Fertility preservation in children and young adults undergoing treatment for malignancy

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ABSTRACT

Advances in cancer therapy have improved the long-term survival of young patients suffering from malignancies. However, the adverse effects of the treatment are sterility and loss of gonadal function especially in females. Preservation of fertility in males by sperm freezing is more practical and already established. For young women undergoing cancer treatment, the availability of preserving the gonadal function and fertility has just begun. Today, we can cryopreserve the oocytes, the embryos or the ovarian tissue and in those undergoing pelvic irradiation, laparoscopic lateral ovarian suspension can be considered. Because women with non-gynecological malignancies seek advice from a general surgeon or a medical oncologist, increasing the awareness of the physicians and general public is recommended.

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Advances in cancer therapy have improved the long-term survival of young patients suffering from malignancies. However, the adverse effects of this treatment are sterility and loss of gonadal function. Diseases commonly treated with radiation or chemotherapeutic agents in young patients are breast cancer, lymphoma, leukemia, blood dyscrasia, glomerulonephritis, lupus erythematosus and rheumatoid arthritis. With 65% overall survival rates, the prevalence of long-term survivors in young adult population has been estimated to be 1 in 1000.[1] Mackie et al[2] evaluated gonadal function in 101 postpubertal children treated with multiple chemotherapies for childhood Hodgkin's disease. Following the treatment, 89.1% of the males had elevated serum follicular stimulating hormone (FSH) levels indicating severe germinal epithelial damage. In addition, 24.4% of them had raised serum luteinizing hormone (LH) suggesting subtle Leydig cell dysfunction. Seventeen women (53%) had elevated serum gonadotropins, and 10 of them presented with symptomatic ovarian failure. These findings suggest the magnitude of the problem. Accordingly, every attempt should be made to preserve the gonadal function of young men and women treated with anti-cancer drug.

Chemotherapy. Chemotherapeutic agents may induce azoospermia in males and cause premature ovarian failure in women.[2] In vitro studies of rat have shown that granulosa cells are the primary targets for cyclophosphamide induced ovarian failure.[3,4] Ataya et al[5] demonstrated that the growing follicles are more vulnerable to cyclophosphamide, and gonadotropin releasing hormone analog (GnRHa) administration resulted in suppression of these follicles. Accordingly, the process of recruitment from the quiescent pool of primordial follicles into the cyclophosphamide-sensitive pool is halted and potentially the ovarian function is preserved. The severity of gonadal damage is dependent on the type of chemotherapy, the treatment protocol, and the age and gender of the patients.[6-8]

Type of the chemotherapy. The main chemotherapeutic agents that induce gonadal damage are alkylating agents such as

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cyclophosphamide, melphalan, and chlorambucil. Meirow et al[9] reported that the use of alkylating agents increases the risk of premature menopause by 4.5 fold. Other drugs such as cis-platinum and vinca alkaloids have also been implicated.

Treatment protocol. The dose of the chemotherapeutic agents, the duration of administration, and the total dose received by the patient are important factors. Furthermore, patients who receive several cycles of chemotherapy or combination treatment are more likely to have gonadal damage. For example, combined chemotherapy is associated with ovarian failure in 34% of treated female[9] and permanent azoospermia in >90% treated males.[10,11]

Age and gender. The younger the patient, the lower the likelihood of premature ovarian failure.[12] Compared to adult ovaries, prepubertal ovary is more resistant to chemotherapy.[6] On the other hand, testis is more sensitive to irradiation and chemotherapy than the ovary.[13-15] Short-term follow up of boys treated with chemotherapy for Hodgkin's disease showed that testicular damage occurs in 89% of the cases.[14]

Radiotherapy. The damage caused by radiotherapy depends on the type of radiation, the total dose of radiation and the dose per fraction. Immature sperm cells are very sensitive even to low radiation dose. As low as 0.1-1.1 Gy have resulted in damage of dividing spermatogonia and in disrupting cell morphology.[16] A higher dose of irradiation of >20 Gy lead to permanent Leydig cell damage.[14] The recovery of spermatogenesis from surviving cells is unpredictable and may occur more than 5 years after treatment.[16] Contrary to that of irradiation, Leydig cells are more resistant to chemotherapeutic agents. Accordingly, testosterone production and the development of secondary sexual characteristics are preserved even in the presence of azoospermia. Leydig cell damage is directly related to the dose of the cytotoxic agent and inversely to the age of the child.[1] In contrast, follicle function and sex steroid production are interdependent where damage of either results in failure of both functions.[1] The LD50 or lethal dose of irradiation required to eliminate 50% of the human primordial follicles is estimated to be 4 Gy. In adolescent girls, an irradiation dose of >30 Gy is likely to cause permanent ovarian damage.[14] Recent data demonstrated that uterine function might also be compromised following radiotherapy. Increased incidence of fetal loss and intrauterine growth restriction has been reported following pelvic irradiation in pre-pubertal age. This could be due to reduced elasticity of the myometrial tissue, decreased endometrial receptivity or uterine vascular damage.[14,17]

Fertility preservation. a) Males. Strategies for preservation of male fertility depend on the sexual maturity of the patient. 1) Freezing and banking of spermatozoa - currently, freezing and banking of spermatozoa obtained prior to cancer treatment is the well-proven and practical clinical option. The problem arises when the pubertal boy is unable to ejaculate. In such cases, electro-ejaculation and epididymal or testicular sperm retrieval can be considered. The spermatozoa can then be used for future intracytoplasmic sperm injection (ICSI) if needed.[14] 2) Gonadotropin suppression - clinical studies have failed to demonstrate any benefit of suppressing the testis with either agonist or antagonist.[18,19] 3) Cryopreservation of spermatogonia - in prepubertal boys where spermatogenesis has not commenced, a testicular biopsy may be performed in an attempt to cryopreserve the spermatogonia. However, testicular biopsy in young boys could lead to psychological trauma.[20]

In a mouse model, a life birth has been reported after transplantation of fresh testicular cell suspension.[21] The efficacy of this technique in human remains to be seen. Furthermore, the risk of relapse due to transmission of microscopic disease should be considered.

b) Females. In contrast to preservation of male fertility, the availability of technique to preserve female fertility has only been recently developed. 1) Medical - the role of medical treatment remains controversial. Since the dividing cells are sensitive to the cytotoxic agent, it has been suggested that inhibition of the pituitary-gonadal axis would reduce the risks of ovarian damage. Blumenfeld et al[22] evaluated the effect of co-treatment of GnRHa with chemotherapy in 18 young women with lymphoma (aged 15-40 years). Gonadotropin releasing hormone analog was administered 7-10 days before starting the chemotherapy for a maximum of 6 months. They reported resumption of ovulation in 93.7% of cases compared to 39% in those not receiving GnRHa. On the contrary, Whitehead et al[12] could not find any protective effect of oral contraceptives on ovarian damage induced by chemotherapy in a large number of patients. A similar findings with GnRH-a, oral contraceptives, or progestins has been reported.[9] To date, there is no convincing evidence of clinical benefit of co-treatment with GnRH agonist or antagonist. 2) Surgical - a) cryopreservation of ovary or ovarian cortical tissue. The criteria of ovarian cryopreservation at McGill Reproductive Center is maximum age of 35 years, minimum age of 14 years (except if surgery is needed for her disease), a 5-year survival rate of >50%, and the treatment carries significant risk of permanent sterility. In animal model, ovarian tissue cryopreservation and transplant have been followed by successful pregnancies and deliveries.[23-25] Using human ovarian tissue as xenografts in immunodeficient mice, follicular growth has also been observed.[26,27] Recently, Bedaiwy et al[23]

reported that autotransplantation of intact frozen-thawed sheep ovaries with microvascular anastomosis could restore ovarian hormones production. This technique however is impractical. Experience with allografts of ovarian tissue in human is limited. The ovarian tissue can be placed in the ovarian fossa or in the subcutaneous tissue. Grischenko et al[28] transplanted cryopreserved human ovaries tissue subcutaneously with restoration of menstrual cycle in human. In another report, orthotopic transplantation of frozen-thawed ovarian cortical strips was associated with return of ovarian hormone production.[29] A similar finding was reported with transplantation of ovarian tissue in the subcutaneous tissue of the inner arm and in a muscle pocket of the abdominal wall.[30] To date, however, there has been no live birth reported with this technique. One of the concerns with allotransplantation of ovarian tissue in cancer patients is the risk of transmission of microscopic disease. It is important, therefore, to examine the removed ovarian tissue histopathologically. b) Ovarian transposition - pelvic irradiation is often indicated in some women with Hodgkin's disease, genitourinary or low intestinal malignancies. Depending on the site and the extent of the disease, radiation can be administered locally or to a larger area. It is highly effective but may result in the loss of ovarian function. In order to avoid radiation to the ovaries, ovarian transposition either by laparotomy or by laparoscopy have been advocated. The ovaries can be transposed medially behind the uterus, laterally outside the radiation field or to distant sites.[31,32] The most simple and effective method is laparoscopic lateral ovarian transposition. We recently reported that laparoscopic ovarian transposition of women less than 40 years is associated with preservation of ovarian function in 88.6% of cases.[33] This compares favorably to the similar procedure by laparotomy. Before surgery, a radiation oncologist can outline the field of radiation. This will give an idea how high and lateral the ovaries should be transposed. In practice, placing the ovaries above the pelvic brim and as lateral as possible will place them outside the radiation field. The transposed ovaries should be securely sutured to the peritoneum. The inferior border of the ovary is marked with a vascular hemoclip bilaterally. Contrary to previous reports, ovarian transposition can be performed with preservation of the integrity of the Fallopian tube allowing a possible future spontaneous conception. This is illustrated in a case of 34 years patient with rectal cancer. The ovaries were transpositioned laterally and anteriorly to the level of the anterior superior iliac spines. We transected the ovarian ligament and transposed the ovaries without cutting the fallopian tubes. Despite large doses of pelvic radiation, she continued to menstruate regularly and conceived spontaneously after 2 years of surgery and delivered a healthy baby.[34] During laparoscopy, a portion of the ovary could be removed for ovarian cryopreservation. This allows the patient to maintain her options of fertility and of autografting the ovary if ovarian failure occurs. 3) In vitro fertilization and embryo cryopreservation. In vitro fertilization (IVF) can be performed before chemotherapy or radiotherapy, and the embryos can be frozen for later embryo transfer. Embryo cryopreservation is restricted by the time, sexual maturity and the presence of stable male partner. The main disadvantage of this procedure is the need for ovarian stimulation delaying the cancer treatment. In addition, hormonal stimulation might be deleterious to the primary disease particularly in estrogen dependent cancer. Alternatively, natural cycle IVF can be performed. However, the number of retrieved oocytes is limited. This procedure is currently limited to those with polycystic ovaries. Tamoxifen stimulation appears to result in adequate number of embryos and may provide a safe method of IVF and fertility preservation in breast cancer patients.[35] In order to avoid delay in cancer therapy, IVF could be performed between the cancer's treatment cycles. However, there is a concern of oocytes exposure to chemotherapy. To date, there has been no report of chromosomal or congenital abnormalities in the offspring.[36,37] 4) Oocytes cryopreservation. Oocytes cryopreservation is an attractive option for cancer patients who do not have enough time to complete a stimulation cycle before cancer treatment, and for those with no male partner. The major limitation of oocytes cryopreservation is the low pregnancy rate. Oktay[38] in his review reported 12 pregnancies and 8 deliveries resulting from 254 thawed oocytes. Due to their fragile nature, there is a concern that cryopreservation might damage the oocytes. Poruc et al,[39] however reported that among 13 children born after fertilization of frozen-thawed oocytes, there have been no congenital malformation, physical or intellectual abnormalities. 5) In vitro maturation. In women with polycystic ovaries, retrieval of the immature oocytes is an option. The advantages of this approach are no need of FSH stimulation and no delay in initiation of cancer treatment. The embryos resulted from oocyte maturation and fertilization can then be cryopreserved. In the absence of male partner, oocyte freezing can be performed.

In conclusions, preservation of fertility in males by sperm freezing is already established. For young women suffering from cancer, the availability of preserving the gonadal function and fertility has just begun. Today, we can cryopreserve the oocytes, the embryos or the ovarian tissue. In those undergoing pelvic irradiation, laparoscopic lateral ovarian suspension can be considered. Because women with non-gynecological malignancies usually seek advice from a general surgeon or a medical

oncologist, increasing the awareness of the physicians and general public is recommended.

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