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ONCOFERTILITY: PRESERVATION OF REPRODUCTIVE POTENTIAL

Ina N. Cholst*

INTRODUCTION

Contemporary cancer treatment in the developed world has enabled most young cancer patients to survive their disease. With successful treatment comes an opportunity—even a mandate—to address quality-of-life issues, including the future fertility of the survivors. Practice guidelines from both the American Society of Clinical Oncology and the American Society for Reproductive Medicine (ASRM) emphasize early discussion of fertility preservation options, prompt referral to an appropriate specialist, and the promotion of research and clinical trials to improve reproductive preservation.¹

This Article will review the medical options available for fertility preservation, including options for gamete donation, and will touch on the limits of medical technology to address social and cultural problems.

The diagnosis of cancer in a young person is a devastating event. Life itself is at stake. Furthermore, our current—albeit often successful—treatments for cancer, such as extirpative surgery, radiation, and chemotherapy, are painful, humiliating, and perilous ordeals.² An opportunistic infection may take advantage of the compromised immune system, or permanent damage may be done to the heart, kidneys, lungs, or brain—sometimes leading to death and sometimes leaving the individual alive but disabled. Compared to the possible effects on vital organs, the effects of surgery, radiation, and chemotherapy on the reproductive system are of lesser significance. Nonetheless, they have important psychological and social implications. Fortunately, the past two decades have seen significant advances in fertility preservation after cancer treatment.

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2. The medical slang for these treatments is “slash, burn, and poison.”
II. Overview of Fertility Preservation

Fertility preservation is a consideration for some, but not all, people undergoing cancer treatment. Fertility has been spared in more patients as treatments for cancer have become not only more successful, but also less toxic. For example, an invasive, potentially lethal malignant melanoma may be successfully treated by surgery alone (wide excision and lymph node removal) without impact on future fertility. Some chemotherapeutic agents are less toxic than others; sometimes gonads can be shielded from—or even moved out of—the radiation fields. However, treatment can compromise fertility when, for example, it includes surgery to remove reproductive organs, radiation fields that include the pelvis, or chemotherapy toxic to the gonads. The degree of compromise depends on factors including the age of the person with cancer, the field and dose of radiation, and the toxicity and dose of chemotherapy. Bone marrow transplants, toxic chemotherapeutic regimens designed to destroy all rapidly dividing cells (with the destroyed blood producing cells of the bone marrow restored with cells from a donor) that is generally reserved for aggressive cancers or cancer recurrence, invariably lead to infertility.

It is also important to emphasize that not all medically indicated fertility preservation is for cancer patients. Some people with benign disease require treatment that may be harmful to future fertility. For example, extensive benign surgery (for endometriosis or a benign ovarian or testicular tumor, for example) may result in infertility. Gonadotoxic chemotherapy may be indicated for lupus, rheumatoid arthritis, or ulcerative colitis. Bone marrow transplants may be performed in cases of serious noncancerous diseases such as Beta Thalassemia. Some women may have a known genetic predisposition to premature ovarian failure (such as Fragile X carriers and women with Turner’s Syndrome variants). Additionally, for some women who are BrCa carriers and who have a high risk of developing ovarian cancer, surgical removal of the ovaries at a young age may be recommended for prevention of ovarian cancer.

Finally, in the developed world, where education and career building take a long time, childbearing may be delayed and infertility may result. We see the technology developed for medical fertility preservation increasingly used to address these social needs.
A. Fertility Preservation for Men

Any quick overview of the medical means of fertility preservation will reveal a gender discrepancy.\textsuperscript{3} The technology to freeze (or cryopreserve) germ cells is not equal. Sperm are tiny cells. They have been successfully frozen, thawed, and used to create human pregnancies since 1953.\textsuperscript{4} The procedure requires little technology and is relatively inexpensive, with little or no medical risk and a high rate of success. Men facing therapy toxic to the testes, if appropriately counseled and informed, can choose to quickly freeze and “bank” sperm—usually millions of sperm—with low risk, relatively low cost, and without causing a delay in the initiation of cancer therapy. While there may not yet be universal access to sperm cryopreservation, it is within reach.

B. Fertility Preservation for Women

For women, the issues are different. The mature egg is a large cell that freezes only with difficulty. Generally, only one egg is formed each month, and it is formed only at a certain time. In order to produce more than a single egg, a woman must take strong injectable fertility drugs. Her eggs must be retrieved under anesthesia by a needle puncture of the ovary during in vitro fertilization (IVF). At each stage of the procedure, she encounters risks—from the hormones, from the impact on the ovaries caused by the production of multiple eggs, and from the puncture. IVF is stressful, emotionally taxing, and expensive. Finally, IVF takes time. The planned cancer treatment will be delayed between two to five weeks.

Even then, successful freezing of eggs is not a proven therapy. The mature egg is a large cell containing much water. If it is frozen in the same way that sperm are frozen, large ice crystals will form inside the egg. These ice crystals can damage delicate structures within the cell. Because water expands when it freezes (think of a can of soda in the freezer) the cell membrane of the egg can rupture. Thus, egg freezing is a delicate process. The water must be slowly removed from the egg, dehydrating it without damaging it. Antifreeze-like chemicals (cryoprotectants) help the dehydration process and also replace some of the water in the egg with substances that do not expand when frozen. Finally, methods have been developed to freeze the egg so

\begin{thebibliography}{99}
\bibitem{3} Tobias S. Köhler et al., Results from the Survey for Preservation of Adolescent Reproduction (SPARE) Study: Gender Disparity in Delivery of Fertility Preservation Message to Adolescents with Cancer, 28 J. ASSISTED REPROD. GENETICS 269 (2011).
\end{thebibliography}
quickly that small amounts of water still present in the egg can become solid without forming ice crystals (vitrification). A method for successfully freezing eggs has taken a long time to develop, is difficult to do, is dependent on the skill and experience of the operator, and should still be considered experimental. Only in the last few years have medical practitioners achieved reasonable success rates.

An alternative to egg freezing is the freezing of embryos (eggs that have previously been fertilized by sperm and have become embryos). Embryo freezing is not as difficult as egg freezing, it has a proven track record, and it is not considered experimental. However, embryo freezing requires that the young woman have a committed partner or use donor sperm. The procedure still involves fertility drugs and the retrieval of eggs and thus involves medical risk, treatment delays, and considerable expense. In addition, we add ethical, emotional, and legal problems when we move from the freezing of gametes to the creation (and potential disposition) of human embryos.

C. Fertility Preservation for Children

Unfortunately, none of the above techniques are applicable to preadolescent children. The current recourse for children is to surgically remove and freeze sections of the ovary or testes. This technology is the most experimental of all, and it raises serious concerns about parental rights, informed consent, and the emotional and social implications of the frozen tissue once it exists.

D. Refusing Fertility Preservation

The medical, legal, and psychological complexity of all these methods means that cancer patients may choose to demur, even when these methods have a reasonable statistical chance of success. The young cancer patient faces physical and emotional ordeals, as well as a daunting array of difficult choices to make in a short period. Sometimes one less procedure is a good choice. The importance of being a parent varies for individuals, and the importance of being a genetic parent varies as well. Hopefully the advisors—oncologists, reproductive endocrinologists, psychologists, lawyers, and others—can support not only patients who choose to pursue fertility preservation, but also those who choose to decline it.

III. **Donor Egg or Sperm as an Option**

For some people who wish to be parents, genetic connection to their children is not a major concern. In some circumstances, people would prefer to have nongenetically related children; for example, people who carry a deleterious gene that they prefer not to transmit. Thus, medical practitioners should be careful to include discussions, sometimes even detailed ones, of parenting alternatives to fertility preservation, including adoption and pregnancy through the use of donor eggs or sperm.

Use of a donor egg will not be everyone's cup of tea, and for some it will be morally, religiously, or emotionally out of the question. However, the use of a donor egg has much to offer those for whom the experience of parenthood is not delimited to the transmission of genes. It has been with us for a quarter of a century and has a track record of success.\(^7\) In the United States, for example, 18,121 donor oocyte cycles were performed in 2008, and 55% of recipients delivered a live baby after a single fresh donor oocyte transfer.\(^8\) The success rates are much higher—approaching 100%—if recipients undergo multiple attempts.\(^9\)

Some young women recently diagnosed with cancer will be carriers of cancer predisposition genes. Breast ovarian cancer syndromes (BrCa1 and BrCa2), retinoblastoma, and hereditary nonpolyposis colorectal cancer are only some examples.\(^10\) Without any doubt, more genes will be identified in the future. We have already seen that some of these young people will wish to have children who are not affected.\(^11\)

Technology—Preimplantation Genetic Diagnosis (PGD)

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11. See Claire Julian-Reynier et al., *Professionals Assess the Acceptability of Preimplantation Genetic Diagnosis and Prenatal Diagnosis for Managing Inherited Predisposition to Cancer*, 27 J. CLINICAL ONCOLOGY 4475 (2009); Chantal Lammens et al., *Attitude Towards Pre-Implantation Genetic Diagnosis for Hereditary Cancer*, 8 FAMILIAL CANCER 457, 461 (2009); M. Sagi et al., *Preimplantation Genetic Diagnosis for BRCA1/2—A Novel Clinical Experience*, 29 PRENATAL
with transfer of only unaffected embryos or prenatal diagnosis with termination of affected fetuses—offers one set of solutions. However, these are added interventions to what is already a technology-intensive, high-stress reproduction. Both procedures carry risks, and when the gene is dominant, half of the embryos or fetuses so conceived will be carriers. Thus, for example, everything else being equal, a young breast cancer patient carrying a BrCa gene will find that, if she wishes to preserve fertility through embryo freezing and have a non-affected child, the success rate for reproductive preservation will be half that of a similar young breast cancer patient without a genetic predisposition. Some recently diagnosed cancer patients who carry predisposition genes will see the use of a donor egg as a simpler solution: a proven, highly successful way to build a family and, at the same time, eliminate a deleterious gene.

The intent here is not to minimize the cultural and emotional meaning of genetic reproduction. I simply wish to emphasize that, for some people, using a donor egg—or adoption or child-free living—is the best possible solution to a difficult situation. Sometimes medical practitioners best help patients by expanding their gaze beyond the dazzle of what can be done to the simpler pleasures and satisfactions that surround us all the time and that are more easily within reach.

IV. CLINICAL PRACTICE OF OOCYTE DONATION

To this end, I believe it is important that advisors discuss oocyte donation from the beginning, and sometimes even in detail, along with other options for fertility preservation. Some patients may want to hear a lot about it, others may not. But it is all part of an ultimately hopeful message that, while life may be different, it will go on.

In the very near future, the majority of oocyte donation cycles may be done using cryopreserved and stored oocytes, similar to the current practice of sperm banks. At the time of this writing, though, most oocyte donation is done using fresh oocytes, with the cycles of donors and recipients synchronized. The mechanics of oocyte donation thus involve a number of steps: First, medical practitioners must recruit suitable donors and obtain informed consent from both parties. Second, medical practitioners stimulate the donor’s ovaries to obtain multiple eggs, prepare the recipient’s uterus hormonally for transfer, and synchronize it to the donor’s stimulation cycle. Finally, medical prac-

titioners inseminate the retrieved oocytes with the appropriate sperm and transfer the resulting embryos into the prepared recipient’s uterus.

A. Recruitment of Donors

Third-party reproduction is one of the most ethically complex aspects of reproductive health care. Some countries (such as Germany and Italy) do not allow oocyte donation at all. Among societies that do allow egg donation, even those with generally similar values may legislate donor recruitment very differently. Thus, some countries (such as Denmark, France, and Spain) have mandated anonymity while others (Austria, Netherlands, New Zealand, Sweden, Switzerland, United Kingdom, and the Australian state of Victoria) have mandated that donors be identifiable to their genetic offspring. Some countries (such as Canada and China) do not allow monetary compensation or strictly regulate it, while others regulate more loosely. In others (such as India and the United States), compensation is unregulated, though it may be constrained by professional guidelines and, of course, market forces.

In the United States, it is not surprising that there is much fewer regulation. U.S. law allows both anonymous and known donation, and the ASRM guidelines suggest that both are acceptable. Compensation is not regulated. A 2007 ASRM Ethics Committee Report set the following professional guidelines for compensation:


17. In August 2011, the Washington legislature enacted a law providing a child conceived through assisted reproduction with access to identifying information of the donor of the gametes so long as the donor has signed an affidavit of nondisclosure with the fertility clinic. WASH. REV. CODE § 26.26.750 (West, Westlaw through Apr. 6, 2012). The opt-out provision still allows both anonymous and known donation.

18. 2008 Guidelines, supra note 16.
[S]ums of $5,000 or more require justification and sums above $10,000 are not appropriate. . . .

... To avoid putting a price on human gametes or selectively valuing particular human traits, compensation should not vary according to the planned use of the oocytes (e.g., research or clinical care), the number or quality of oocytes retrieved, the outcome of prior donation cycles, or the donor's ethnic or other personal characteristics.19

Medical professionals screen and care for American oocyte donors. Many IVF programs recruit donors themselves. However, commercial, for-profit agencies (run mostly by business people, although sometimes by lawyers and occasionally by medical professionals) recruit a large, but difficult to quantify, proportion of American donors. There are about 150 of these independent egg donor agencies in the United States, and only about one third assented to sign agreements to abide by ASRM guidelines. Furthermore, a recent review of 53 websites of the assenting agencies found that, despite their signed agreements, 24.5% advertise compensation that does not follow ASRM guidelines.20

For many reasons, including both the relatively recent cultural pressure to delay childbearing and the comparative availability of egg donors, oocyte donation is a large and growing part of American fertility treatments. In light of this trend, it is particularly important to evaluate the policies, procedures, and ethics surrounding egg donation.

B. Trans-Border Reproductive Care

Practically speaking, donor recruitment is easier when anonymity is allowed and when donors can be compensated legally. Thus, in Europe, IVF centers performed 11,475 oocyte donation cycles in 2005, 3% of the total number of European IVF cycles done that year.21 By contrast, in the same year, IVF centers in the United States performed 16,161 oocyte donation cycles, 12% of all 2005 U.S. IVF cycles.22

It should be noted that over half of the European donor egg cycles performed in 2005—5,875 oocyte donation cycles—were performed in

one country: Spain.\textsuperscript{23} Spain has a strong tradition of anonymous tissue and organ donation and an ethical policy that allows for compensation for time and expenses. A quick perusal of websites reveals that the Spanish procedures include not only the trans-border reproductive care of recipients, but also the trans-border recruitment of donors.\textsuperscript{24}

Thus, differences in policy have fostered trans-border reproductive care.\textsuperscript{25} Not only do recipients travel for oocyte donation services, but centers also actively recruit donors across national borders. Not surprisingly, more prosperous countries generally recruit from less prosperous countries. For some donors, the small stipend, travel, meals, and hotel stay are enticing indeed, if not coercive.

In addition, the intended parents are increasingly staying in the comfort of their own homes while gametes and embryos do the international travel. For example, an intended father’s sperm may be flown from Canada to the United States and used to create embryos using an American egg donor, with the resulting embryos frozen and flown back to Canada to be transferred into the Canadian recipient’s womb.

\section*{C. Anonymous Versus Known Donation}

Presently, most oocyte donation worldwide is anonymous. However, family and known donation is the best choice for some recipients. This may be especially true for some cancer survivors. A sister, cousin, or a friend may have good reason to decide to donate to a survivor and may derive great satisfaction from the action. For the recipient, the opportunity to have a child who is genetically related to her family (such as a sister or cousin) or the kindness of the gift can also make it a good choice.

However, family and known donation also carry higher risks of coercion and higher risks of complicated family dynamics. This may be particularly true when the recipient is a cancer survivor. For these reasons, ASRM recommends psychological screening of all involved

\textsuperscript{23} Andersen et al., supra note 21, at 1269 tbl.1.

\textsuperscript{24} See Giles Tremlett, Spain Becomes the Destination of Choice for Fertility Tourists from Britain, \textit{GUARDIAN}, May 12, 2006, at 16; Claire Murphy, Rush to Spain for IVF Is Up 100pc., \textit{HERALD.IE} (Sept. 9, 2009), http://www.herald.ie/news/rush-to-spain-for-ivf-is-up-100pc-1881428.html.

parties—the prospective donor, recipient, and their respective partners—before proceeding with a known donation.\footnote{26}{2008 Guidelines, supra note 16; Ethics Comm. of the ASRM, Family Members as Gamete Donors and Surrogates, 80 Fertility & Sterility 1124 (2003).}

Finally, “identity release” refers to donation that is anonymous at the time of the donation, but in which donor-conceived persons, on reaching adulthood, can request identifying information about their donor. Generally, identity release agreements in the United States are voluntary, and their legal status is not well defined.\footnote{27}{But see WASH. REV. CODE § 26.26.750 (West, Westlaw through Apr. 6, 2012).}

D. Screening Procedures

1. Infectious Disease Screening of Donors

The FDA regulations have improved some aspects of the safety of oocyte donation. However, the regulated tests, which are extensive and expensive, are biased toward the safety of the recipient versus that of the donor or the donor-conceived child. For example, there are no U.S. regulations concerning genetic testing of donors or issues of donor safety during stimulation.

2. Genetic Screening

Genetic screening of oocyte donors is directed by guidelines rather than laws, and the guidelines are minimal and vague, likely by intention. The only test specifically recommended for all donors is cystic fibrosis.\footnote{29}{2008 Guidelines, supra note 16.}
Even so, some evidence suggests that IVF programs’ compliance with these minimal guidelines varies widely. In a 1999 survey, only 22% of responding IVF programs tested oocyte donors for cystic fibrosis.\footnote{30}{Vivian Lewis et al., Survey of Genetic Screening for Oocyte Donors, 71 Fertility & Sterility 278, 279 (1999).}
Even in 2004, a survey found that only 19.5% of responding IVF clinics met ASRM guidelines for genetic screening of oocyte donors and that 25% of responding clinics did no genetic screening at all.\footnote{31}{Z. Powis et al., Genetic Screening of Oocyte Donors, 82 Fertility & Sterility S188, S188 (Supp. II 2004).}
It may make sense for genetic screening guidelines to be vague. The field of genetics is progressing rapidly, and recommended screening tests change very quickly. On the other hand, the absence of strict guidelines does not decrease practitioners' responsibility to act in the best interests of the donor, the recipient parents, and most of all, the potential child. The testing of oocyte donors and the dissemination of information so acquired carry ethical, medical, and psychological implications. Thus, ideally, a genetic counselor should counsel every prospective oocyte donor before testing and should be the person who conveys these test results when positive.32

3. Psychological Screening

Psychological evaluation of the donor, the recipient, and when applicable, their families can be extremely useful. Third-party reproduction is a complex process with potential long-term repercussions. Participants have both the right and the responsibility to explore the consequences and emotions that accompany these decisions. Advisors can listen, explore feelings, support, and educate donors and recipients in a way that helps all parties to make choices that are right for them. Psychological consultation is very helpful for all recipients of donated oocytes and is specifically recommended for recipients considering known donation.33 These sessions are, at least partly, “psycho-education.”

E. Matching of Donors and Recipients

Although there has been little scientific inquiry into the criteria that make for success in families created with donated gametes, current practice has widely included phenotypic matching. Thus, most programs worldwide include an attempt to match donors and recipients using criteria such as coloration, height, and ethnic background. In fact, most recipients (and donors) express interest in some degree of phenotypic matching.

However, European donor oocyte programs are generally less concerned about phenotypic matching than American ones. In addition, several societal trends suggest that phenotypic matching may assume a lesser role in the future. First, adoption practices have increasingly relinquished proscriptions against interfaith and interracial adop-

33. 2008 Guidelines, supra note 16; Ethics Comm. of the ASRM, supra note 26.
Some of these historical proscriptions have come to seem old-fashioned or even racist. Second, there is an increased tendency for, and increased professional advice in favor of, disclosure of means of origin to individuals conceived through gamete donation. Third, there is a growing interest (some of it legally mandated) toward identity release donation. These trends decrease the need for secrecy that may have been a part of phenotypic matching. Finally, families have become more diverse and the concept of a family has been expanded. All of these tendencies together may lessen the importance of phenotypic matching in the future. Nonetheless, at the present time, most recipients (and many donors) express interest in at least some degree of phenotypic matching.

F. Care of the Oocyte Donor

The oocyte donor is traditionally a young healthy person who takes on medical risks without receiving medical benefits. From an ethical point of view, she is more like a research subject than a patient. The aim of the physician caring for the oocyte donor should be to reduce the rate of complications to as near to zero as possible.

V. Conclusion

Medical practitioners in the field of oncofertility have an understandable desire to be optimistic and encouraging to their young cancer patients. However, these patients also need support as they adjust to the very real losses that accompany a cancer diagnosis. These losses range from the loss of both innocence and the feeling of invulnerability to the physical losses that accompany surgery, chemotherapy, and radiation; to the changes in life expectations, including potential loss of reproductive options; and, finally, to the potential loss of life itself. A focus on technological solutions alone for quality-of-

35. 2008 Guidelines, supra note 16.
36. See generally Andrea Kalfoglou, Navigating Conflict of Interest in Oocyte Donation, 1 Am. J. Bioethics W-1 (2001).
life issues may deny the newly diagnosed cancer patient the opportunity to reconsider values and to put life events in perspective.

At moments of great loss, a certain clarity may come to us. The minutiae of daily life, once so urgent and so critical, are suddenly set in perspective against the impermanence of all things. We know that genetic reproduction is important to all living things, but we also know that the genetic imprint that an individual makes is erased in a few generations. Some of the lives that we look to for inspiration and that have contributed so much to the world have left no genetic mark. Those who have raised children know that they are ours only for a brief time and that the mark of our good parenting is that they leave us. We can impart some of this to our patients. We can also, by not offering false promises or over-emphasizing the importance of “fixing” everything, allow patients to discover some of these truths on their own.