Medicine

Assisted Reproduction

There were two articles in recent issues of *Human Reproduction* concerning uterus transplantation. In the June issue, Liza Johannesson and co-authors reported the performance of autologous transplantation of the uterus, fallopian tubes, and ovaries in baboons.[1] Autologous transplantation involves removing the organs from an animal and then returning them to the same animal; it was done in this study to refine surgical technique and assess long-term uterine function. To assess uterine function, the animals were separated into two groups. A previously reported surgical approach was used in the first group, while a modified technique was used in the second group.

All the animals in group 2 survived in the short term, compared with two-thirds of the animals in group 1. Ovarian cycles resumed in 80 percent of animals in group 2 but in only 66 percent of those in group 1. However, normal menstruation returned after uterine transplantation in group 2 only—specifically, in 60 percent of the animals in that group. The animals in which menstruation occurred were then presented to males for timed mating for at least five menstrual cycles, but no pregnancies resulted.

In the second article, the authors evaluated their surgical technique for uterine transplantation specifically focusing on microsurgical connections and the blood flow of the transplanted uterus.[2] They performed uterine autotransplantation in two cynomolgus monkeys, using slightly different surgical techniques in each, and

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[1] Liza Johannesson et al., "Uterus Transplantation in a Nonhuman Primate: Long-Term Follow-up after Autologous Transplantation," *Human Reproduction* 27.6 (June 2012): 1640–1648.

[2] Makoto Mihara et al., "Uterine Autotransplantation in Cynomolgus Macaques: The First Case of Pregnancy and Delivery," *Human Reproduction* 27.8 (August 2012): 2332–2340.

demonstrated that in one of the animals menstruation resumed and a pregnancy was achieved. A cesarean section was performed because of early placental separation. The newborn had suffered fetal distress and was not resuscitated. The authors state that this is the first report of a delivery after uterine transplantation in primates. The first human uterine transplantation occurred in 2000, but, complications necessitated a hysterectomy ninety-nine days after the transplantation.[3]

As with most medical science reports, these articles illustrate advancements in medicine and efforts to push forward the frontiers of medical science, exploring new and potentially beneficial technologies for the treatment of human maladies. That these studies involve a drastic intervention in the mechanics of procreation, however, gives me pause—perhaps because uterine transplantation is an intervention that affects one of the most sacred human acts, or perhaps because it does not correct a life-threatening condition.

In the more clinically relevant area of assisted reproduction technology (ART), the authors of "Cumulative Birth Rates with Linked Assisted Reproductive Technology Cycles" found that success rates for ART are lower than natural fecundity rates.[4] Their study was designed to test the theory that for women receiving ongoing ART treatment, success rates over the course of treatment (cumulative live-birth rates) are a more important measure than live-birth rates per cycle. Using data collected from 2004 to 2009 from the clinic-outcome reporting system of the Society for Assisted Reproductive Technology, the authors estimated cumulative live-birth rates by linking data from ART cycles to individual women. The results are based on data from the 140,859 live births of 246,740 women who underwent 471,208 cycles of ART.

Nearly half of the women (47 percent) were younger than thirty-five and 15 percent were older than forty. Live births occurred in 30 percent of the cycles, and in 57 percent of the women. When a woman's own oocytes were used, live-birth rates went down as the woman got older and as she submitted herself to additional cycles of ART. When donor oocytes were used, however, live-birth rates in older women were similar to those in younger women. Overall, the rate of live births fell below the natural fecundity rate of the general population, which is estimated to be 65 percent after six months. It is not surprising that artificial means of reproduction are inferior to natural processes. I believe there is some very good reason for this observation.

Conflict of Interest

Clinical practice guidelines, developed by experts in specific fields, serve physicians across various disciplines by helping to guide decisions in the management of medical conditions. The guidelines do so by linking scientific evidence with sound clinical judgment. Because of the relationships physicians have with pharmaceutical and other medical technology companies, however, the ethical foundations of these guidelines may be called into question, specifically with respect to financial conflicts of interest (FCOIs).

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[3] Wafa Fageeh et al., "Transplantation of the Human Uterus," *International Journal of Gynecology and Obstetrics* 76.3 (March 2002): 245–251.

[4] Barbara Duke et al., "Cumulative Birth Rates with Linked Assisted Reproductive Technology Cycles," *New England Journal of Medicine* 366.26 (June 28, 2012): 2483–2491.

An effort to identify and manage FCOIs is reported in "Conflicts of Interest Ethics: Silencing Expertise in the Development of International Clinical Practice Guidelines," by D. J. Jones and colleagues in the June 5, 2012, issue of the *Annals of Internal Medicine*. The authors developed an ethics framework to guide experts' conduct in the process of meeting to create the guideline. The framework allowed experts with FCOIs to recuse themselves from discussions prior to voting on a clinical practice guideline. This allowed the researchers to see whether recusal affected the deliberations and the voting. The setting was a single meeting of thirty-four experts from fifteen countries to develop a guideline on the management of upper gastrointestinal bleeding.

All experts were briefed on the conflict-of-interest ethics framework at the start of the meeting, but they were not informed beforehand that votes could be discounted to prevent FCOIs from affecting the results. More than half of the experts (twenty-one of thirty-four) reported at least one FCOI, and eight of the twenty-one draft recommendations in the guideline were considered "at risk" of presenting FCOIs. Experts recused themselves from discussions of six of these eight recommendations; none of the experts perceived a relevant FCOI in the other two.

The overall voting outcomes did not appear to change when the votes of recused members were included. The authors note, however, that while the recusals did not affect voting outcomes, they may have "diluted the richness of the discussions." Although the study has limitations, given the small number of participants at just one meeting, the results suggest that an ethics framework may be useful in recognizing and addressing FCOIs. The study calls to mind the importance of balancing impartiality and expertise, particularly when clinical practices may be affected.

End-of-Life Care

In the August issue of the *Archives of Internal Medicine*, Baohui Zhang and colleagues explored factors influencing quality of life in patients who were dying of cancer.[5] Trained interviewers assessed patients and caregivers at baseline, and then, following the patient's death, physicians and caregivers completed an evaluation. To be included, patients had to have metastatic cancer, an estimated life expectancy of less than six months, and an unpaid, informal caregiver. Over one thousand eligible patients were approached for participation and nearly 30 percent declined participation. Nonparticipants reported significantly more distress than participants as assessed on a five-point rating scale. In-depth interviews with participating patients and caregivers were performed and, following a patient's death, assessments were made as to how physicians and caregivers would rate the patient's level of physical distress, psychological distress, and overall quality of life just prior to death. The study sample of 396 patients (mean age, fifty-nine years) was mostly white (65 percent), Christian (71 percent) and medically insured (61 percent). Quality of life at the end of life was worse in patients who were younger and closer to death. A better

[5] Baohui Zhang, Matthew E. Nilsson, and Holly G. Prigerson, "Factors Important to Patients' Quality of Life at the End of Life," *Archives of Internal Medicine* 172.15 (August 13, 2012): 1133–1142.

quality of life was noted in patients whose caregivers' health was better overall. Random-effects modeling suggested that potential predictors of worse quality of life were depression, post-traumatic stress, panic disorder, and baseline worry. Also, patients who received any procedure that prolonged their life, and who received care in the ICU tended to have significantly worse quality of life. A better quality of life was noted in patients who had a sense of inner peacefulness at baseline, who reported receiving pastoral care, whose religious beliefs or activities helped them cope with their illness, and who participated in religious activities prior to receiving their cancer diagnosis. Zhang and colleagues note, "Deaths in the ICU and hospital were associated with significantly worse [quality of life], whereas deaths at home were associated with significantly better [quality of life] at the [end of life]." Using cross-validation analysis to determine the best model to predict quality of life, the authors found that dying in the hospital and staying in the ICU during the last week of life were the most important factors in determining poor quality of life for patients. Chemotherapy and feeding tube use also appeared in the final model, and the authors suggest that limiting these types of "aggressive [end-of-life] care may be an effective strategy to enhance [quality of life] at the [end of life]."

The authors are to be commended for investigating patient care at the end of life, and for trying to identify ways in which the care of the dying may be positively enhanced. My concern is that this area is extremely complex, with a very diverse and heterogeneous mix of patients with different religious, cultural, ethnic, geographic, and socioeconomic backgrounds, among others. Given such diversity, we must be cautious that published reports such as this may be afforded more weight than is deserved. Generalization of findings to other groups and circumstances can be very dangerous. For example, while, in retrospect, dying in the hospital and ICU stays in the last week of life predicted poor patient quality of life, it is probably best not to make prospective clinical decisions (such as to not admit a patient with advanced metastatic cancer who can benefit from a hospital ICU admission) based on this knowledge. Further, the use of feeding tubes remains a morally controversial topic and deserves very careful attention. I fear that linking limited feeding-tube use with enhanced quality of life too casually (in other words, without the appropriate moral analysis and consideration) will potentially result in more unethical actions.

Along similar lines, an article concerning physicians' orders for life-sustaining treatment (POLST) appeared in the January 2013 issue of the *Journal of General Internal Medicine*.[6] This article reflects my apprehension about the direction of medical literature on end-of-life care. POLST are instruments used to ensure that a patient's preference with respect to specific treatments, which may be relevant to their care at some point, be honored. Often they indicate preferences to limit specific therapies such as CPR, dialysis, or tube feeding. In this article, Neil Wenger and co-authors report on POLST implementation in California nursing homes eighteen months after POLST were introduced in the state. Overall, 283 nursing homes

[6] Neil S. Wenger et al., "Implementation of Physician Orders for Life Sustaining Treatment in Nursing Homes in California: Evaluation of a Novel Statewide Dissemination Mechanism," *Journal of General Internal Medicine* 28.1 (January 2013): 51–57.

responded to the survey. In 82 percent of the responding nursing homes, staff received education about POLST, and 59 percent of the nursing homes had a POLST policy. Eighty-one percent of the nursing homes administered a POLST. Nearly 54 percent of residents had a POLST. Few nursing homes reported that they had difficulty following POLST orders, although 21 percent had difficulty with POLST interpretation, and in 28 percent there was family disagreement with POLST content.

In our society the word "choice" has become a lightning rod for interlocutors on the morality of various so-called women's reproductive health issues. These are well recognized and their attendant moral issues frequently written about in the pages of this journal. What may be happening on the other end of the life spectrum is that the term "choice" is creeping into the dialogue concerning the end of life. As patient autonomy continues to be espoused as a preeminent principle of medical ethics, and it seems to imply that there is something in itself unethical if patients do not have a "choice." We should thus subject the whole matter of POLST to very careful scrutiny. The premise that it is always necessary to have choices, even when the choices are between immoral options, contributes to the ethical bankruptcy of our medical systems.

A perspective piece in the July 12, 2012, issue of the *New England Journal of Medicine* continues the dialogue in the medical community about physician-assisted suicide;[7] however, as has been noted previously, a linguistic sleight of hand is occurring as this morally repulsive conduct is being referred to more and more often as "assisted dying."[8] In this article, the authors propose a system that removes physicians from the direct process of patients' suicides. The authors clearly make the argument that patients who wish to control the timing and circumstances of their death be allowed to do so. They hold that, if the physicians are not willing to comply with this, there should be some state or even federal mechanism in place to enable a patient to carry out this act. In their argument the authors note opponents' objections, but frequently cite the Oregon experience with the Death with Dignity Act to counter those objections. However, one objection that cannot be countered by the Death with Dignity Act is that allowing the practice of assisted suicide undermines respect for the sanctity of life. To this objection, the authors simply dismiss the concern as a "subjective moral question" and suggest that, like abortion, legalization benefits those who want the option, but does not affect those who object to the practice. This obviously could not be further from the truth. Apart from the perils of moral relativism, the key point that is almost never considered in such debates is how offensive it is that someone takes their life, and in doing so cheapens the apparent value of all human life.

Health Insurance

The authors of a viewpoint article in the July 11, 2012, issue of *JAMA* are of the opinion that requiring a person to buy health insurance is morally appropriate.[9]

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[7] Julian J. Prokopetz and Lisa S. Lehmann, "Redefining Physicians' Role in Assisted Dying," *New England Journal of Medicine* 367.2 (July 12, 2012): 97–99.

[8] See John M. Travaline's medical narrative in *National Bioethics Quarterly* 9.2 (Summer 2009): 354–355.

[9] Tina Rulli, Ezekiel J. Emanuel, and David Wendler, "The Moral Duty to Buy Health Insurance," *JAMA* 308.2 (July 11, 2012): 137–138.

They base this opinion on the claim that there is a moral duty to reduce burdens that one may place on another. While this may be true, questions concerning the Patient Protection and Affordable Care Act seem far more complex. Further, I should like to note that one of the authors of the article, Ezekiel Emanuel, special adviser for health care to the Obama administration, also co-authored an article in which similarly strong language was used to discuss the moral obligation of people to participate in biomedical research.[10] I have some concerns about being told what is moral and what is morally obligatory by people whose opinions are not clearly expressed as based on solid moral foundations and by persons suspected of having strong political biases.

Organ Donation

A major limitation of solid-organ transplantation is the insufficient number of donated organs. One way of increasing the donor pool is through donation after circulatory determination of death (DCDD), in addition to donation after use of neurologic criteria for establishing death. DCDD, however, seems to be the subject of concerns over role conflict between clinicians caring for the patient and those involved in acquiring donated organs from the patient once the patient is removed from life-sustaining therapy. In order to explore the factors affecting decision making by critical care physicians and nurses who are involved in the management of potential donors after circulatory determination of death, and to assess the presence of role conflict and its effects on end-of-life care, Joanna Hart and colleagues analyzed data from questionnaires completed by 684 physicians and 438 nurses.[11] Overall, their findings were positive with respect to clinicians' views of DCDD. For example, they found that most critical care physicians (73 percent) and most nurses (74 percent) surveyed felt they should participate in the management of potential donors after circulatory determination of death, particularly if the patient had a signed donor card. Only about 15 percent of physicians and 14 percent of nurses felt that such management would create professional role conflicts. With regard to DCDD and end-of-life care, however, nurses (55 percent) were more likely than physicians (34 percent) to report that managing DCDD patients would improve the quality of end-of-life care. While proponents of DCDD are likely to view these findings positively, it is the underwhelming response regarding the effect of DCDD on the quality of end-of-life care that should give pause and receive greater attention. Why did many nurses and most physicians not report that DCDD would improve the quality of end-of-life care?

Deacon John M. Travaline, MD

[10] G. Owen Schaefer, Ezekiel J. Emanuel, and Alan Wertheimer, "The Obligation to Participate in Biomedical Research," *JAMA* 302.1 (July 1, 2009): 67–72.

[11] Joanna L. Hart, Rachel Kohn, and Scott D. Halpern, "Perceptions of Organ Donation after Circulatory Determination of Death among Critical Care Physicians and Nurses: A National Survey," *Critical Care Medicine* 40.9 (September 2012): 2595–2600.