
Ethical Discussions in Approaching Fertility Preservation

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Abstract

Cancer survivors may wish to become parents, if they have lost their reproductive function, by using previously stored gametes or gonadal tissue. Fertility preservation serves such a wide range of medico-social circumstances, some quite unique, that patient care requires an individualized and multidisciplinary approach. In particular, fertility specialists offering fertility preservation options to cancer patients should be properly trained and knowledgeable to discuss patient's treatment plan, prognosis, as well as unusual health risks for future offspring and the potential harmful effects of pregnancy. Overall, there should be no ethical objections to offer these services since they are offered with the scope of preserving future fertility. However, in practice, there are objections: many options are still experimental; posthumous use of stored tissue or gametes carries some legal issues; concerns exist about the welfare of offspring resulting from an expected shortened life span of the parent; concerns exist about the welfare of children born using gametes frozen after chemotherapy already started; and reseeded of cancer is possible after transplanting cryopreserved tissue.

Keywords

Autonomy • Beneficence • Nonmaleficence • Justice • Veracity • Informed consent • Ethical principles in fertility preservation

Ethical Principles: General Considerations

Before discussing the ethical dilemmas associated with fertility preservation, it is necessary to describe the ethical constructs most commonly used to formulate guidelines. It is also important

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to realize that any policy or guideline needs to have a certain degree of built-in flexibility, because natural rights and human dignity, in the context of creating families, cannot always be clearly defined. It is understandably difficult to balance an individual right to reproductive autonomy and privacy with the societal obligations to protect the potentiality of life.

The most common ethical norms used to conduct ethical analyses are based on the five principle-based ethics. These principles are autonomy, beneficence, nonmaleficence, justice, and veracity.

Autonomy

Autonomy or *respect* for persons, acknowledges an individual's right to hold views, makes choices and takes actions on the basis of personal values and beliefs. This principle is at the base of informed consent and respect for privacy. In the reproductive field, this principle is the basis for reproductive rights and reproductive choices. Some examples: Should fertility preservation be offered to a woman who knows that her prognosis for long-term survival is uncertain? Should a widower be permitted to use embryos frozen while his wife was alive, and to use a member of his wife's family as a gestational carrier?

As to each question posed, the formulation of guidelines must take into account the right of an individual to decide, with the understanding that procreative liberty has some limits when these rights conflict with the child's best interest. In formulating an informed consent, it is therefore important to anticipate these scenarios and request disposal directives for cryopreserved reproductive tissue or gametes or embryos.

Beneficence

Beneficence represents the obligation to promote the patient's well-being. Beneficence represents the balancing of risks and benefits of an intervention. It is the principle that dictates that subjects

be protected from harm and that efforts be taken to secure their well-being. It may conflict with the principle of autonomy. For example, the woman with breast cancer that requests controlled ovarian hyperstimulation despite being positive for estrogen and progesterone receptors and carrying breast cancer gene mutations.

Nonmaleficence

Nonmaleficence is the obligation to "do no harm" also known by its original Latin expression of "primum non nocere," which needs to be balanced with the principle of autonomy. Both beneficence and nonmaleficence may overlap, for example, a patient who wants to postpone the beginning of chemotherapy treatments and, contrary to the oncologist opinion, insists in undergoing fertility preservation.

Justice

Justice concerns fairness and equity, i.e., the need to be fair in sharing the burden (costs) and the distribution (benefits) of resources to all members of the community. In particular, the concept of *distributive justice* is often applied to situations requiring a decision about the equitable allocation of resources. The current practice of IVF in general and fertility preservation in particular however, is not fair. Since many options to preserve fertility are experimental, insurance companies are not covering these services. Particularly for low income people, these services are only offered on institutional grants or on charitable basis; consequently, most patients are unable to have access to these services.

Veracity

The principle of *veracity* stipulates that a provider always tells the truth to his/her patient and avoids the exploitation of vulnerable populations.

Fertility Preservation for Cancer: Ethical Considerations

Ethical Consideration for Fertility Preservation in Adults

Fertility preservation developed first with the intent of preserving the potential for genetic parenthood in adults or children at risk of sterility due to chemo- or radiotherapy. Today, many young patients with cancer are surviving (the 5-year survival rates for Caucasian and Hispanic American women have increased for Hodgkin's lymphoma from 86 to 98% in the quarter century to the year 2000, and for breast cancer from 78 to 91%) [1]. At the same time, diagnoses of some malignant diseases have become more prevalent (e.g., breast and testicular cancer) [2]. The net effect has been an increase in numbers of patients in their reproductive years at risk of sterilization or early menopause [1]. As a result of this progress, quality of life issues after cancer is becoming increasingly more important and protection of fertility is a preeminent quality of life paradigm.

Although there are many strategies to preserve fertility, embryo freezing and sperm freezing are the only established options while all the others are still considered experimental; experimental procedures include oocyte freezing, ovarian tissue or whole ovary freezing, and in vitro maturation of oocytes or in vitro folliculogenesis.

Likewise, for men, when the option of semen cryopreservation is not available as for prepubertal boys, the harvesting and isolation of spermatogonial cells from testicular biopsies or the freezing of testicular tissue for later transplantation or even xenografting, are being tested but remain highly experimental.

When using experimental techniques, the informed consent is essential and both women and men have the right to know all options concerning fertility preservation and their implications including the risks and costs involved. In addition, experimental procedures are considered under the umbrella of research protocols and thus should also be reviewed and approved by institutional review boards.

Providing thorough informed consent in recruiting persons to participate in research is the foundation for the ethical conduct of research. It is based on three components: adequate, comprehensible information; a competent decision-maker; and a voluntary decision process.

Patients have the right to know what will happen if they or any children that are created are injured or disabled, including issues related to health insurance and compensation. Providers obtaining consents for experimental techniques must focus not simply on disclosure but also on effective communication and comprehension. The use of quizzes and documenting responses to questions after information is presented are effective tools to assist in demonstrating that patients understand the experimental or innovative nature of some modes of fertility preservation. Consent to the use of one of the many therapeutic strategies may require involving a surrogate decision maker in the case of young children or mentally impaired persons.

From an ethical standpoint, the key reason for pursuing fertility preservation is to restore personal autonomy to those who might, in the future, become unable to conceive [3, 4]. The presentation of risk information is complicated by the fact that both the adult and their offspring may be involved. A core principle of medical ethics is to do no harm. Ideally, the decision about who is candidate for fertility preservation should be rendered by a team including a medical oncologist, a reproductive endocrinologist, a pathologist and a psychologist, all guided by written protocols that can be shared with patients [4]. Patients should not be provided with false hopes. Alternative plans including no intervention with the prospect of adoption or childlessness should also be a part of the discussion. Equity or ownership interests of caregivers in novel technologies utilized in research must be disclosed to potential subjects. It is reasonable in the absence of grant funds to seek reimbursement from patients to cover the expenses of the research, but there should be no charge for clinical fees until the experimental options have been proven safe and effective.

Concerns about the children of mothers affected by cancer fall into three categories: first, the possible shortened life expectancy of mothers

should cancer recur meaning that children could be orphaned at an early age. Another is the health of the mothers' posttreatment and the fear that they will not have the energy and stamina to care for their children. The third is the health of the children born after the thawing and retransplantation of ovarian cortical tissue or from the in vitro maturation of follicles or oocytes. Therefore, in the absence of any long-term follow-up studies or registries, it is imperative that those involved with these techniques continue monitoring each of these issues. It also means that novel forms of fertility preservation involving, for example, ovarian and testicular harvesting for freezing should be performed only in a few specialized centers working with proper IRB permission, the capacity for follow-up with subjects, adequate social service support, and subjects signing ethics committee approved consents.

Ethical Consideration for Fertility Preservation in Children

Impaired future fertility is a possible consequence of exposure to cancer therapies even for children. This risk may be difficult for children to conceptualize, but potentially traumatic to them when they become adults.

Since the modalities that are available to children for preserving their fertility are limited by their sexual immaturity, they are all considered experimental. For prepubertal boys who cannot produce mature sperm, harvesting and cryopreservation of testicular stem cells with the hope of future autologous transplantation, or in vitro maturation, represent potential methods of fertility preservation. For girls, isolation and cryopreservation of ovarian cortical strips/primordial follicles followed by in vitro maturation of gametes, when fertility is desired, is a possible option. Extensive research is still required to refine these modalities to safely offer them to patients as therapies [4].

Again, assisted reproductive technologies must be scrutinized on the basis of efficacy and safety and they must be subjected to rigorous ethical deliberation by independent review board committees before they can be offered. The

modalities involved in fertility preservation of young children are no exception to these rules.

In addition to ensuring that the basis for offering the intervention is scientifically sound, the execution of the intervention must be deemed ethically sound. This determination requires that the intervention in question be evaluated within an ethical framework that considers it in terms of beneficence, respect for persons (autonomy), and justice [5].

It can be argued that fertility preservation aimed at children is ethical because it prevents morbidity (reproductive and psychosocial) and it safeguards their reproductive autonomy [6]. Therefore, the main ethical question concerns the process and the techniques necessary to protect fertility. The special situation of children as research subjects and at the same time patients makes the provider open to potential abuse of the technologies in an impetus to have a breakthrough [6, 7]. To avoid this risk, it is prudent to have multiple caregivers involved in the consent process.

Programs must make every effort to minimize financial barriers to access for children and to work with patient advocacy groups to seek coverage for children and families who cannot afford to participate in fertility treatment or research. Research involved in childhood fertility preservation should be conducted on patients who could experience personal benefit from the research, eliminating the prospect of exploitation for the gain of others.

Children represent a unique and vulnerable population with respect to medical research. They have diminished autonomy, diminished capacity to understand the risks and benefits of research objectives and lack the ability to provide consent for research studies. As a result, they require special protection against potential violation of their rights that may occur during research investigations [4, 5]. Until very recently, institutional attitudes impeded significant participation by children in medical research for the fear of exploitation.

Children should not be exploited to participate in pediatric research, nor should they be deprived of the benefits research has to offer because of their vulnerable status. With respect to childhood fertility preservation, proper attainment of informed consent from a legally authorized representative (i.e., parent or guardian) and of

childhood assent must be ensured [4, 5]. Assent – the active affirmation by the research subject – can be obtained from incompetent minors and it should be obtained from children whenever possible. While the benefits of gamete cryopreservation are promising, they are largely unquantifiable because human data on the survival of gametes after the freeze-thaw-transplant process are limited. Until more data become available providers cannot tell patients what percentage of gametes will survive and what the probability of conception is, and must not provide patients with false hope. Alternatives to gamete cryopreservation should be discussed and patients should be given the option of no intervention [6]. Barriers to the consent process for fertility preservation interventions may develop. While parents may be competent to consent for their children, the scenario is very complex clinically and emotionally [7].

It has been suggested that to overcome some of the practical obstacles involved in the consent process, it should be performed in stages [8]. If a two-stage process is adopted, the issues of gonadal harvesting/storage and gamete manipulation can be handled as two separate topics at distinct time points. The decision to harvest gametes would be made at the time of cancer diagnosis and consent for the procedure would be left to parents/guardians. The decision of whether to use the gametes after they have been isolated can then be made at a future point by the child, when adulthood is reached. At such a point in time, the young patient would be better able to express personal preferences about the handling of the tissue based on an enhanced capacity to understand the ramifications of the possible medical interventions available at that time.

Summary of Clinical Outcomes Within the Context of Informed Consent

Health of Children Born from Oocyte Cryopreservation

Many patients with cancer are choosing the option of oocyte cryopreservation as a fertility preservation strategy. However, despite the birth of

hundreds of children, the ASRM still considers this technology as experimental [9, 10]. Recent summary reports have documented that babies born from the use of cryopreserved oocytes by vitrification methods (outcome of 200 infants born) are not at higher risk for congenital malformations and not at an increased risk of adverse perinatal outcome [9].

Another study summarized 58 reports (1986–2008) that included 609 live born babies (308 from slow freezing, 289 from vitrification, and 12 from both methods) [10]. In addition, 327 other live births were verified. Of the total 936 infants, 1.3% [12] had a birth anomaly: three ventricular septal defects, one choanal and one biliary atresia, one Rubinstein-Taybi syndrome, one Arnold-Chiari syndrome, one cleft palate, three clubfoot, and one skin hemangioma. On the whole, these observations demonstrate that, so far, children conceived from oocyte freezing are healthy and not at an increased risk of adverse outcome.

Health of Children Born from Cryopreserved Embryos

The first prospective study aimed at assessing the postnatal growth and development of children born from cryopreserved embryos was carried out in 1995 [11]. The findings of that study were that children conceived from cryopreservation had a lower mean birth weight and mean gestational age, but the incidence of minor and major congenital malformations was similar to that of a control group and, furthermore, these children performed on a similar functional level as the control group.

A recent systematic review evaluated the medical outcome of children born after cryopreservation, slow freezing and vitrification of early cleavage stage embryos, blastocysts and oocytes during the years 1984–2008 [12]. Most studies found comparable malformation rates between frozen and fresh ART cycles and overall data concerning infant outcome and psychological well-being after cryopreservation of embryos were reassuring. As for oocyte cryopreservation data, the number of properly controlled follow-up

studies of neonatal outcome after embryo cryopreservation is still somewhat limited. Long-term follow-up studies for all cryopreservation techniques are also essential.

Health of Children Born from Frozen/Retransplanted Human Ovarian Tissue

Ovarian cryopreservation and transplantation techniques, either as heterotopic or orthotopic allografts, are becoming steadily more successful. So far, 14 children have been born worldwide as a result of transplanting frozen/thawed ovarian tissue [13–17]. The very first was born in Belgium in 2004 [13] and the subsequent births have been reported in Israel in 2005 [14], Denmark [15, 16], Spain (birth of twins) [17], and in the USA [18]. One of the patients from Denmark gave birth to two children [19]. Recently, [20] birth from a noncancer patient with thawed ovarian transplants grafted in the pelvic sidewall was reported in France.

Many births have also been reported by using fresh ovarian transplants between monozygotic twins [18]. Ten monozygotic twin pairs requested ovarian transplantation and nine have undergone the procedure (some after failing oocyte donation from their sisters) with cryopreservation of spare tissue. All recipients reinitiated ovulatory menstrual cycles and showed normal day 3 serum FSH levels by 77–142 days. Seven conceived naturally (three twice). Currently, seven healthy babies have been delivered out of ten pregnancies using fresh ovarian tissue transplants. The oldest transplant ceased functioning by 3 years, but this patient conceived again after a second transplant using spare frozen-thawed tissue. Very recently, a birth from the transplant of a whole fresh ovary between two sisters HLA-compatible has also been reported [21].

In summary, when providing an informed consent, it is perfectly legitimate to offer these encouraging but still preliminary results. International fertility preservation society and national special interest groups in both USA and Europe are also closely monitoring the field with follow-up registry.

Conclusions

Cancer survivors may wish to become parents, if they have lost their reproductive function, by using previously stored gametes or gonadal tissue. Fertility preservation serves such a wide range of medico-social circumstances, some quite unique, that patient care requires an individualized and multidisciplinary approach. In particular, fertility specialists offering fertility preservation options to cancer patients should be properly trained and knowledgeable to discuss patient's treatment plan, prognosis, as well as unusual health risks for future offspring and the potential harmful effects of pregnancy.

Overall, there should be no ethical objections to offer these services since they are offered with the scope of preserving future fertility.

However, in practice, there are objections:

1. The options available, except sperm storage and embryo cryopreservation, are all experimental. There is a lack of extended follow-ups about their safety.
2. Posthumous use of stored tissue or gametes. When gametes or tissue is stored for later use, written directives for posthumous use may be given effect, and subsequently born children may be recognized as legal offspring of the deceased. Postmortem reproduction with stored gametes or tissue should be honored when the deceased has given specific consent; programs storing gametes, embryos, or gonadic tissue from cancer patients should inform the options for making advance directives for future use. Whether posthumously conceived or implanted offspring will inherit property from the deceased or will qualify for government benefits will depend on the law of the jurisdiction in which death occurs [22].
3. Concerns about the welfare of offspring resulting from an expected shortened life span of the parent. This concern, however, should not be a sufficient reason to deny cancer survivors assistance in reproducing. Although the effect of the early loss of a parent on a child is regrettable, many children experience stress and sorrow from other circumstances of their birth.

The risk that a cancer survivor will die sooner than other parents does not impose an appreciably different burden than the other causes of suffering and unhappiness that persons face in their lives. Protecting such children by preventing their birth altogether is not a reasonable ground for denying cancer survivors' chance to reproduce [22].

4. Concerns about the welfare of children born using gametes frozen after chemotherapy already started.

5. Reseeding of cancer after transplanting cryopreserved tissue.

Future successful production of germ cells de novo could have applications in fertility preservation. Sterile gonads would no longer limit reproduction as it will be possible to produce artificial gametes by dedifferentiation of somatic cells.

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