTs? I'll consider two, the first is a global issue, regulating experimentation on human gametes and embryos and the second is local, controlling the number of embryos for transfer. Of course, inherent in my concept of advocating for increased regulation is an attempt to do so while minimally impeding progress in the field, when and where it is legitimate. Indeed, we must incorporate a mechanism to determine legitimacy, to avoid redundancy in clinical research and to promote statistically significant outcomes through appropriately designed and managed clinical trials.

During my tenure as laboratory director at OHSU, our approach to protocol change or the adoption of a new technique was stepwise and often excruciatingly slow. With the introduction of PGD, a relatively well-established procedure at the time, we first identified qualified personnel and wrote and defended a proposal in front of our Institutional Review Board. Next, we conducted a series of biopsies and genetic characterization on frozen-thawed embryos donated for research and only then did we begin a trial on a group of 20 patients, at no additional cost to the patient, I might add. Although this approach represents one paradigm, there is no defined or widely accepted process by which protocol changes should be made at

minimal risk to the consumer. Rather, in the absence of regulation, approaches are clinic specific, haphazard and often influenced by patient demand; program X or Y is offering ICSI or PGD and therefore we must too and it must be as soon as possible, which is a recipe for abuse.

And we are on the cusp of ethical issues of increasing complexity and potential risk such as somatic cell and therapeutic cloning, embryonic stem cell based therapies and PGD for gender or other selection criteria unrelated to a medical condition. I believe existing regulatory experience in the form of the Reproductive Technology Accreditation Committee in Australia or the Human Fertilization and Embryology Authority in England provides a useful model for study where experimental manipulation of human gametes and embryos is considered and authorized well in advance of any actual experimentation.

A second loophole that might be relatively easy to regulate is the number of embryos transferred that in turn dictates the incidence of high order pregnancies, triplets and above. I have argued this case previously (4) and my opinion has not changed. To me, it is simply unconscionable to transfer more than three embryos, period. The outcomes and consequences are well documented and they are not good. The option of selective fetal reduction, even given that this procedure is now safe for mothers and the untargeted fetuses, undoubtedly creates emotional baggage for the patient that likely lasts a lifetime. The percentage of ART-related triplet and higher order pregnancies in the United States in the mid 1990s was about 7% expressed relative to the number of deliveries (5). This is several hundred times the rate associated with natural conception and these figures do not include fetal loss, which is clearly much greater in high-order multiple gestations. Admittedly, there is some suggestion that this rate has declined more recently (5), perhaps secondary to the ability to transfer fewer embryos at the blastocyst stage and we can all hope that this trend will continue.

But the important point here is that there is no guarantee that the rate will decrease to an acceptable level and stay there in the absence of regulation. Certainly there should be some flexibility in regulation, for instance, based on maternal age as reflected in the guidelines that suggest a maximum of two embryos for patients under 35 and three for those over 35. But I don't think the problem will resolve itself without regulation, despite the possibility of deselecting embryos to the extent that the transfer of single, selected blastocysts might produce acceptable pregnancy

rates. It is difficult to imagine that unregulated programs in a temporary or permanent lull will continue the status quo in the face of ever increasing pregnancy rates reported by the competition. No, left to their devices, they will likely increase the number of embryos per transfer until such time as several high multiple pregnancies force retreat. Similarly, pressure to maximize the number of embryos transferred can come directly from the patient, for instance, the patient who can only afford one ART cycle or who finds that most of the embryo cohort is of low quality. A mechanism for monitoring high-order multiple pregnancies is in place in the form of clinic specific reporting, so the addition of sanctions and a means of imposing them should suffice!

In summary, regulation in this area of health care is impacted by the fact that medical treatment for infertility is an elective procedure and by our presumed God given right to procreate. Existing regulation has unquestionably been influenced by political hot potatoes such as the abortion controversy. Isn't it curious that we can, on the one hand, allow the abortion issue to preclude rational discussion of embryo

research but on the other, allow private ART clinics, with the ability to create and destroy embryos, to operate pretty much on their own? Improved, more comprehensive regulation could fill blatant gaps while creating a better image for the industry. Finally, although I don't know how it will be accomplished, administrative fiat must be removed from the equation while federal dollars are added for sanctioned research involving human gametes, embryos, and embryonic stem cells.

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