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Radiotherapy, Female Fertility and Ootoxicity

Radyoterapi, Kadın Fertilitesi ve Ootoksisite

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ÖZ

Fertilite yaşam kalitesinin önemli bir bileşenidir ve onkolojik hastalar tedavi öncesinde bu konudaki beklentileri açısından sorgulanmalıdır. Radyoterapi(RT), fertiliteyi geri dönüşümsüz ve progresif olarak olumsuz etkileyebilmektedir. Bu nedenle, fertilite isteği olan hastalar RT öncesi değerlendirilmeli ve uygun müdahaleler açısından yönlendirilmelidir. Kranial RT hipotalamus- hipofiz-over(H-H-O) aksını bozarak, pelvik RT ise doğrudan over ve uterusu etkileyerek infertiliteye neden olabilmektedir. Kranial RT'nin neden olduğu endokrinopatilerin uzun latent dönemi nedeniyle bu hastalar uzun dönem takip edilmelidir.Abdominopelvik RT sonrası gelişen doz bağımlı uterin ve over toksisitelerine bağlı olarak hastalar infertilite ve gebelik komplikasyonları açısından yüksek risklidir. Uterus ve overlerin, yaşa bağlı olarak RT sensitiviteleri farklıdır. Yaşla birlikte uterusun RT duyarlılığı azalırken overlerin RT duyarlılığı yaşla artmaktadır. RT ilişkili infertiliteye neden olabilecek eşik dozlar ile ilgili fikir birliği olmasa da, güncel veriler ışığında, hipotalamo-hipofizer aks için 30 Gy, uterus için genç kadınlarda 25 Gy, erişkin kadınlarda 45 Gy, overde akut ovaryen yetmezlik için 10 Gy, prematür ovaryan yetmezlik için ise 35 yaş altında 25 Gy'dir. Gebe kalmadan önce ebeveynlerin radyasyona maruz kalmasıyla çocukta kalıtsal genetik hastalık gelişimi açısından anlamlı ilişki gösterilememiştir.

ABSTRACT

Fertility is an important component of quality of life, and oncological patients should be questioned about their expectations before treatment. Radiotherapy (RT) can adversely affect fertility, irreversibly and progressively. Therefore, patients with expectations of fertility should be evaluated before RT and guided for appropriate interventions. RT negatively affects fertility in many ways. Cranial RT disrupts the hypothalamus–pituitary–ovarian axis, and pelvic RT directly affects the ovaries and uterus. Because of the long latent period of endocrinopathies caused by cranial RT, these patients should be followed up over a long period. Due to dose-dependent uterine and ovarian toxicities that develop after abdominopelvic RT, patients are at high risk of infertility and pregnancy complications. The uterus and ovaries have different radiosensitivities depending on age. With aging, the radiosensitivity of the uterus decreases, whereas the radiosensitivity of the ovaries increases. Although no consensus exists on the threshold doses that can cause RT-related infertility, according to current data, the threshold value is 30 Gy for the hypothalamo-pituitary axis, 25 Gy for young women and 45 Gy for adult women for the uterus, 10 Gy for acute ovarian failure in the ovary, and 25 Gy for premature ovarian failure under 35 years of age. No significant relationship exists between parental radiation exposure and inherited genetic disease in their infants.

Keywords: Radiotherapy, Ionizing Radiation, Female Fertility, Ootoxicity

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INTRODUCTION

Radiotherapy (RT) is an effective treatment used in approximately 70% of cancer patients (1). The effects of radiation on tissues are stochastic and deterministic. The deterministic effect is due to cellular damage, is dose-dependent, and has a threshold dose for its occurrence. Common adverse effects (e.g., radiodermatitis, esophagitis, radiation pneumonitis, infertility) are explained by the deterministic effect. The stochastic effect is mostly associated with DNA damage, a threshold dose cannot be determined, and it has been associated with long-term adverse effects such as radiation-induced cancer development (2).

As a result of the prolonged survival of oncological patients today, the follow-up of late adverse effects and quality of life has become more important. Fertility preservation is an important component of long-term quality of life. Fertility expectation is increasing, and concerns about fertility significantly affect the emotional and mental health of cancer patients (3,4). Approximately 70–75% of patients who have completed their oncological treatment are considering having babies. However, few patients can access appropriate fertility preservation techniques before or during cancer treatment (3).

RT negatively affects fertility in many ways. The hypothalamus–pituitary–ovarian (H-P-O) axis may be affected due to cranial irradiation, leading to hormonal irregularities and eventually fertility problems. Infertility can be seen with irradiation of the pelvis and abdomen, with direct ionizing radiation (IR) exposure of the uterus and ovaries. Fertility expectations should be questioned before RT, and the most appropriate methods for the patient should be determined and applied before treatment. Since the effect of RT on fertility is usually permanent, fertility procedures should be completed before RT begins (3,5). In this review, the relationship between RT and female fertility is evaluated from many perspectives.

RELATIONSHIP BETWEEN RADIOTHERAPY AND HYPOTHALAMUS–PITUITARY–OVARIAN AXIS

Cranial RT plays an important role in the curative and palliative management of patients with primary or metastatic brain tumors (6). Disturbance of the H-P-O axis, endocrinopathy, and infertility are well-known potential complications of cranial irradiation (7). Radiation-induced hypothalamus and pituitary damage is a common, irreversible, and progressive late complication of RT and may result in endocrinopathy, requiring long-term follow-up. The most important mechanism of radiation in the H-P-O axis is direct cellular damage, and impaired vascularization is another. Additionally, the long latent period in RT-related endocrinopathies also suggests the possible effect of RT on the development of secondary pituitary atrophy after hypothalamic injury (3).

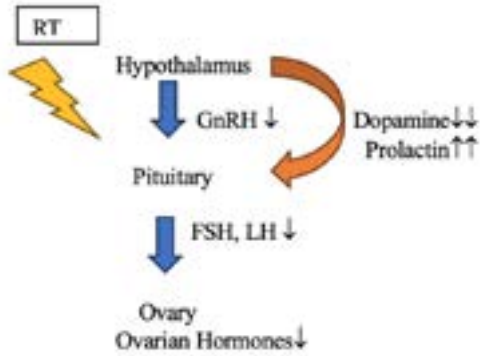
The severity of radiation-induced neurotoxicity varies depending on the total dose of RT, fraction dose, surgery status, concomitant chemotherapy (CT) administration, and tumor location. RT total dose and fraction dose determine the biologically effective dose (BED). Higher BED values are associated with greater damage. Hormonal changes observed in the hypothalamus and pituitary gland after RT have a wide clinical spectrum, from subclinical disease to severe forms (3). Significant gonadotropin deficiency is observed in 20–50% of patients in long-term follow-up (6). In the retrospective study of Koustenis et al., the fertility of patients who underwent cranial RT was evaluated. Patients receiving doses of 30 Gy or more had fewer pregnancies and higher rates of permanent amenorrhea and infertility than those receiving 18–29 Gy or 0–17 Gy. Similarly, Constine et al. determined that the radiation dose threshold, which negatively affects the neuroendocrine axis in the pituitary gland, was 30 Gy (9).

Hormones [gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, and prolactin (PRL)] released from the H-P-O axis have a pulsatile rhythm, which is responsible for the control of fertility. For normal puberty, this pulsatile rhythm should continue in harmony (10,11). Precocious puberty may develop in children due to damage to the H-P-O axis after cranial RT. It can also be observed at doses lower than 30 Gy, which is widely accepted as the threshold for the H-P-O axis. Precocious puberty occurs with disruption of the cortical disinhibition of the hypothalamus. Ogilvy-Stuart et al. evaluated 46 children who underwent cranial RT at a median dose of 30 Gy for primary brain tumors. A relationship was found between cranial irradiation and precocious puberty (12). A similar relationship was observed in the study of Oberfield et al. Additionally, girls are more susceptible than boys to cranial RT–associated prepubertal precox. Lower doses of RT (18–24 Gy) are associated with prepubertal puberty only in girls, whereas higher doses (25–50 Gy) affect both sexes equally (13).

Hyperprolactinemia is another possible outcome of cranial RT

and is associated with a decrease in the inhibitory neurotransmitter dopamine (Figure 1).

Figure 1. Hyperprolactinemia is an adverse effect of cranial RT and is associated with a decrease in the inhibitory neurotransmitter dopamine.



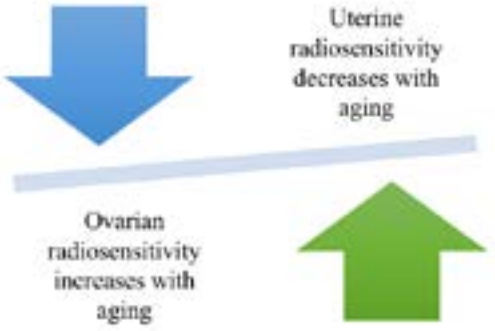
High PRL levels usually do not show clinical symptoms, but they can sometimes cause amenorrhea and galactorrhea in women and puberty problems in children. A mild to moderate increase in PRL levels after RT is observed in 20–50% of adult women and 5% of children (3). In the patient group followed by Pai et al. after cranial RT, 87% had hyperprolactinemia in 10 years. The reason for this high level of hyperprolactinemia may be the long-term follow-up of patients (14) because a long latent period usually occurs before RT-related changes in gonadotropins and other pituitary hormones (15). In the study of Pai et al., the median time for the diagnosis of hypogonadism and hyperprolactinemia in patients followed up after cranial RT was 4 years and 2.5 years, respectively. The length of the latent period of endocrinopathies was emphasized. In this period, when oncological controls became scarce, the importance of controlling endocrine adverse effects was emphasized (14).

RELATIONSHIP BETWEEN RADIOTHERAPY AND UTERUS

The uterus is affected by pelvic irradiation, and RT-related uterine adverse effects can be observed. Endometrial inflammation and fibrosis, myometrial atrophy, and serosal inflammation and fibrosis are observed in the histological examination of the directly irradiated uterus (16). Radiation-related damage to the uterus can cause infertility. Additionally, if pregnancy occurs, it can lead to obstetric complications including abortion, preterm birth, and placental abnormalities (3,15). The severity of uterine damage depends on the total radiation dose, the irradiation site, and the age of the patient at the time of treatment (7).

Uterine damage due to uterine radiation exposure is closely related to the age of the patient. The RT–age relationship of the uterus and ovaries is different. With aging, the radiosensitivity of the uterus decreases, whereas the radiosensitivity of the ovaries increases (Figure 2).

Figure 2. With aging, the radiosensitivity of the uterus decreases, whereas the radiosensitivity of the ovaries increases.



The high sensitivity of the uterus to RT at early ages necessitates the evaluation of patients who have received abdominopelvic RT in childhood. Radiation exposure of the uterus at a young age is a risk factor for future pregnancies. Radiation exposure during childhood causes altered uterine vascularization, decreased uterine volume and elasticity, myometrial atrophy, endometrial fibrosis, and ultimately uterine insufficiency. In elderly patients, uterine and cervical atrophy are observed after RT. In addition to age, menarche status is also important in the uterine damage of RT. When patients were analyzed by menarche status during RT, more preterm births were seen in those who received RT before menarche (17,18). A retrospective study published by Larsen et al. observed that uterine RT exposure in childhood significantly reduced adult uterine volume (19). In a study by Chiarelli et al., patients who received abdominal RT in childhood were analyzed retrospectively. Compared to patients who were only operated, patients who received postoperative RT had significantly higher prematurity, perinatal death, and low birth weight in their pregnancies (20). Research published by Signorello et al. in 2006 was also consistent with the work of Chiarelli et al. This study reported that the risk of preterm birth, low birth weight, and low birth weight for gestational age were increased in the babies of patients who had received RT compared to those who had not (17). In the study of Reulen et al., British childhood cancer survivor data were analyzed. The risk of preterm birth increased by 3 times and the risk of low birth weight increased by 2 times in this patient group (21). Green et al. also reviewed the pregnancy outcomes of childhood cancer patients treated with RT or CT. The probability of infants weighing <2,500 g at birth was significantly higher in patients with pelvic irradiation (22). Based on existing studies, no con-

sensus exists on the radiation dose with which pregnancy will not be sustainable due to uterine damage. However, unsuccessful pregnancy can be predicted in cases receiving >25 Gy in childhood or >45 Gy in adulthood (16). At doses lower than these values, uterine dysfunction may occur. When 14–30 Gy of radiation is applied to the uterus, pregnancy complications due to uterine dysfunction may develop (7). As emphasized in many studies, patients receiving RT in childhood are at high risk of obstetric complications. These patients and their fetuses should be closely monitored during pregnancy.

RELATIONSHIP BETWEEN RADIOTHERAPY AND OVARIES

The most common type of follicle in the human ovary is the primordial follicle, which represents the ovarian reserve. This reserve reaches the maximum level in the intrauterine 5th month in the fetus, then ovarian functions gradually decrease with age, and the menstrual cycle ends by completely losing its activities at an average age of 50–52 years (23). Although a natural decrease occurs in the number of oocytes between birth and menopause, RT can accelerate this, resulting in early menopause and infertility (15). The effects of RT on the ovaries are usually progressive and permanent (3).

In general, cells with high mitotic activity and active DNA replication are more radiosensitive, whereas cells with low mitotic division rates are more radioresistant. However, female germ cells are an exception. Although progenitor female germ cells stop at the first meiotic division, they are extremely sensitive to radiation (3). An article published by Puy et al. in 2021 reported that precursor oocytes are 80 times more radiosensitive than growing oocytes (0.1 versus 8 Gy) (24). A similar result was seen in Stringer et al.'s study: primordial follicles begin to be adversely affected at 0.1 Gy, but the dose for growing follicles is 7 Gy (25). Non-dividing germ cells were previously thought unable to repair genomic damage caused by IR due to a deficiency in DNA repair mechanisms. However, recent research in animal models suggests that mammalian oocytes have a DNA repair capacity. Additional studies are needed to elucidate this (3).

After radiation exposure, the follicles atrophy, and the follicle reserves decrease. Decreased or even stopped production of ovarian hormones can lead to uterine dysfunction due to insufficient estrogen exposure, early menopause, and infertility. The ovarian damage from radiation depends on not only the dose administered but also various factors such as the patient's age, exposure time, concomitant CT, and surgical history (3). Oocytes are highly radiosensitive, with an LD50 (dose required to destroy 50% of oocytes) estimated at <2 Gy (26). The LD50 of oocytes was previously estimated at <4 Gy. In the mathematical model that Wallace revised in 2003, the LD50 of the human oocyte was calculated to be <2 Gy (27). The D0 value is a parameter that measures intrinsic radiosensitivity(28). The D0 value of an oocyte (reciprocal of the slope on the exponential portion of a survival curve) is 0.12 Gy, and according to Duncan et al., infertility was predicted in 5% and 50% of women who received 2–3 Gy and 6–12 Gy, respectively (29).

The relationship of RT with ovarian damage and age is widely studied in the literature. In the mathematical model that Wallace published in 2005, ovarian failure was estimated depending on the age and dose of RT exposure. In this modeling, the risk of ovarian failure after radiation was defined as the effective sterilization dose (ESD). According to this model, the ESD of newborns is 20.3 Gy, the ESD of 10-year-old patients is 18.4 Gy, the ESD of 20-year-old patients is 16.5 Gy, and the ESD of 30-year-old patients is 14.3 Gy (30). In a retrospective analysis, a 20-Gy pelvic RT dose increased the risk of premature ovarian failure (POF) in women younger than 35 years. Even at lower radiation doses, POF can be observed in women older than 35 years due to naturally reduced oocyte reserves (15). The study of Chiarelli et al. observed that the risk of POF caused by radiation increased in a dose-dependent manner. Infertility rates of 22% and 32% were reported at doses of 20–35 Gy and above 35 Gy, respectively (31). In Larsen et al.'s retrospective study, 100 female cancer patients treated with CT and/or RT in childhood were compared with a control group. The median age of the patients was 5.4 years at diagnosis and 25.7 years at enrollment. Seventy patients with spontaneous menstrual cycles had a smaller ovarian volume (4.8 cm3 vs. 6.8 cm3, p<.001) and fewer antral follicles per ovary (7.5 vs. 11, p<.001) compared to the control group. These results show that the ovarian reserve may be decreased in cancer patients with spontaneous menstrual cycles (19).

We do not have enough data on whether different types of radiation (e.g., X-rays, gamma, particulate therapy) have different effects on the ovaries. In Puy et al.'s study, primordial follicle radiosensitivity was compared after exposure to two types of radiation, gamma radiation and X-rays, and the LD50 was calculated as 47 mGy and 38 mGy, respectively (24). Although the effect of IR on the ovaries, whether gamma radiation or X-ray, is predicted to not differ dramatically, insufficient data exist. Studies are needed to evaluate the effects of particle therapy (e.g., proton therapy, carbon ion therapy) on the ovaries and oocytes.

In addition to germ cells, the ovaries contain somatic cells, and these also contribute to the quality and quantity of germ cells. Somatic cells make up the majority of the ovarian cortex and are distributed as follows: stromal cells (83%); oocytes (0.2%); perivascular cells (10%); endothelial cells (5%); granulosa (1.2%); theca and immune cells (0.4%) (23). The fact that these non-oocyte cells undergo apoptosis and necrosis within hours after radiation shows that they are also radiosensitive. The bidirectional relationship between oocytes and non-oocyte ovarian cells is important for follicle survival and quality (29). While evaluating the RT–ovarian relationship, the oocyte microenvironment should also be evaluated, but insufficient research exists on this.

Another concern with ovarian irradiation is the possibility of fetal malformations when irradiated patients become pregnant. Observation of genetic effects in irradiated animals suggests that this effect can also be seen in humans. Animal data show that oocyte radiosensitivity varies widely with the follicle or oocyte stage and mammalian species. In animal experiments, after the ovaries were exposed to high doses (1–5 Gy), congenital anomalies were observed in ongoing pregnancies. However, the extrapolation of animal data to humans requires caution. The probability of such events is low compared with the spontaneous risks of genetic effects, and no increased fetal anomalies were noted in human observations (32). In Mueller's study evaluating female child cancer patients, no significant increase in fetal malformation was observed in their future children (33). The study of Sudour et al. examined the next pregnancy processes of 84 children who received pelvic RT, and no increase in fetal malformation was observed in these babies (34). In addition to RT studies, the relationship between parental radiation exposure and child anomalies has been evaluated by epidemiological studies after radiation accidents and the Hiroshima bombing. Most epidemiological studies have found little evidence of parental radiation-related illness, but these studies are not powerful enough to assess the problem. Some epidemiological studies have found a link between paternal exposure to radiation and babies' neural tube defects, but this association is very weak. Despite growing concern about fetal malformation based on animal experiments, insufficient data from human studies exist to directly prove this relationship (32).

The majority of studies on ovaries and oocytes are based on animal experiments or retrospective observations. Doses predicted to cause damage in preclinical studies were administered over a short time. Not enough information exists about the effect of relatively low-dose exposures in the long term (5,23). In the preclinical study of Reiser et al., 0.1 Gy was applied to the ovary, and this dose had no significant effect on primordial follicles (23). Similarly, in the study of Kimler et al., no change was observed in ovarian follicles with 0.1 Gy, whereas a significant decrease was observed at 1 Gy in a mouse model (35). In the animal model of Kerr et al., a decrease in primordial follicles was observed after 0.45 Gy of gamma radiation (36). The dose of 10 mGy, which is equivalent to a CT scan, did not appear effective on most oocyte- and embryo-level parameters. Based on these data, oocytes can be assumed to repair low-dose radiation damage (37). However, determining a safe radiation dose threshold for the ovaries is not yet possible.

CONCLUSIONS

Fertility is an important component of quality of life, and oncological patients should be questioned about fertility expectations before treatment. RT can irreversibly adversely affect fertility in many ways. Patients with expectations of fertility should be evaluated in terms of RT-induced infertility before treatment, and appropriate interventions should be recommended. Patients receiving cranial RT should be followed up over a long period for endocrinopathies. Dose-dependent uterine and ovarian adverse effects can be observed in patients receiving abdominopelvic RT. These patients are at high risk of infertility and pregnancy complications and should be closely monitored. Parental radiation exposure does not appear significantly associated with inherited genetic disease in their infants.

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