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Fertility considerations and the pediatric oncology patient

Lara Raffoul, MD[a,1], Carmen Capito, MD, PhD[a,1], Sabine Sarnacki, MD, PhD[a,b,*]

[a] Department of Pediatric Surgery, APHP, Necker Enfants Malades Hospital, Paris, France
[b] Paris Descartes University, Sorbonne Paris Cité, Paris, France

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ABSTRACT

Recent years have witnessed marked improvement in cytotoxic treatments with a parallel increase in patient survival. Despite efforts done to minimize long-term side effects of these treatment regimens, it is estimated that 40% of survivors of pediatric cancer will suffer from those. Some will be mild whereas others such as impaired fertility will be a heavy load on parents' expectations and patient's quality of life. Gonadal damage and severe loss of function is not a rare condition among children cured for cancer. Despite the young age of those patients, methods exist to try to reduce gonadal insult or to preserve gonadal function. Some of them are well studied and controlled; others are more experimental with encouraging results so far. This article aims to summarize all the procedures that can be offered to young patients treated for cancer in order to protect, as possible, their fertility potential.

Introduction

Childhood cancers are rare diseases as they represent 130–160 cases per million children with considerable variations between countries.[1,2] Most of them are embryonic tumors, the genesis of which is quite different from tumors encountered in adulthood. Improvements in therapy and intensive care have increased the overall 5-year survival rate from 45% for patients diagnosed in the mid-1970s to 80%.[3] Estimates place the number of childhood cancer survivors in the United States at 420,000 at the end of 2013.[4] Long-term survivors of childhood cancer are, however, at risk for serious, disabling, life threatening, or fatal treatment-related late effects including second malignancies, cardiac and vascular abnormalities, and pulmonary complications.[5,6]

Testicular or ovarian damage may be caused by radiation therapy directly to the gonads or brain (hypothalamic–pituitary axis damage) or by cytotoxic chemotherapy. The risk of infertility depends not only on the type of malignancy and its specific treatment, but also on the sex of the patient, as the effects of chemotherapy and radiation therapy manifest differently in the male and female reproductive systems.[7,8]

Gonadotoxic chemotherapeutic agents include mainly alkylating agents that act as inhibitors of DNA synthesis by creating covalent lesions between DNA strands and ultimately block cellular division. The most injurious of the alkylating agents are chlorambucil, cyclophosphamide, ifosfamide, melphalan, busulfan, and procarbazine.[9] Myeloablative chemotherapy regimens (e.g., high-dose cyclophosphamide combined with busulfan or Thio-tepa), increasingly used as preparation for stem cell transplantation, induce a high incidence of ovarian function impairment.[10]

Ionizing radiation acts on dividing and nondividing cells. As with chemotherapy, the effects of radiotherapy on ovarian function depend on the patient's age, field of treatment, daily treatment doses, and total amount of radiation received. Doses of 10–20 Gy in children and 4–6 Gy in adults are associated with permanent ovarian failure.[11] In addition, irradiation of the uterus in the childhood is known to predispose to premature delivery or to get offsprings with low birth weight.[12]

As the follicle pool is fixed at birth (nearly one million primordial follicles) and decreases with time, the risk of partial or total acute ovarian failure (AOF)—that is, loss of ovarian function within 5 years following completion of cancer treatment—induced by chemotherapy or radiotherapy increases as the patient ages. The global incidence of AOF in childhood cancer survivors ranges from 6.3% to 12%, and the relative risk of AOF after chemotherapy ranges from 2 to 9 compared with control subjects. Even when childhood cancer survivors retain ovarian function after completing cancer treatment, the risk of developing premature ovarian failure, defined as cessation of menses before age 40 years, is increased.[9,13]

In males, alkylating agents may affect spermatogenesis, but testosterone secretion is usually well preserved. In contrast, radiation therapy affects both spermatogenesis and testosterone secretion. Sperm production is susceptible to damage at doses of

* Corresponding author at: Department of Pediatric Surgery, Hôpital Necker Enfants-Malades, 149 rue de Sèvres, 75015 Paris.
E-mail address: sabine.sarnacki@aphp.fr (S. Sarnacki).
1 These two authors contributed equally to this work.

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more than 1.2 Gy, whereas residual Leydig cell function seems to be present even at radiation doses up to 20 Gy. Prepubertal boys seem to be more susceptible to the effects of irradiation on spermatogenesis and Leydig cell function than adolescent and adult males.

Thus, while most of the children will now successfully be treated for cancer, the question of fertility preservation has become a major question and a real challenge. Assisted medical procreation technologies are indeed restrained by the prepubertal state of the gonads at the initiation of treatment, which excludes embryo cryopreservation, mature oocytes cryopreservation, or semen cryopreservation.

Fertility preservation in ovarian and female genital tract

Benign ovarian tumors represent 85–90% of ovarian lesions in children, and consist of teratomas (benign germ-cell tumors) and more rarely, serous or mucinous cystadenomas (benign epithelial tumors). When clinical, imaging, and biological features plead for these benign lesions, ovarian sparing surgery is mandatory for the following 2 main reasons: (1) up to 13% of ovarian teratomas are bilateral (either synchronous or metachronous)[14]; (2) unilateral ovariectomy leads to depletion of the total number of primordial follicles and therefore might increase the risk of premature or early menopause, although not clearly demonstrated in children.[15]

In everyday practice, deciding whether to spare the ovary because the lesion seems benign or to perform a total ovariectomy because signs of malignancy are present is not always straightforward. Two different situations should be considered. In the first case, the young girl is painless and the surgeon has enough time to perform and analyze reliable imaging ensuring that it does not show any sign of malignancy and to dose tumor markers (AFP, BHCG, Inhibine B, AMH, and Calcemia). In contrast, when the patient is complaining of an acute abdomen due to adnexal torsion (that could be secondary to an ovarian lesion) or ovarian rupture, the best approach is to perform a laparoscopic exploration in emergency. If an ovarian rupture is diagnosed, peritoneal inspection, sampling of ascites, and complete ovariectomy or adnexectomy should be done. If an adnexal torsion is seen, simple detorsion is recommended as it allows them to perform imaging and markers dosage in the post-operative period. Decision could be then taken according to the first situation. Operative technique always starts with the exploration of abdominal cavity through laparoscopy, along with sampling of ascites or any peritoneal suspect lesion (particularly on the diaphragm). Ovarian sparing surgery is then performed through a Pfannenstiel incision. Although this approach is debatable, as some surgeons still prefer laparoscopy, this technique allows to spare as much as possible of ovarian parenchyma and avoid any spillage of the peritoneum in case of the presence of a non secreting malignant component in the lesion. Finally, follow-up with repetitive ultrasounds of pelvis during childhood should be performed in order to rule out metachronous ipsilateral or contralateral lesions at an early stage. This follow-up gives the opportunity to inform the young girl about the symptoms that should alert for a potential adnexal torsion and in case of an important amputation of the ovarian parenchyma of the different assisted medical procreation techniques available after puberty.

Preservation of fertility should also be considered when surgery is planned for genital tract tumors. Different entities encountered with, by frequency are as follows: rhabdomyosarcoma (RMS) of the vagina or uterus cervix, malignant germ-cell tumors (GCT) of the vagina, and other rare entities such as clear cell adenocarcinoma, this last subtype being diagnosed later in life.[16] Prognosis of these tumors relies on the local tumor control obtained nowadays with less radical surgical management than in past decades. For urogenital RMS, treatment could be achieved without surgery when remission is obtained after chemotherapy, or be completed by local brachytherapy avoiding mutilating surgery, which is currently exceptional.[17–19] For vaginal GCT, surgical resection of the primary location is always mandatory but efficiency of neo-adjuvant chemotherapy usually allows to avoid mutilating surgery and to perform a partial colpectomy.

Fertility preservation in female patients submitted to gonadotoxic treatments

Ovarian transposition

Ovarian transposition has been the first procedure proposed for children with cancer in order to preserve ovarian function from damage due to abdominal and pelvic radiation.[20] It should be considered in all cancer children with tumors requiring radiotherapy that extends to the pelvis. Rhabdomyosarcoma of the bladder, vagina, or uterus, and Ewing and non-Ewing bone and soft tissue pelvic sarcomas, are the main tumors requiring ovarian transposition. Such tumors are managed with 42–58 Gy, doses that are much greater than those causing ovarian failure. The aim of ovarian transposition is to mobilize the ovaries outside of the radiation field after ruling out a possible tumor extension to the ovaries. The place where the ovaries have to be positioned is guided by the radiotherapy plan, in agreement with the surgeon and the radiotherapist. Metallic clips are usually used as a landmark for the radiotherapy planning. When the tumor is not located in the pelvis or when no initial surgery is planned, ovarian transposition is performed through laparoscopy.[20–23] So far, very few studies have reported long-term results of ovarian transposition in children.[22,24] Preservation of endocrine function has been estimated to range between 60% and 83%.[25–27] Concerning side effects, the major complication reported is painful ovarian cysts,[28] which raises the question of a detransposition upon completion of treatment. This side effect is not systematic and depends on the procedure performed.[22] Thus, it seems reasonable to adopt a wait and see policy before planning a detransposition. In order to avoid reoperation, De Lambert et al.[23] proposed a temporary transposition of the ovary via a stitch passed through the abdominal wall and the skin in cases of short pelvic radiation treatment. Other side effects include abdominal pain and bowel obstruction.

Ovarian suppression

The use of oral contraceptives or gonadotropin-releasing hormone (GnRH) analogs for ovarian suppression during chemotherapy is one of the suggested strategies to preserve fertility. It creates a pseudoprepubertal state with an overall decrease in ovarian function.[29,30]

However, the protective effect of such a treatment during chemotherapy is quite debatable. A recent meta-analysis and systematic review conducted by Elgindy et al.[31] showed that GnRH analogs during chemotherapy do not significantly increase resumption of ovarian function after the end of chemotherapy (RR = 1.12, 95% CI: 0.99–1.27), with no convincing evidence that the analog offers protection of ovarian reserve. On the contrary, other studies conducted by Oktay et al.,[32] and Lambertini et al.[33] proved that ovarian suppression during chemotherapy do reduce premature ovarian failure. The previously cited studies concern the adult population and this approach may be discussed in our