Who is the best candidate for oocyte cryopreservation research?

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Clinical studies of oocyte cryopreservation have gained momentum within the recent years; however, no guidelines have yet been established for patient selection. This article discusses the controversial aspects of selecting candidates for oocyte cryopreservation research. (Fertil Steril® 2010;93:13–5. ©2010 by American Society for Reproductive Medicine.)

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Research on oocyte cryopreservation has gained momentum in the recent years, bringing further ethical discussion on the applicability of this technique to routine fertility preservation to establishment of donor egg banks. Oocyte cryopreservation does bring the promise of simplifying many aspects of assist reproduction. First, cryopreservation of surplus oocytes, rather than embryos, would avoid some of the social, legal, and ethical issues regarding embryo freezing. Second, it would widen the options for fertility preservation in young, single women for cancer and noncancer-related indications. Third, it can make third-party reproduction more practical for clinics, avoiding the effort that goes into synchronizing patients. Oocyte banks can also create more choice and reduce wait periods for recipients.

Oocyte banking, conversely, can increase the upfront cost for donor egg programs, as the donors will have to be paid before a recipient is available. Routine availability of egg banking for egg donation would also prompt further screening and quarantine requirements from the U.S. Food and Drug Administration, similar to the ones required for sperm banking. There is also the concern that the oocyte cryopreservation can be used prematurely to cash in on the desire of young professional women to delay their childbearing, before the technology reached its maturity. Others have argued that cancer patients maybe too vulnerable to undergo oocyte cryopreservation, because they are "too sick," and the technology has not yet been proven (1).

However, in the article by de Melo-Martin and Cholst (1), where some of the ethical issues surrounding oocyte cryopreservation research have been discussed, the investigators did not carefully consider the recent developments in oocyte cryopreservation. For example, in a recent meta-analysis published in this journal, we obtained raw data from all published manuscripts and abstracts, as well as some those that have not yet been published on pregnancies resulting from cryopreserved oocytes (2). The meta-analysis included data up to March 2006. In this work, we compared the slow freezing (SF) and vitrification (VF) success rates to each other and to SART data with unfrozen oocytes for the similar time period. We found that although SF success rates are considerably lower compared with VF, and IVF with fresh oocytes, VF success rates were close to those reported by SART with fresh oocytes. In fact, recent data from Europe (3) and Korea (4) corroborate the success with VF, pregnancy rates being 32.5% and 43.3% (mean age 33.7 ± 4.6), respectively. In the study by Antinori et al. (3), they cryopreserved surplus oocytes of the patients who underwent IVF with fresh oocytes and compared the success rates of the same group of patients with vitrified and nonvitrified oocytes. They found that the pregnancy (32.5% vs. 28.6%) and implantation (13.2% vs. 10.3%) success rates with vitrified oocytes were similar to the rates with fresh oocytes. However, the number of livebirths is still fewer with VF compared with SF, owing to more recent employment of this technique, and the follow-up on children born from cryopreserved oocytes is limited. Furthermore, it appears that a higher mean number of embryos are being transferred after IVF with vitrified oocytes compared with those frozen with the SF technique (2). This and selective reporting may be partially responsible for the seemingly better success with VF compared with SF. Nevertheless, there is hardly a question that overall success with oocyte cryopreservation is improving, and further research is warranted into this area.

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The most noble use of cryopreservation technologies is when an otherwise healthy person is faced with cancer treatment-induced premature ovarian failure and infertility. Because of its highly organized and scientific nature, the cancer field has made big strides, and cancer can hardly be considered a "death sentence" in this day and age. Instead, the current focus is on the quality of life past survival; the goal is not just to rescue the individual's life, but give back the life as it was before cancer. In contrast to the outdated opinion that the cancer patients are sick and vulnerable (1), today the people with cancer are among the most educated and well informed, thanks to the teaching initiatives by many patient and professional organizations. The level of their informedness is no more obvious than the fact that they seek fertility preservation. When no alternatives exist, and when the probability of cancer treatment-induced infertility is high, not offering these patients the option to participate in oocyte cryopreservation trials under institutional review board-approved protocols in our opinion is unethical, and would violate the "respect for persons" and "justice" principles.

To exclude cancer patients just because they may not use their cryopreserved oocytes as fast as we would like to answer our research questions, as it has been argued by de Melo- Martin and Cholst (1), is also a violation of the beneficience principle; the research participants should derive a benefit from the research participation. In the case of cancer patients, the minimal benefit is believed, which may help them cope with their cancer treatment better (5). Furthermore, it is not entirely accurate to state that cancer patients do not use their frozen oocytes in the short term. In the case of breast cancer, which is the most common cancer in reproductive-age women, we observed that many women wish to conceive shortly after completion of chemotherapy, especially with the help of gestational carriers (unpublished data). On the other hand, obtaining oocytes just for the purpose of laboratory research and not for fertility preservation would not be ethical in cancer patients, given that these oocytes cannot be replenished once these women experience ovarian failure.

De Melo-Martin and Cholst suggest that the most suitable group for oocyte freezing research is donor egg recipients "low" on the waiting list (1). This is one of the most coercive options. Offering recipients a fast track to the top of the list with the condition that they agree to use frozen–thawed oocytes violates many principles of ethics. Perhaps women with infertility and premature ovarian failure are among the most emotionally vulnerable, and such an approach would exploit their immense desire to have a child. It should be remembered that those patients who are on the waiting list went on that list with the purpose of having a baby. They have already established a physician–patient relationship, and their expectations have been solidified based on the information already given to them at the time of their initial consultation. If these patients are asked by the same physicians later on that whether they would wish to participate in an egg freezing research in exchange for a shorter wait, they may not be able to practice full autonomy as they have already been locked in. In addition, with that approach, the researchers would have created an incentive for themselves to keep the waiting list longer, whereas one of the primary goals of a donor egg program is to keep the waiting list to a minimal. This would violate the beneficence and justice principals. If all patients preferred to be fast tracked to the front of the waiting list, how would the researchers prioritize the research participants? Perhaps the recipient waiting list would simply turn into an egg-freezing research waiting list? Furthermore, although some argue that the subjects who participate in egg-freezing research should not be charged (1), in the setting of egg donation, they would be incurring significant charges for consultations, hormonal preparation, required diagnostic workup and blood work, and embryo transfer for a procedure with unknown success rates. This appears to be a violation of the justice principle.

Offering oocyte cryopreservation for social indications is among the most controversial subjects in fertility preservation. However, it is dubious to bar healthy women from participating in oocyte cryopreservation research for elective reasons on the basis of the risks involved with ovarian stimulation and oocyte retrieval. If one subscribes to that reasoning, one should also deny ovarian stimulation and egg retrievals to egg donors who have no clinical justification to assume the risks of these procedures. It is, however, risky to offer elective egg freezing outside the scope of research protocols and under commercial pretext as suggested by de Melo-Martin and Cholst (1), at least because of lack of data on fertility maintenance by that approach.

If the purpose of an egg-freezing research project is to simply determine the success rates of current technologies, there cannot be a better group than the single females who are about to lose their fertility because of cancer treatments. If alternatives are not acceptable to them (embryo cryopreservation with donor sperm, future egg donation, or adoption), and given the fact that many babies have already been born from frozen eggs, there cannot be an ethical question in offering this procedure to an individual who would otherwise have no chance of having a baby. Contrarily, if the purpose of research is to study molecular aspects of egg freezing, and the research would not serve to preserve fertility of the participant, cancer patients would not be suitable. In that case, there could be many other acceptable arrangements such as obtaining oocytes from women undergoing voluntary sterilization procedures with minimal ovarian stimulation.

Finally, because one of the premises of oocyte cryopreservation is to replace embryo freezing in an infertile population, data obtained from healthy donors or a uniform group of women without significant infertility problems will affect the conclusions of such research. Every effort should be made to test the oocyte cryopreservation technologies in a cross-section of women representative of the mix of patients that an average practitioner would encounter. To counsel infertility patients on oocyte cryopreservation based on research data obtained from a healthy population of egg donors may be

misleading, and may violate "respect for persons" principle. If oocyte cryopreservation is to become a standard technique in assisted reproductive technology, it has to be tested in the general infertile population.

Although oocyte cryopreservation does not seem to have consistent success, it must be remembered that in the early days of IVF and embryo freezing there were many failures, and many were doubtful about the future of these procedures. It is highly likely that oocyte cryopreservation is undergoing the same process, and an open-minded yet ethical approach is possible and perfectly compatible with the Hippocratic Oath.

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