CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 21-2010: A Request for Retrieval of Oocytes from a 36-Year-Old Woman with Anoxic Brain Injury

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PRESENTATION OF CASE

The family of a 36-year-old woman with anoxic brain injury requested oocyte retrieval for the purpose of posthumous conception.

The patient had been well until 11 days earlier, when she collapsed approximately 7 hours into an international airplane flight. She had taken zolpidem before departure and slept for most of the flight in one position. She arose to go to the bathroom and collapsed in the aisle shortly thereafter. A physician on the airplane did not find a pulse, and cardiopulmonary resuscitation (CPR) was initiated. An electrocardiogram (ECG) showed pulseless electric activity. The trachea was intubated, and epinephrine and atropine were administered; a pulse was restored after 30 to 60 minutes. Ventilation was reportedly limited because of apparent trismus and biting on the endotracheal tube; the tube was removed, and hand-ventilation with the use of a bag-valve device and a face mask was begun. Approximately 2 hours after the patient collapsed, the airplane made an emergency landing in Boston.

The patient was transported to the emergency department of this hospital, arriving approximately 2.5 hours after her collapse. A history was obtained from her family. The patient had no history of coagulation disorders. She was married, with no children, and was employed in an office position. She did not use tobacco or illicit drugs. Her only medication was an oral contraceptive.

On examination, the patient was unconscious, intubated, and mechanically ventilated. The temperature was 35.6°C, the blood pressure 94/60 mm Hg, the pulse 140 beats per minute, and the oxygen saturation 100% while she was ventilated with 100% inspired oxygen. The eyes opened to voice stimulation and sternal rub; the pupils reacted to light. The eyes were roving and did not track, and the gaze was disconjugate. Corneal, cough, gag, and deep-tendon reflexes were intact; plantar responses were flexor. She purposefully withdrew from painful stimuli, more clearly on the right side than the left side. She did not follow commands. The remainder of the examination was normal. An ECG showed atrial fibrillation with a ventricular response rate of 139 beats per minute and nonspecific ST-segment and T-wave abnormalities. The level of white cells was 17,500 per cubic millimeter (reference

range, 4500 to 11,000), with 90% leukocytes, and the D-dimer level was greater than 10,000 ng per milliliter (reference range, <500); the hematocrit and levels of hemoglobin, platelets, bilirubin, protein, albumin, and globulin and tests of renal and liver function were normal; screening tests for creatine kinase isoenzymes and troponin I were negative; a hypercoagulability evaluation was normal. While the patient was undergoing ventilation with 100% oxygen, the arterial pH was 7.26 (reference range, 7.35 to 7.45), and the partial pressure of oxygen was 378 mm Hg (reference range while a patient is breathing ambient air, 80 to 100); the level of carbon dioxide was normal.

Computed tomographic (CT) scans of the head without contrast material showed no intracranial hemorrhage, mass, midline shift, or evidence of acute infarct. CT scans of the chest showed multiple bilateral pulmonary-artery emboli and mild bowing of the interventricular septum, features thought to be suggestive of right heart strain, and CT of the pelvis and lower legs showed a filling defect within the right popliteal vein that extended into the right common femoral vein and was consistent with deep-vein thrombosis. CT angiography of the head and neck, after the administration of contrast material, was normal, and magnetic resonance imaging (MRI) of the brain showed no evidence of infarction, ischemia, herniation, or edema. Alteplase was administered over a 2-hour period, and a heparin infusion was begun. Normal sinus rhythm returned spontaneously.

On the fourth day, the pupils became fixed and dilated. A CT scan of the brain showed cerebral edema, with patchy loss of gray–white differentiation. Mannitol and hypertonic saline were administered, and the patient was hyperventilated. The administration of propofol was increased, and heparin was stopped. Protamine and fresh-frozen plasma were given, and an external ventricular drain was placed. The initial intracranial pressure was too high to record; the first measured reading was 38 cm of water, and the readings gradually fell to 11 to 15 cm of water. Repeat MRI scans showed restricted diffusion in the basal ganglia and cortex, particularly in the posterior regions, a feature consistent with diffuse hypoxic–ischemic injury. Sedation was withdrawn. The patient opened her eyes to painful stimuli and had intermittent posturing unrelated to stimulation.

On the ninth day, an electroencephalogram (EEG) showed markedly reduced amplitudes and diffuse slowing. The next day, after discussions with the patient's family were held regarding her poor prognosis, the endotracheal tube was removed. Several hours later, in the middle of the night, the family approached the on-call physician and asked that maximal medical therapy be resumed, to permit consideration of oocyte retrieval from the patient, for the purpose of posthumous conception of future offspring.

A management decision was made.

DIFFERENTIAL DIAGNOSIS

Dr. David M. Greer: This young woman had a cardiac arrest after a massive pulmonary embolism, resulting from venous thrombosis that occurred while she slept in a sitting position on a long airplane flight. Although she had no personal or family history of hypercoagulability, she was taking oral contraceptives, which may increase the risk of thromboembolic events.[1] The risk of thrombosis and pulmonary embolism, sometimes fatal, during long airplane flights has been reported previously.[2]

DETERMINING NEUROLOGIC PROGNOSIS AFTER CARDIAC ARREST

Despite aggressive measures, the patient remained comatose after several days in the intensive care unit (ICU), and severe cerebral edema and signs of herniation developed. The patient most likely had catastrophic cerebral anoxic injury due to the prolonged cardiac arrest (despite the use of CPR), in addition to the severe hypoxia due to her pulmonary embolism and the ineffective ventilation due to blockage of her endotracheal tube. The determination of prognosis in a patient such as this one after a cardiac arrest requires the use of clinical, radiographic, and electrographic tools. The practice parameters set forth by the American Academy of Neurology designate the neurologic examination on day 3 after cardiac arrest as the most reliable but stipulate that patients must have a lack of pupillary or corneal reflexes and have a motor response of extensor posturing or no movement to be classified in the poor-prognosis category.[3] This patient did not fulfill these strict clinical criteria for poor prognosis. The patient's neuroimaging scans were unremarkable early in her course, which is not surprising, since the ischemic changes that occur after cardiac arrest often have a delayed appearance radiographically.[4] How-

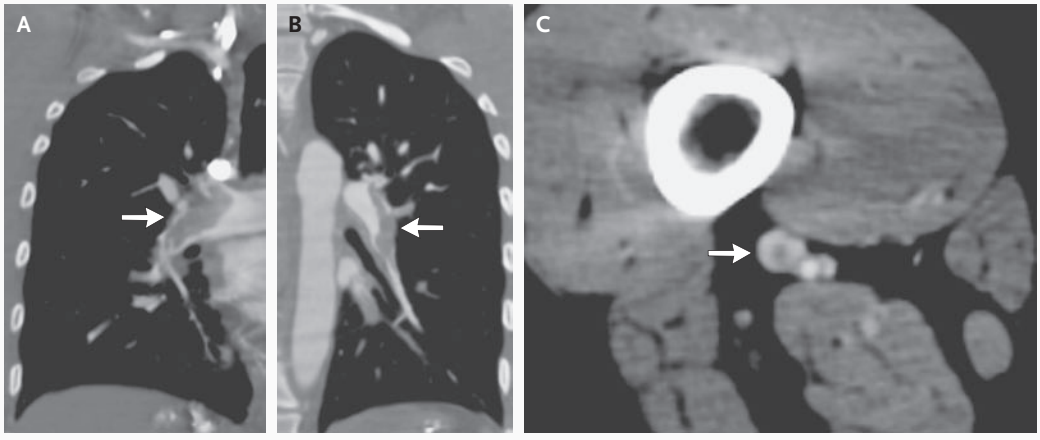

Figure 1. CT Angiographic Scans on Admission.

Reformatted coronal images from a CT angiogram of the chest obtained on admission (Panels A and B) show large filling defects in both pulmonary arteries (arrows) after the injection of an iodinated contrast agent, features consistent with pulmonary emboli. A CT scan of the right leg (Panel C) shows a central filling defect in the popliteal vein that extends into the common femoral vein (arrow), a feature consistent with deep-vein thrombosis.

ever, neuroimaging and EEG findings, such as slowing or low-amplitude waveforms, have not been validated as prognostic tools after cardiac arrest.[5]

May we see the imaging studies?

Dr. Javier M. Romero: A CT angiogram of the chest on admission (Fig. 1A and 1B) showed large filling defects in both pulmonary arteries after the injection of an iodinated contrast agent, features consistent with pulmonary emboli. CT of the pelvis and lower legs (Fig. 1C) after the injection of an iodinated contrast agent showed a filling defect within the right popliteal vein and extending into the right common femoral vein, a feature consistent with deep-vein thrombosis. On the fourth day, a CT scan of the brain (Fig. 2A) showed increased cerebral edema, with loss of gray–white differentiation and decreased attenuation of the basal ganglia. A repeat MRI scan on the same day (Fig. 2B and 2C) showed restricted water diffusion in the basal ganglia and cortex diffusely, a feature consistent with severe hypoxic–ischemic injury.

Dr. Greer: The conclusion that this patient would have a poor neurologic prognosis was arrived at on the basis of the poor and deteriorating neurologic examination, cerebral edema (as manifested by her elevated intracranial pressure), the markedly abnormal EEG, and the neuroimaging findings that were suggestive of widespread anoxic–ischemic cerebral injury. After discussing these issues with the patient's family, they elected to withdraw aggressive care and institute comfort measures only. Within a few hours, however, they reversed this decision and requested reintubation. Because of the unusual nature of the request and the lack of a clear path, the on-call physicians reintubated the patient so that medical, ethical, and legal standpoints could be considered.

PREGNANCY AND ORGAN DONATION AFTER NEUROLOGIC CATASTROPHE

Some people have advocated that once a patient is dead, "any right she may have had to direct and control how she is treated by physicians and nurses ceases with her death . . . unless some treatment provides medical benefits for others, as in the case of organ donation or a pregnant woman."[6] There are well-documented cases of pregnant women who had a neurologic catastrophe, and even in some circumstances were declared brain-dead, and yet were systemically supported so that the baby could be successfully delivered.[7,8] When the patient is pregnant and has knowingly continued the pregnancy before the neurologic catastrophe, signifying an interest in having children, the medical, ethical, and legal courses of action may be straightforward. In our case, there was no such evidence that the patient was inter-

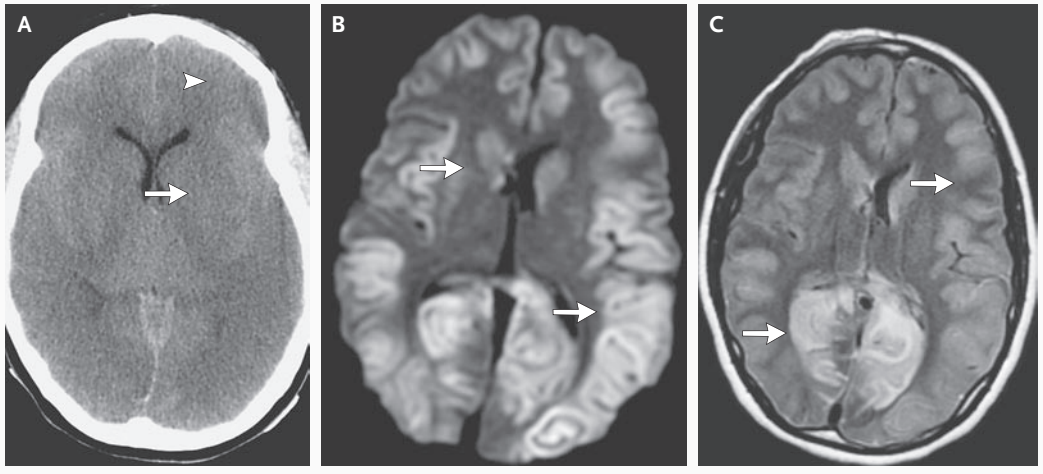

Figure 2. Brain Imaging on Day 4.

A CT scan of the brain (Panel A) shows cerebral edema, with patchy loss of gray–white differentiation (arrowhead) and low attenuation of the basal ganglia (arrow). Diffusion-weighted (Panel B) and fluid-attenuated inversion recovery (Panel C) images from repeat MRI on the same day show restricted water diffusion and cytotoxic edema (arrows) in the basal ganglia and cortex, particularly in the posterior regions, features consistent with severe hypoxic–ischemic injury.

ested in having children or that she would wish to do so posthumously.

Patients who have had neurologic catastrophes may become organ donors if they are brain-dead; if they are not brain-dead, they may become donors after cardiac death. Since patients cannot give consent in these circumstances, the family is required to give surrogate consent, ideally with an understanding and a consideration of what the patient would want done. Could such inferred consent be used in a similar fashion for gamete retrieval in this case? A consensus opinion argues that gamete retrieval for the purpose of creating new life is not the same as decisions about advance directives and that a stricter standard must be used.[9] In addition, in the circumstance of gamete retrieval, those providing evidence of the patient's wishes may have a potential conflict of interest.[10]

This patient's husband, his parents, and the patient's parents all consistently stated that proceeding with oocyte retrieval and posthumous reproduction was the course of action the patient would have wanted. However, there was no such written documentation by an unbiased third party. We communicated with the patient's primary gynecologist, who looked through all her notes on the patient's chart for documentation of pregnancy wishes, but none was present. Furthermore, this gynecologist stated that it was standard practice for her to ask her patients about pregnancy wishes. The fact that no wishes were documented was evidence, in her opinion, that the patient did not discuss this with her.

In this case, at the time of the family's request, the patient did not meet criteria for brain death, which are coma, apnea, and the complete lack of all clinical brain function, including brain-stem function.[11] Thus, the principles of consent for organ donation in a patient with brain death could not be applied, and the patient's comfort and well-being remained the primary responsibility of the neurology ICU team. We asked for consultation from the reproductive endocrinology and infertility and ethics services.

DISCUSSION OF MANAGEMENT

Dr. Aaron K. Styer: The family of this patient wanted us to retrieve oocytes from her for the purpose of posthumous reproduction. We considered the following ethical questions: Would the patient have consented to becoming a parent after her death? Would the patient have agreed to oocyte

retrieval, in vitro fertilization, and a gestational carrier in order to achieve this? How would a gestational carrier be identified?

POSTHUMOUS REPRODUCTION

There are three possible scenarios of posthumous reproduction. The most common involves fertilization, conception, and pregnancy before the death of a parent but delivery after the death. This typically occurs when the biologic father dies while the mother is pregnant and before delivery of the child. The second scenario involves assisted reproductive technology, in which sperm, oocytes, or embryos obtained after ovarian stimulation with exogenous gonadotropins, oocyte retrieval, and in vitro fertilization have been cryopreserved before the death of a partner, and the surviving partner wishes to use the cryopreserved gametes or embryos to create a pregnancy.[12] The most unusual scenario is perimortem retrieval of gametes for posthumous conception, as characterized by this case. This scenario involves perimortem oocyte retrieval, fertilization, conception, pregnancy, and delivery (with the use of a gestational carrier) after the death of the biologic mother. Although there are several examples of perimortem and postmortem sperm retrieval in the literature,[13,14] there were no reports of terminal oocyte retrieval to guide us in this clinical scenario.

Documenting the Patient's Consent

In this case, a potential biologic mother has sustained a life-threatening injury, is unable to discuss treatment options, and cannot consent to elective fertility therapy or confirm her desire to become a parent posthumously. The crucial portion of our consultation was to clearly delineate the patient's and her husband's desire to build a family. We were obligated to investigate inferred consent, since there were no advance directives or any other reliable evidence of the patient's reproductive wishes. Several meetings were held with members of the neurology ICU physician and nursing teams, the reproductive endocrinology and infertility staff, the ethics committee, the husband, the husband's parents, and the patient's parents. The husband confirmed that the patient was taking oral contraceptive pills, for the primary purpose of contraception. Neither he nor his wife had a current desire for children. He stated that the patient had voiced a desire to have children in the future, whereas he had not; however, he emphasized that this was something they had planned to discuss. After two meetings during the next 24 hours, we were unable to find clear evidence of the patient's desire to have children, now or in the future.

Future Participants

The most complex yet commonly overlooked aspects of perimortem and posthumous reproduction concern the future offspring and the gestational carrier. In cases such as this one, when the loss of a family member is inevitable, the creation of a symbolic replacement (a "commemorative child") of the deceased may soften the bereavement process.[15] Unfortunately, the social and emotional outcomes of a child born posthumously are unknown. The other participant, the gestational carrier, would carry the pregnancy after embryo transfer. The traditional indications for a gestational carrier include a contraindication for pregnancy and the lack of a functional uterus in the biologic mother. There was no legal, medical, or scientific precedent for using a gestational carrier in a case such as this. There was an initial suggestion that a sister of the patient could be a potential gestational carrier, but after extensive discussions, the family did not confirm the commitment of a sibling for this role.

Medical Issues Surrounding Oocyte Retrieval

There were several clinical concerns about performing an oocyte retrieval in this case. One was the possible detrimental effects of the patient's long-term use of oral contraceptives, which could have resulted in excessive ovarian suppression, a reduced response to exogenous gonadotropin therapy, and minimal oocyte yield.

A second concern was that the typical protocol for controlled ovarian hyperstimulation involves 7 to 10 days of gonadotropin stimulation before oocyte retrieval. The neurology ICU team would have needed to determine whether the patient could be supported for that length of time.

Finally, oocyte retrieval typically requires the patient to be supine in the dorsal lithotomy position during the procedure. This patient had cerebral edema and elevated intracranial pressure while in the upright position. Retrieving the oocytes while the patient was in the required position would have increased her intracranial pressure and thus her risk for brain herniation, possibly hastening her death.

During our discussions, the family inquired specifically about the options of embryo cryopreservation and oocyte cryopreservation. Dr. Toth will discuss these options.

CRYOPRESERVATION OF EMBRYOS AND OOCYTES

Dr. Thomas L. Toth: If oocytes could be harvested from this patient, the options would be to fertilize the oocytes and cryopreserve embryos or to cryopreserve unfertilized oocytes. The cryopreservation of male gametes and embryos has become a common technique for assisted reproduction, but oocyte cryopreservation has not.

This patient was married and therefore had a male partner, so embryo cryopreservation would have been an option. Typical live-birth rates that are associated with frozen embryos that have been thawed and transferred are approximately 29% among patients with underlying infertility.[16] However, there are many ethical, religious, and legal dilemmas surrounding cryopreservation and the long-term storage of human embryos.[17,18] Embryo cryopreservation has been forbidden or severely restricted in several countries.[19,20] In most states in this country, the embryo is considered neither person nor property, but in some states, the frozen embryo cannot be discarded, although this is not the case in Massachusetts. Although embryo cryopreservation would have been possible for this family, it poses a number of problems, since specific plans for a pregnancy were not in place and a gestational carrier had not been identified.

Cryopreservation of an unfertilized oocyte may be preferable in cases such as this, in which the future of a potential embryo is uncertain. Oocyte cryopreservation has been a goal for many years, since it has potential applications for women undergoing cancer chemotherapy[21] or for women who want to delay childbearing for personal or professional reasons and who do not have a sperm donor. However, cryopreservation of unfertilized human ova has proved much more difficult than that of the fertilized egg or embryo,[22] although success rates have been improving, especially during the past 5 years.[23] Although oocyte cryopreservation could have been an option for this patient, according to the institutional review board protocol, it is considered experimental by the American Society for Reproductive Medicine. Another technique under development is cryopreservation of ovarian tissue; also, preliminary efforts are being made that involve in vitro maturation of immature oocytes collected for cryopreservation and future fertility.[24-26]

The use of cryopreserved oocytes or embryos for posthumous reproduction raises legal considerations. We obtained advice from our hospital's legal counsel, who thought there was insufficient precedent to permit a definite statement about the correct legal decision in this situation. We have invited Professor Charles Kindregan to discuss the legal issues as they relate to this case.

Charles P. Kindregan, J.D.: I see three legal principles that are applicable in this case. The first is that the law does not force a person to become a parent without his or her consent. The second is that gametes cannot be retrieved from a person without his or her consent (with an exception that I will consider shortly). The third (called "placement" or "transfer") refers to the use of gametes or embryos to cause a pregnancy. Merely because a gamete has been harvested does not mean that the law favors its placement, unless the consent of the gamete provider is established. In this case, the retrieval and fertilization of the eggs of the incompetent patient could raise family disputes over who had the power to control their use, but if fertilized with the sperm of the husband, his decision would control. In Massachusetts, the statute would not bar the progenitor(s) of a cryopreserved embryo from deciding to destroy the embryo.

Since this patient cannot consent to anything at this time, the only guide we might have to her wishes would be her expressed consent before she became incompetent. Did she say anything, or execute a document, that would authorize the removal of her eggs in these circumstances? That expressed consent would be relatively rare. However, the Model Act Governing Assisted Reproductive Technology proposed by the American Bar Association says that there has to be expressed consent in either an electronic or a written record for gamete retrieval.[27]

What is the role of the husband? Consent may be obtained from the next of kin for medical and surgical procedures on an incompetent patient, but only for procedures that directly benefit the patient. Retrieval of gametes is a procedure that does not directly benefit the patient, unless she had specifically indicated that she wanted a child posthumously. If this woman were dead, the husband would have some legal rights (e.g., to consent to the removal of organs from his wife's body for

donation or to the disposition or burial of her body). But while she is alive, unless oocyte retrieval and posthumous conception were clearly her wish, I do not think he can legally consent. The potential grandparents (the patient's parents) have no legal standing in this case, as long as the husband is alive.

The Model Act[27] does propose an exception to the need for an incompetent patient's consent for gamete retrieval, invoking the principle of preserving the status quo. In this scenario, if it is asserted by someone with some standing that the patient did in fact consent but the record is not immediately available (e.g., if a lawyer in her home city knew of such a document) and if a physician determines that the only way of preserving the gametes is immediate harvest, the law would allow the removal of the gametes on an emergency basis, pending determination of consent. The future use of the gametes would be subject to a subsequent determination by a judge with competent jurisdiction that there was consent.

In a case of posthumous reproduction, we must also focus on the legal status of a potential child, which mainly concerns the rights of the child as an heir. The first type of posthumous reproduction — a child conceived while the parent was alive but born after the death of the parent — has long been recognized in the law. What is the legal status of a child conceived after the death of a parent? This scenario is relatively new to the law, so we have very little in the way of case law dealing with the status of such a child. In one case in Massachusetts,[28] the court ruled that when the sperm of a deceased husband is used by his widow to conceive a child for whom social security benefits are being claimed as his heir, the evidence must show not only that he was the genetic father of the child but also that he consented before his death to the posthumous use of his gametes.

Dr. Styer: As Professor Kindregan has emphasized, we relied on ascertaining inferred consent. The guidelines of the American Society for Reproductive Medicine ethics committee regarding posthumous reproduction[29] were helpful. The guideline states: "A spouse's request that sperm or ova be obtained terminally or soon after death without the prior consent or known wishes of the deceased spouse need not be honored."[29] In this case, in which there was no evidence of a plan for family building and no reasonable implied consent to undergo superovulation for the purpose of oocyte retrieval and posthumous reproduction, a unanimous decision was made by the multidisciplinary team not to honor the request for perimortem oocyte retrieval.

Dr. Greer: During the 48-hour period when these discussions occurred, the patient's neurologic status continued to deteriorate but the corneal reflex and cough remained present; she still did not meet the criteria for brain death. Since she had cough and corneal reflexes, apnea testing was not performed.

The assisted reproduction team determined that approximately 2 weeks would be required for the initiation of exogenous gonadotropin therapy and controlled ovarian hyperstimulation before attempting oocyte retrieval. In addition, the procedure itself would have required the patient to lie flat for an extended period, which would most likely have precipitated brain herniation and death. The neurology ICU team did not believe that it would be possible to keep this patient alive during the time required for the ovarian hyperstimulation. Furthermore, they thought that subjecting her to an operative procedure that would have precipitated her death was not in her best interest. Thus, for medical as well as ethical and legal reasons, we did not offer the procedure. The next day, after discussion with the family, comfort measures only were instituted, the patient was extubated again, and she died shortly thereafter.

This case was presented at the Fourth Annual Fredric and Alba Frigoletto Symposium, Obstetrics and Gynecology Grand Rounds, December 4, 2008.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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