

## REVIEW

# Should Ovarian Cryopreservation be Offered to Girls With Cancer

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Current therapy of childhood cancer makes long-term survival a realistic outcome for most patients. However, some treatment regimens entail a significant risk of infertility. No established method for preservation of female fertility is currently available. Ovarian cryopreservation is an experimental technology that is being offered with increasing frequency to women undergoing cancer therapy. It has not yet been reported in children and adolescent girls. The aim of this review is to stimulate discussion on the possibility of performing

ovarian cryopreservation in pre-menarcheal girls in advance of therapies that may induce ovarian failure. We present a multi-disciplinary discussion of the risks and benefits associated with the procedure and propose guidelines for its implementation. We propose that all girls about to receive treatment that has a high risk for infertility be offered consultation about the possibility of ovarian cryopreservation. *Pediatr Blood Cancer*

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## INTRODUCTION

The majority of children and adolescents with cancer can be expected to be cured and become long-term survivors [1]. In this context, quality of life issues are assuming increasing importance in the planning and delivery of cancer treatment in children [2]. The effects of chemotherapy and radiotherapy on future fertility are of paramount concern for patients with cancer and their families. Many treatment regimens in pediatric oncology are potentially gonadotoxic and may thus negatively affect future childbearing potential [3,4]. Methods to reduce treatment-related gonadotoxicity are needed. Cryopreservation of sperm is an effective method in fertility preservation that is offered to pre- and post-adolescent males [5,6]. Female gametes are not readily amenable to cryopreservation. In vitro fertilization (IVF) may be offered to young women, especially if married, and if cancer treatment can be postponed. Retrieved oocytes may be fertilized in vitro and then cryopreserved to enable future pregnancy when ovarian failure is anticipated. IVF, however, is not a practical option for many female cancer patients. For this group of patients, alternative methods of fertility preservation should be sought.

Ovarian cortex cryopreservation is an experimental technology with some success in animal, and recently in human transplantations [7,8]. Although the technique remains investigational, it is being increasingly offered to women undergoing cancer treatment. In present day pediatric oncology practice, fertility preservation is rarely, if ever, a viable option for pre-adolescent female cancer patients. Moreover, there is no uniform approach or standard of practice concerning fertility preservation in children undergoing cancer treatment [9]. There is a pressing need to change this situation. Female pediatric patients and their families should be counseled regarding side effects of chemotherapy

on ovarian function, as well as on methods to limit this damage.

We raise the possibility of offering oophorectomy and ovarian cryopreservation for pre-menarcheal girls in advance of therapies that could induce ovarian failure. This discussion was prompted by a case of a 9-year-old girl who was about to undergo whole abdomen radiation therapy for Stage III Wilms' tumor. In the course of the dialog with the patient's parents on issues of potential long-term toxicities of treatment, the issue of fertility preservation was raised, and specifically the possibility of ovarian preservation. In light of the complex medical and bioethical issues involved in such an approach, we convened a multi-disciplinary team of specialists in pediatric hematology-oncology, reproductive endocrinology and infertility, pediatric surgery, pediatric anesthesiology, and bioethics to critically explore the feasibility of offering ovarian tissue preservation to pre-adolescent girls with cancer. The purpose of this article is to present the results of this multi-disciplinary discussion and to offer

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guidelines for offering ovarian cryopreservation to girls undergoing cancer therapy.

## PEDIATRIC HEMATOLOGY-ONCOLOGY PERSPECTIVE

In the last three decades significant progress has been made in the treatment of childhood cancer. Current estimates are that two thirds of children diagnosed with cancer will be cured [10,11]. For some common pediatric cancers such as Wilms tumor, Hodgkin disease (HD), and B-cell non-Hodgkin lymphoma (B-NHL) cure rates approach 90% [12–14]. These high cure rates result in a growing number of children who will become healthy long-term cancer survivors [15]. Quality of life issues will become the major concern for these individuals. Among these, future fertility will be paramount.

These high cure rates in pediatric malignancies are achieved, in some circumstances, at a great cost of long-term organ toxicity. For most childhood cancers there is a clear relationship between the intensity of chemotherapy administered and the probability of cure [16]. The most successful chemotherapy regimens used in pediatric oncology utilize multi-drug combinations given in high doses and in intensive schedules. Some of these cytotoxic drugs, especially the alkylating agents, produce damage to both male and female gonadal tissue [17]. Some pediatric chemotherapy regimens such as MOPP for HD, and high-dose cyclophosphamide and busulfan for bone marrow transplantation, cause sterility in a significant number of patients [18–21].

Other regimens such as high dose cyclophosphamide for B-NHL and Ewing sarcoma, are associated with a significant risk for fertility impairment. No comprehensive data exists on the exact rates of fertility impairment associated with current pediatric oncology therapeutic regimens. Hence, it is virtually impossible to give the patient or his/her parents an accurate assessment of the risk to fertility. It is, however possible to define treatment regimens associated with either a low or high risk of infertility [22]. It can thus be predicted that a significant number of long-term survivors will have severely reduced fertility [23,24].

Pediatric oncologists have been aware of this dilemma for many years and several approaches have been developed to reduce treatment-related gonadotoxicity. The ideal approach is to design treatment regimens that will maintain high cure rates while decreasing or eliminating agents with significant tissue toxicity. This approach is the driving force behind the current concept being tested in clinical trials for pediatric HD. Boys with HD, who are more susceptible to the sterilizing effects of chemotherapy, are treated with lower doses of chemotherapy combined with radiation. Conversely, girls, who have a prohibitively high risk of radiation-induced secondary malignancies (especially breast cancer) and are less prone to chemotherapy-induced gonadal damage, are

treated with more intensive chemotherapy but without radiation when feasible [25,26].

Reduced chemotherapy and/or radiation therapy in diseases with high cure rates such as HD is conceptually appealing and may be efficacious. This approach, however, is not feasible in many pediatric malignancies. For example, high-risk acute lymphoblastic leukemia, neuroblastoma, Ewing sarcoma, high-risk rhabdomyosarcoma, and high grade B-cell lymphoma are all treated with dose-intensive schedules that rely heavily on the use of alkylating agents [14,27–29]. Most patients treated with these regimens are expected to become long-term survivors, *and* to experience significant gonadal damage. Female patients with stage III Wilms tumor who receive whole-abdomen radiation therapy are also at a high risk for fertility impairment [30]. Unfortunately, it is unlikely that these regimens will be supplanted in the foreseeable future by equally effective but less gonadotoxic regimens. The same applies to pediatric patients undergoing bone marrow transplantation, the overwhelming majority of whom will develop gonadal failure [21]. Therefore, it is vitally important to develop effective approaches to fertility preservation that may be offered to pre-adolescent children who are about to receive cancer treatment that is associated with a high risk of gonadal damage.

## REPRODUCTIVE ENDOCRINOLOGIST'S PERSPECTIVE

Progress in the treatment of pediatric cancer has significantly increased children's survival rates. We have noticed a constant increase in the number of young married women who had received intensive chemotherapy or radiation therapy as children and now face fertility problems. Since chemotherapy and radiotherapy alter gametes and reproductive function, discussion of future fertility is of major concern to pre-adolescent girls with cancer and their parents. A method to preserve fertility potential must be planned.

In young women who have a partner, embryo freezing is the most reliable method to preserve fertility [31]. Cryopreservation of unfertilized oocytes (Table I) has resulted in few pregnancies [32–36], and this method is usually not appropriate for pediatric patients.

Cryopreservation of ovarian tissue has been proposed for a few years in a growing number of medical centers. The main advantages are that ovarian stimulation is not necessary to achieve fertilization and a large number of immature oocytes are conserved. Mature oocytes that will be lost in the oocyte cortex cryopreservation process could be aspirated and frozen separately [37]. However, ovarian cryopreservation requires a surgical procedure that must be justified. At Hadassah University Hospital we have thus far banked ovarian cortex for 81 patients, including 9 patients ages 8–20. A laparoscopic approach was successful in all patients, performed under general anesthesia, and, when indicated,

TABLE I. Methods for Fertility Preservation for Women With Cancer

		Hormonal stimulation required	Reported success rate	Appropriate for girls	Comments
Oocyte cryopreservation	Matured in vivo	Yes	2%	No	● Human results improving
	Matured in vitro	No	No reports	No	● Future
Ovarian cortex cryopreservation	Cortex-orthotopic	No	2 babies	Yes	● Current method
	Cortex-Heterotopic	No	No reported delivery	Yes	● Grafting to ovary or adjacent to it
Whole ovary cryopreservation	Orthotopic	No	No human data	Yes	● Many trials of grafting to forearm
					● Maybe future, no ischemic loss

concomitantly with another procedure, such as insertion of an indwelling catheter for venous access, or bone marrow aspiration and biopsy.

Ovarian cryopreservation should still be considered an experimental method. Two human deliveries achieved after re-implantation of cryopreserved ovarian tissue were recently reported [8,38]. Preparations for transplantation of cryopreserved ovarian cortex for the first patients in our institution are underway. The vast majority of patients who have banked frozen ovarian cortex are either in active treatment or have recently completed treatment for their malignant disease. Other patients are still too young, or have not yet met the man with whom they wish to have children. Some patients have died. Thus, the potential that human ovarian cortex will enable resumed fertility remains based on animal data and isolated reports in humans.

### Techniques for Transplanting Ovaries

Ovarian cryopreservation would appear to be technically feasible in children and adolescents. Ovarian transplantation can be done using one of different approaches (Table I). In heterotopic transplantation, the ovarian cortex slices are subcutaneously grafted into the space above the brachioradialis fascia of the forearm. IVF and embryo transfer (ET) procedure are required to conceive. On the other hand, this technique does not require general anesthesia or abdominal surgery, and allows the ovarian tissue to be more closely monitored. If there is a need, ovarian removal will be easier compared to a graft implanted in the pelvis. Oocyte retrieval and fertilization was reported but no pregnancy ensued [39].

Two live-births have been reported after orthotopic transplantation of cryopreserved ovarian tissue. In these case reports, the frozen-thawed ovarian cortex was grafted to the remaining ovary [8] or into the adjacent peritoneum [38]. The major obstacle to the wide-spread application of ovarian cortex cryopreservation, is the loss of the large majority of follicles after a-vascular grafting mostly due to ischemia. We have thus proposed intact ovarian cryopreservation and transplantation [40] (Table I). Although results are promising [41] a pregnancy has not yet been reported. If fertility preservation was not performed, pregnancy may still be achieved using oocyte donation. Although pelvic radiation

may affect the uterus and limit patient's ability to conceive [42], chemotherapy is not toxic to the uterus and normal pregnancies, and deliveries can be achieved.

Consultation on fertility preservation should be offered to young female patients and their family prior to cancer therapy. Patients who develop premature ovarian failure following cancer treatment should be treated with hormonal replacement. Continuous developments will enable to preserve and restore fertility in a growing number of cancer survivors.

### PEDIATRIC SURGERY PERSPECTIVE

Ovarian cryopreservation involves the surgical harvesting of ovarian tissue. An important prerequisite for performing this procedure is a critical appraisal of the feasibility and safety of ovarian surgery in children. Pathological conditions of the ovary are encountered in infancy and childhood. Ovarian cysts, torsion, or masses, can be treated surgically in infancy and even the in neonatal period when indicated [43,44].

Over the last decade operative endoscopy and the concept of minimally invasive surgery has changed the practice of surgery. Following improvement and miniaturization of the required equipment, pediatric surgeons adopted laparoscopic and thoracoscopic surgery [45,46]. Laparoscopy has the advantage of exploring the abdominal cavity through a small incision, evaluating both ovaries before resection for fertility preservation. Laparoscopic oophorectomy is performed by isolating the fallopian tube from the ovary and gaining control of the ovarian blood supply. The ovary can be removed in a special bag through one of the trocar sites or a small lower abdominal incision. The reported rate of complications is very low [47]. When performed by experienced surgical and anesthetic teams, oophorectomy for fertility preservation either by laparotomy or by laparoscopy, can be done with minimal complications.

### PEDIATRIC ANESTHESIOLOGY PERSPECTIVE

The safety of neonatal and pediatric anesthesia has significantly improved during the past 25 years, due to improved understanding of pediatric physiology and better patient monitoring. This notwithstanding, anesthesia-related

complications remain more common in pediatric patients than in adults. The risk of complications is greatest in children under 1 year of age, significantly decreases after age 3 years, and then continues to slowly decline. From about age 15, children and adults have equivalent anaesthetic risks. Age is of course not the only parameter. Other factors of importance include the health status of the child at the time of the procedure and treatment by specialist pediatric anesthesiologists.

Because of the increased surgical and anesthetic risks in young children, we favor not performing ovarian cryopreservation before the age of 3 years. If the child is scheduled to undergo additional diagnostic or therapeutic procedures which require general anesthesia (e.g., bone marrow aspiration, central venous catheter insertion) ovarian cryopreservation is best performed concomitantly in one anesthetic session. The girl should be well prepared for laparoscopy. Hematological, infectious, biochemical, and other disorders should be appropriately addressed prior to surgery. The anesthesia should be administered and the laparoscopic oophorectomy performed by expert pediatric anesthesia and surgical teams with appropriate training and equipment [48].

## BIOETHICS PERSPECTIVE

Bioethics mandates examination of the parental (or other legal guardian's) obligation to act in the child's best interest. In the current context, her "best interest" includes both her *present* interest in minimizing risk and her *future* interest in fertility preservation.

It is well established in the philosophical literature that when parents do not act in their child's best interests, the state should intervene on behalf of the child in its traditional role of *'parens patriae'* ('parent of the nation'). If the scope of parental liberty is defined around the notion of the child's best interests, then parents can only retain authority to accept or reject ovarian cortex cryopreservation procedures for their child if this procedure is generally considered to be "in the child's best interest."

Evaluating medical risks and success rates is a clinical task. Specialists from various disciplines have generally concluded that the risk is reasonable, even though success rates are not yet known. Evaluating the patient's future interest in fertility preservation seems to be the crucial factor in justifying the procedure.

Feinberg [49] argues that there is a special category of rights, which he entitles "rights in trust," that is peculiar to children. These are rights "that are to be *saved* for the child until she is an adult, but that are sometimes violated "in advance," so to speak, before the child is even in a position to exercise them." Davis [50], in his footsteps, points to "the right to reproduce" as a striking example: "A young child cannot physically exercise that right (...) but clearly the child, when he or she attains adulthood, should have this

right. Therefore the child *now* has the right not to be sterilized, so that she may exercise the right to have children in the future."

A child's right to fertility preservation is thus acknowledged in the bioethical literature as a "right in trust." If the medical risk is acceptable, it seems that parents have an ethical right to request fertility preservation. Because of the experimental nature and as-yet unproven value of ovarian cryopreservation, the decision on whether to pursue the procedure should rest entirely with the parents. When the patient has already reached an age at which it is possible to explain the procedure's purpose, it is of course preferable to get her own assent.

## SYNTHESIS AND SUMMARY

The majority of children diagnosed with cancer are expected to be cured and become long-term survivors. A substantial number of these survivors are expected to face impaired fertility secondary to the gonadotoxic effects of chemotherapy and radiation.

No established method for cryopreservation of female gametes is currently available. However, there are promising experimental approaches to ovarian cryopreservation, and the first human pregnancies achieved with technology have been reported. We thus believe that serious consideration should be given within the pediatric oncology community to the possibility of offering ovarian cryopreservation to premenarchal girls with cancer [51,52].

As with any form of medical intervention, the risks and benefits associated with ovarian cryopreservation must be clearly stated. Because ovarian cryopreservation is a relatively new technology, it is currently impossible to provide the patient and her parents with an accurate assessment of the likelihood of success. This difficulty is further compounded by the fact that the actual attempt of using ovarian tissue, cryopreserved in a young girl, may take place after a long period of time. This fact may affect the success of the procedure in positive and negative ways, that is, the presently unknown effects of prolonged cryopreservation versus the anticipated progress in this field and the increased likelihood of successful pregnancy induction. Thus, one must be cautious in offering this procedure. With the first successful pregnancies achieved with this technology in humans, there is now proof of principle that this method constitutes a valid approach to fertility preservation in female cancer patients.

Despite the fact that fertility is a central concern for long-term childhood cancer survivors no guidelines exist regarding the options of fertility preservation in childhood cancer in general or in pre-menarchal girls in particular. A group from the UK has proposed guidelines (the Edinburgh criteria) for selection of patients for cryopreservation of ovarian cortical tissue but did not specifically incorporate guidelines for applying the procedure to pre-menarchal girls with cancer [22].

There are indirect reports of centers already performing ovarian cryopreservation in pre-menarchal girls [53,54] but, as stated above, the issue has not been comprehensively debated, nor have practice guidelines been suggested or formulated. Clearly, any meaningful discussion of ovarian cryopreservation must include a clear assessment of the potential risks involved in the procedure. Based on an analysis of the risks of general anesthesia and laparoscopic and ovarian surgery in children, we conclude that the procedure is safe and that the risks involved in performing ovarian cryopreservation in pre-menarchal girls appear to be small. However, based on this analysis, we suggest that, at least initially, the procedure not be offered to girls under 3 years of age because of the increased anesthetic risks in this age group.

To provide an additional margin of safety, we propose that if another necessary medical or surgical procedure is planned (e.g., insertion of an indwelling venous catheter, bone marrow aspiration, or harvest), then ovarian cryopreservation should be performed during the same anesthetic session.

As an additional consideration, we also propose that, at least until additional evidence concerning the safety and efficacy of the procedure accrues, ovarian cryopreservation be offered only to girls about to undergo medical treatments with a *high risk* for gonadal damage—such as bone marrow transplantation, whole abdomen irradiation (e.g., Wilms tumor), or with a *moderately high risk* such as alkylator-intensive chemotherapy regimens (i.e., high-grade B-cell lymphoma, Ewing sarcoma).

Clearly, any procedure for fertility preservation that is still experimental, should be offered only after a detailed discussion and informed consent process with the parents, and, where age appropriate with the child herself. The experimental nature of the procedure should be clearly stated. In addition, centers undertaking ovarian cryopreservation should form a multi-disciplinary team that will be able to handle the complex medical, technical, and ethical issues involved.

A summary of our proposed guidelines for offering ovarian cryopreservation to girls with cancer is presented in Table II.

We realize that the above-mentioned considerations depend greatly on the evolving experience and expertise in performing ovarian cryopreservation, and that the proposed guidelines must be constantly re-evaluated and modified to provide the best benefit-to-risk ratio for the patients. However, we believe just as strongly, that pediatric oncologists have an obligation to provide girls with cancer undergoing medical treatments which carry a high risk of future infertility with the opportunity of fertility preservation.

We hope that these suggestions will spur a timely and necessary discussion on the issue of fertility preservation in girls with cancer, and will promote further research and the development of clinical guidelines in this critical aspect of pediatric oncology practice.

**TABLE II. Suggested Guidelines for Offering Ovarian Cryopreservation to Pre-Menarchal Girls With Cancer**

The treating team will have a detailed discussion of the risks and potential benefits of ovarian cryopreservation with the parents/guardians, and, where age-appropriate, with the patient. Ovarian cryopreservation will be offered in cases where necessary medical treatments pose a high-risk of ovarian damage (bone marrow transplantation, whole-abdomen radiation therapy, alkylator-intensive chemotherapy)

Ovarian cryopreservation will be offered to girls over 3 years of age to reduce anesthetic risks (may be modified with increasing experience). Ovarian cryopreservation should preferably be performed during a medically indicated anesthetic session (insertion of an indwelling venous catheter, bone marrow biopsy, autologous bone marrow harvest)

Medical centers providing pediatric oncology care should form multi-disciplinary teams to offer this treatment

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