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ÇOCUKLUK ÇAĞI VE ADOLESAN KANSER HASTALARINDA FERTİLİTEYİ KORUMA STRATEJİLERİ

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ÖZET

Gonadal (over) yetmezlik ve erken kalıcı menopozda bu gruptaki hastalarda son yıllarda daha çok farkedilir hale gelmiştir. Dolayısıyla fertilitenin bu hastalarda korunması giderek önemi atran bir şekilde gündeme gelmektedir.Üstelik kendisi kanser olmadığı halde kanser tedavisi ve kemik iliği nakli gerektiren bazı hastalıklarda da aynı riskler mevcuttur. Tuner sendromu ve galaktozemi gibi bir diğer grup hastalıkta ise erken ce hızlı folikül kaybı mutlak erken menopoz ile sonuçlanmaktadır. Görüleceği üzere fertilitenin korunması sadece kanser hastalarına sınırlı değildir. Bu derleme pediatrik yaş grubu kanser hastalarında fertiliteyi koruma stratejilerini içermektedir.

ABSTRACT

Ovarian failure and other poor reproductive outcomes at long-term are now being recognized as important sequelaes of previous exposure to chemo and/or radiotherapy during childhood. Therefore, preservation of gonadal function and fertility has recently emerged as an important quality of life issues for pediatric cancer patients. Furthermore, the indications for fertility preservation have also extended beyond cancer since patients with certain precancerous and benign illnesses such as myelodysplasia, thalassemia, systemic lupus erythematosis may have to receive cytotoxic chemotherapy/radiation and stem cell transplantation for the cure. Certain disorders which are genetically predisposed to premature ovarian failure (POF) such as Turner syndrome and galactosemia are also potential candidates for fertility preservation. Therefore, we aimed in this review article to discuss the needs and outline the current fertility preservation strategies in these patients.

FERTILITY PRESERVATION OPTIONS IN PEDIATRIC CANCER PATIENTS

Strategies to preserve the reproductive potential of pediatric cancer patients are limited mainly due to sexual immaturity (Figure 1) (1). Ovarian tissue cryopreservation is the only method for sexually immature child. But oocyte freezing can also be an option for adolescent patients.

Ovarian tissue freezing

Ovarian cryopreservation maybe the only option for fertility preservation, especially in prepubertal children and those who do not have time to undergo ovarian stimulation for oocyte or embryo cryopreservation (1). Ovarian tissue cryopreservation does not require ovarian stimulation and ovarian tissue can be harvested laparoscopically without any preparation. The ovarian cortex contains primordial follicles with oocytes arrested in the diplotene of prophase of the first meiotic division. It has been suggested that the relatively high surface/volume ratio, low metabolic rate and the absence of zona pellucida make primordial follicles less susceptible to damage from freezing (2). Common indications for

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ovarian tissue freezing in pediatric patients are summarized in the table-1. As can be seen, the indications extend beyond cancer since some other benign illnesses either require chemotherapy and stem cell transplantation for treatment such as systemic lupus eryhtematosis; or are characterized by accelerated follicle atresia and early depletion of the stockpile in the ovary such as Turner's syndrome and galactosemia. In the procedure one of the ovaries are laparoscopically removed. Bilateral gonadectomy is indicated in the case of Y-chromosome mosaisicm in the ovary due to the increased risk of malignant germ cell tumor development. If the indication for ovarian tissue freezing is Turner syndrome or galactosemia cryopreservation of both ovaries can also be considered since accelerated follicle atresia in both diseases will inevitably culminate in premature ovarian failure. Pathological examination of removed ovaries is a prerequisite to rule out any microscopic tumoral invasion in the ovaries especially in cancers with a high risk of ovarian metastasis such as leukemia, neuroblastoma and genital rhabdo-myosarcoma (3). Slow freezing is the conventional method for cryopreservation of the ovarian tissue (4). While vitrification is the method of choice for oocyte and embryo freezing, data on its applicability in ovarian tissue freezing is limited (5).

Pregnancies and live births reported after orthotopic transplantation of frozen thawed ovarian grafts in adult cancer patients have proved that this procedure, albeit still experimental, may help protect the fertility potential of cancer patients who face the risk of premature gonadal failure as a result of cytotoxic chemotherapy and radiation regimens (6-17). Encouraged by these cases more adult cancer patients are now being informed about and offered ovarian tissue freezing and other fertility preservation options. In contrast a considerable portion of pediatric cancer patients and their parents are still not counseled for the adverse effects of cancer therapies on reproductive functions, future parenthood, and current fertility preservation strategies (18). The results of two recent surveys are two striking examples. One of them showed that fertility preservation options were offered to only 38 girls (8.2%) in a total of 463 girls diagnosed with cancer. The most common reasons given for not discussing fertility preservation options included 'not at significant risk' in 29% of cases, 'too young' in 27%, 'techniques unproven' in 22%, 'no facilities' in 10% and 'no funding' in 8% (19).

Even though some oncologists appear to discuss routinely a treatment's impact on fertility, few indeed refer their patients to reproductive endocrinologists according to the results of the other survey conducted among 249 oncologists. When planning treatment, 30% rarely consider a woman's desire for fertility. Gynecologic oncologists were more likely to routinely consider fertility compared with other oncologists (93% vs. 60%). Gynecologic oncologists also were more likely to provide a less effective regimen to better preserve fertility (61% vs. 37%). Most oncologists (86%) would be willing to sacrifice less than a 5% reduction in disease-free survival if a regimen offered better fertility outcomes; 36% felt patients would be willing to sacrifice >5% (20). These results underscore the critical role of oncologists at academic medical centers in informing the parents about the risk of future infertility and other treatment related adverse reproductive outcomes in the child and in referring them to reproductive endoc-rinologists for fertility preservation options. The practice committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology states that ovarian tissue freezing hold promise for future female fertility preservation and is an experimental procedure and therefore should be performed under IRB guidance (21). To date seven case series of ovarian tissue freezing were reported in a total of 266 pediatric and adolescent patients (age range 8 months-21 years) (22-28). There is no data regarding the viability of frozen ovaries in pre-pubertal girls since none of them were transplanted back and none of the pregnancies reported so far were obtained from ovarian grafts frozen before puberty. But given the fact that the technique of ovarian tissue freezing in pre-pubertal patients is not different from that of adults; and prepubertal ovaries are histologically identical to adult ovaries and harbor more primordial follicles (29) there is almost no doubt about the viability of frozen-thawed immature ovarian grafts. Moreover there are reports of obtaining restoration of ovarian activity after transplantation of frozen-thawed immature ovaries in animals (30).

Ovarian Transposition

Transposing the ovaries out of the radiation field is an option for preserving gonadal function. Females treated with whole abdominal and/or pelvic irradiation for Hodgkin disease, Wilms tumor, or other solid tumors (e.g., rhabdomyosarcoma, neuroblastoma) are at high risk of AOF (27). When no chemotherapy is planned, the ovaries can be moved outside the pelvis (transposition) to shield them from radiation therapy. When ovarian transposition is performed prior to radiotherapy, ovarian function is retained in the majority of young girls and adolescent females (31-32). Spontaneous pregnancies and live births have been reported after transposition of the ovaries (33). If the patient is to undergo an abdominal surgery, the ovaries can be transposed simultaneously, or if she is to be treated nonsurgically, laparoscopic transposition can be performed before the scheduled radiotherapy. The success with fertility preservation by ovarian transposition prior to radiotherapy varies between 16% and 90% (27). Success rates are affected by the degree of scatter radiation, vascular compromise, the age of the patient, dose of radiation, whether the ovaries were shielded, and whether concomitant chemotherapy is used (27). Fallopian tube infarction, chronic ovarian pain, ovarian cyst formation, and migration of ovaries back to their original position before radiotherapy reported complications (34). The candidates for ovarian transposition should be selected carefully, accounting for all the variables that may affect its success rates. It should also be kept in mind that, when gonadotoxic chemotherapy is used along with radiation, there is no strong rationale to perform this procedure and that ovarian transposition will not circumvent the harmful effects of radiation on the uterus and other pelvic structures.

Intensity modulated Radiotherapy (IMRT)

Successful tumor treatment using external beam radiation therapy generally requires relatively high doses of radiation administered to the known areas of disease as well as to adjacent regions that potentially contain cancer cells. Scattered or incidental irradiation of adjacent normal structures is inevitable during such therapy. This radiation to normal tissues must be minimized to reduce both acute and long-term side effects. Advances in computer technology led to the development of sophisticated three-dimensional radiotherapy planning systems and computer-controlled radiotherapy delivery (35). IMRT is a new conformal radiotherapy that delivers radiation to tumor more precisely while sparing the surrounding tissues. Its ability of simultaneously creating multiple targets and multiple avoidance structures may enable the treating physician to minimize the scattered dose to the ovary (36-37). Compared to most other treatment techniques, IMRT can achieve a higher degree of accuracy in conformation of the radiation to the planned target, while sparing normal tissue. The advantages of IMRT are particularly evident when the target volumes have complex shapes, concave regions, or are adjacent to many critical normal structures. Therefore IMRT can be an option to decrease the dose of scattered radiation to the ovaries is intensity-modulated radiotherapy (IMRT).

Gonadotropin Releasing Hormone (GnRH) Analogues to Preserve Gonadal Function?

It has been hypothesized, largely based on the debated role of gonadal suppression in men to preserve testicular function against chemotherapy, and partially the misconception that prepubertal females are not affected by gonadotoxic cancer treatment, that ovarian suppression can be protective. There are some animal studies with conflicting results of the protective effect of GnRH agonists against chemotherapy and radiotherapy (38-39) and several uncontrolled case series reports and cohort studies with short term follow-up and historical controls (40) that claimed benefit. But none of the randomized prospective study conducted so far has confirmed these findings (41-42). In a prospective randomized study by Waxman et al., GnRH analogs did not preserve gonadal function in men and women with lymphoma. The only pregnancy occurred in the control group (41). German Hodgkin Study Group investigated the use of gonadotropin-releasing hormone-analogues (GnRH-a) and oral contraceptives (OC) in young women with advanced-stage Hodgkin lymphoma. Women (18-40 years) were randomly assigned either to receive daily OC or monthly GnRH-a during escalated combination therapy with bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and

prednisone (BEACOPPesc). Hormonal levels were determined at baseline, during therapy, and at follow-up. The study was closed prematurely after an interim analysis of 12 patients in arm A (OC) and 11 in arm B (GnRH-a), 9 and 10 are assessable for the primary end point. Women's median age was 25 years in both arms. The anti-Mullerian hormone level after at least 12 months was reduced in all patients. For the entire study cohort, the respective ovarian follicle preservation rate was 0% (95% confidence interval 0% to 12%)(42). In another recent report, 49 women with breast cancer were randomized to receive or not receive a GnRH analog. After 30 months follow-up, there was no difference in the incidence of ovarian failure as determined by serum FSH and Inhibin-B levels. Likewise, the only pregnancies were in the control group (43). Similar results were obtained another prospective study in 29 women with Hodgkin's lymphoma treated with chemotherapy to assess the ovarian reserve and the ovarian protective effect of GnRH-analog (GnRH-a) (44). These findings, coupled with the fact that human primordial follicles do not express FSH or GnRHa receptors, and that prepubertal children are hypogonadal, do not support the use of GnRHa as a fertility preservation technique in children and young individuals.

Sphingosine-1-Phosphate (S1P)

S1P is an antiapoptotic signaling phospholipid that protect rodents' ovaries from chemotherapy and radiation induced damage(45). There are reports of its protective effects against apoptosis during cryopreservation of human ovarian tissue freezing and in vitro culture conditions (46-47). Randomized controlled studies will reveal if this drug offers some protective effects against ovarian follicle damage induced by cancer drugs and radiation in human ovary.

Conclusion

The options of fertility preservation in pediatric cancer patients who are at risk of developing gonadal failure are more limited than in adults and include

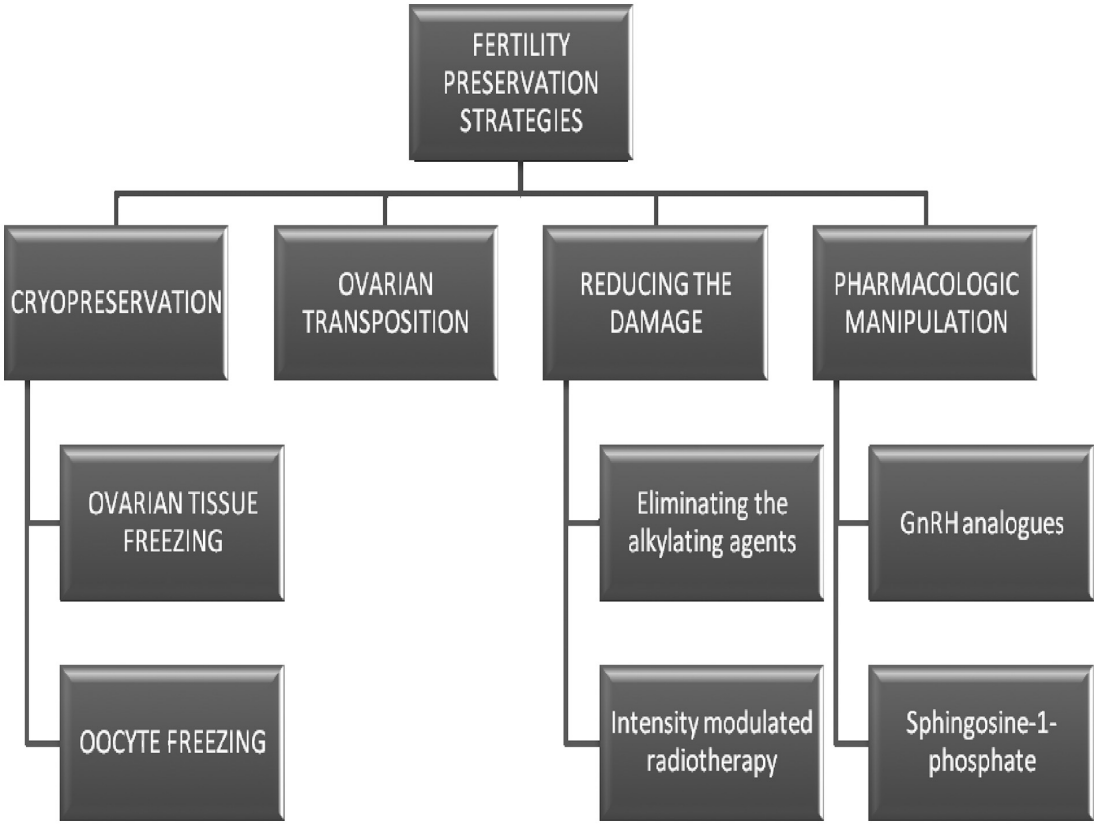

Figure 1–Fertility preservation strategies in the pediatric cancer patients

ovarian tissue cryopreservation and ovarian transposition. Even though ovarian failure may not occur immediately after chemo- and/or radiotherapy, there are still significant risks for poor reproductive outcomes in adulthood due to the diminished germ cell reserve and reproductive end organ damage. Ovarian transposition will not prevent adverse affects of radiation on the uterus. Overall, The risk of premature ovarian failure is several times higher in the survivors of childhood cancers compared to their siblings. In addition, if they have also been exposed to pelvic/abdominal radiotherapy during childhood, their pregnancies are complicated by low-birth weight, preterm labor, spontaneous abortions, and perinatal death. Therefore every child or teenager diagnosed with cancer (and their parents) should be counseled thoroughly about the future risks for adverse reproductive outcomes and the options for fertility preservation. Unfortunately there are no effective medical treatments to protect or preserve gonadal function.

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