

ERİŞKİN YAŞA GELEN ÇOCUKLUK ÇAĞI VE ADOLESAN KANSER HASTALARINDA UTERİN FONKSİYON VE REPRODÜKTİF SEYİRLERİ

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ÖZET

Pediyatrik tümörlerin tedavisinde kullanılan kemo/radyasyonun üreme sistemi üzerine olan olumsuz etkileri overler sınırlı değildir. Malesef bu hastalar erişkin çağa ulaştıklarında hamilelikleri preterm eyle ce SGA bebekleri ile sıkça komplike olmaktadır. Hemde kemoterapi hemde radyoterapiden olumsuz etkilenen overlerin tersine uterus sadece radyoterapiden etkilenmektedir. Tek başına kemoterapinin uterus üzerinde olumsuz etkisi yoktur. Bu derlemede radyoterapinin uterusu üzerine olan olumsuz etkileri ve mekanizmaları ile gebelik seyirleri konusunda bilgi verilmesi amaçlanmıştır.

ABSTRACT

The impact of cancer therapy for pediatric tumors is not limited to the ovary in the reproductive system. Unfortunately, adverse pregnancy outcomes such as preterm births and delivery of small for gestational age babies are observed in the survivors of childhood cancers as a consequence of previous exposure of the uterus to radiation during childhood. While ovarian function is compromised by both chemotherapy regimens and radiation therapy, uterine dysfunction develops only after exposure to radiation. Chemotherapy alone does not appear to affect uterine function. This review entails the hazardous effects of radiation on the prepubertal uterus and adverse reproductive outcomes in the survivors exposed to radiation prepubertally.

UTERINE FUNCTION AND PREGNANCY OUTCOMES IN THE ADULT SURVIVORS OF CHILDHOOD CANCERS

Uterine function is particularly compromised by radiotherapy. Different compartments of the uterus are being affected by irradiation. First, vascular structures of the uterus are altered leading to decreased uterine blood flow. If pregnancy occurs, this will potentially impair cytotrophoblast invasion resulting in decreased fetal-placental blood flow and fetal growth restriction [1-2]. Uterine elasticity and volume can be decreased from radiation-induced myometrial changes, which can lead to preterm labor and deliv-

ery [3]. For instance one series showed that only four of 38 patients who had received whole-body irradiation (20–30 Gy) during childhood had documented pregnancies and all resulted in mid-trimester miscarriage [4]. Women exposed to radiation postpubertally have a larger uterus and greater likelihood of live birth than those exposed prepubertally [5]. Furthermore, women with ovarian failure secondary to whole-body irradiation (20–30 Gy) have significantly reduced uterine size with no improvement in blood flow and endometrial thickness in response to exogenous sex hormones and absence of uterine artery blood flow by Doppler ultrasonography [6]. Endometrium is another target of radiation, which

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prevents normal decidualization and causing disorders of placental attachment, such as placenta accreta [3, 6-7]. These adverse reproductive outcomes are depicted in the figure.

It was suggested that pregnancy complications including hypertension, fetal malposition, fetal loss or spontaneous abortion, preterm labor, and low birth weight have been observed in association with specific diagnostic and treatment groups [8]. A striking example of this is Wilms tumor. A recent report from the National Wilms Tumor Long-Term Follow-Up Study evaluating 1,021 pregnancies (955 liveborn singletons) observed that the percentages of low birth weight (less than 2,500 g) and preterm (less than 37 weeks of gestation) offspring born to women in the cohort increased with flank radiation dose. In addition, women treated with flank radiation therapy for unilateral Wilms tumor had a higher risk of hypertension complicating pregnancy, fetal malposition, and premature labor [9].

As in the case of ovarian failure, conditioning with total body irradiation for hematopoietic stem cell transplantation particularly increases the risk of early pregnancy loss, preterm birth, and delivery of low birth weight neonates. One study showed that spontaneous abortion terminating the pregnancy was significantly higher in female patients conditioned with TBI compared with rates occurring in those conditioned with cyclophosphamide (37% compared with 7%, $P=.02$). Preterm delivery was also higher than the expected population incidence of 8% to 10% ($P<.001$) and occurred at significantly higher rates in female patients conditioned with TBI compared with those conditioned with cyclophosphamide (63% compared with 18%, $P=.01$). All preterm deliveries resulted in low or very low birth weight neonates with an overall incidence of 25%, which is higher than the expected incidence of 6.5% for the general population ($P<.001$) [10]. The report of the Childhood Cancer Survey Study

in 2002 states that radiation therapy is associated with lower birth weight in the offspring and a higher risk of miscarriage in childhood cancer survivors [11-12]. Children who received 25Gy to the abdomen or pelvis have a higher risk for the development of pregnancy-related complications such as lower birth weight and perinatal death. Survivors' children were more likely to be born preterm than siblings' children (21.1% versus 12.6%; OR=1.9, 95% confidence interval [CI]= 1.4 to 2.4; $P<.001$). Compared with the children of survivors who did not receive any radiotherapy, the children of survivors treated with high-dose radiotherapy to the uterus (>500 cGy) had increased risks of being born preterm (3.5 times higher), low birth weight (6.8 times higher), and small for gestational age (SGA) (4 times higher). Increased risks were also apparent at lower uterine radiotherapy doses (starting at 50 cGy for preterm birth and at 250 cGy for low birth weight). Late effects of treatment for female childhood cancer patients may include restricted fetal growth and early births among their offspring, with risks concentrated among women who receive pelvic irradiation [12]. However, relative risk of malformations among the children of cancer survivors is not significantly different from that of their siblings [13] [14]. Later, in 2009 Childhood Cancer Survey Study in its latest report confirmed these findings in 4,029 pregnancies of 1,915 female survivors of childhood cancers [15]. The study showed that offspring of women who received uterine radiation doses of more than 5 Gy were more likely to be small for gestational age (birthweight <10 percentile for gestational age; 18.2% vs. 7.8%; odds ratio =4.0; 95% CI, 1.6 to 9.8; $P=.003$). Interestingly prior treatment with doxorubicin or daunorubicin increased the risk of low birth weight independent of pelvic irradiation. However, on the other hand the rate of live birth was not lower and the rate of stillbirth was not higher for the patients treated with any particular chemother-

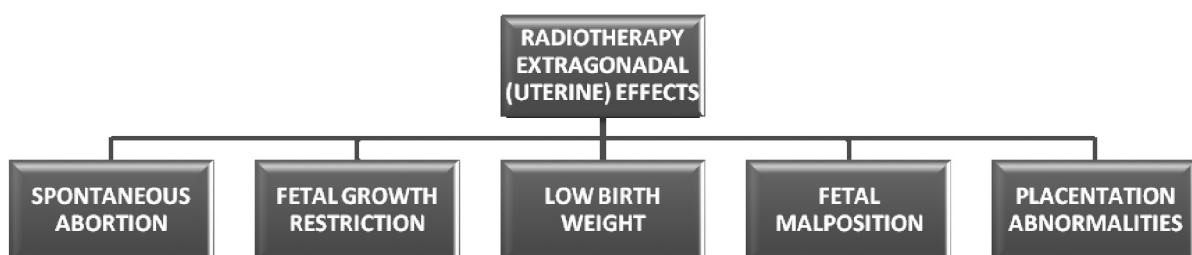


Figure 1-

apeutic agent in comparison to those who had not been treated with the agent. The cumulative doses of several chemotherapeutic agents were divided into tertiles. There was no significant difference in the rate of live birth, miscarriage, or medical abortion by tertile [15]. Apart from the impact of irradiation on uterine function when the uterus is within the radiation field, cranial irradiation (RR=1.4; 95% CI, 1.02 to 1.94) also appears to increase the relative risk of miscarriage –although the risk is lower than those treated with craniospinal irradiation (RR=2.22;95%CI, 1.36 to 3.64)-compared with those who received no radiation therapy [15]. The study also found no differences in the proportion of offspring with simple malformations, cytogenetic syndromes, or single-gene defects. There was no evidence for an increased risk of congenital malformations. Similar results were obtained in other studies such as linked cancer-birth registry analysis, British Childhood Cancer Survivor Study and Danish nationwide cohort study [16-18]

In summary, the offspring of women whose treatment included pelvic irradiation are more likely to be premature, have a low birthweight, and be small for gestational age. The risk of miscarriage was increased among women whose treatment included high-dose cranial or craniospinal irradiation. Prior treatment with doxorubicin or daunorubicin increased the risk of low birthweight independent of pelvic irradiation. But the rates of live birth and stillbirth for the patients treated with any particular chemotherapeutic agent are not different from those who had not been treated with the agent. Relative risks of malformations and congenital anomalies among the children of cancer survivors are not significantly different from that of their siblings.

REFERENCES

- Oktem, O and Oktay, K, Preservation of menstrual function in adolescent and young females. *Ann N Y Acad Sci* 2008; 1135: 237-43.
- Hawkins, M M and Smith, R A, Pregnancy outcomes in childhood cancer survivors: probable effects of abdominal irradiation. *Int J Cancer* 1989; 43: 399-402.
- Knopman, J M, Papadopoulos, E B, Grifo, J A, et al., Surviving childhood and reproductive-age malignancy: effects on fertility and future parenthood. *Lancet Oncol* 2010; 11: 490-8.
- Wallace, W H, Shalet, S M, Crowne, E C, et al., Ovarian failure following abdominal irradiation in childhood: natural history and prognosis. *Clin Oncol (R Coll Radiol)* 1989; 1: 75-9.
- Bath, L E, Wallace, W H, and Critchley, H O, Late effects of the treatment of childhood cancer on the female reproductive system and the potential for fertility preservation. *BJOG* 2002; 109: 107-14.
- Critchley, H O, Bath, L E, and Wallace, W H, Radiation damage to the uterus — review of the effects of treatment of childhood cancer. *Hum Fertil (Camb)* 2002; 5: 61-6.
- Norwitz, E R, Stern, H M, Grier, H, et al., Placenta percreta and uterine rupture associated with prior whole body radiation therapy. *Obstet Gynecol* 2001; 98: 929-31.
- Hudson, M M, Reproductive outcomes for survivors of childhood cancer. *Obstet Gynecol* 2010; 116: 1171-83.
- Green, D M, Lange, J M, Peabody, E M, et al., Pregnancy outcome after treatment for Wilms tumor: a report from the national Wilms tumor long-term follow-up study. *J Clin Oncol* 2010; 28: 2824-30.
- Sanders, J E, Hawley, J, Levy, W, et al., Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. *Blood* 1996; 87: 3045-52.
- Green, D M, Whitton, J A, Stovall, M, et al., Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Am J Obstet Gynecol* 2002; 187: 1070-80.
- Signorello, L B, Cohen, S S, Bosetti, C, et al., Female survivors of childhood cancer: preterm birth and low birth weight among their children. *J Natl Cancer Inst* 2006; 98: 1453-61.
- Boice, J D, Jr., Tawn, E J, Winther, J F, et al., Genetic effects of radiotherapy for childhood cancer. *Health Phys* 2003; 85: 65-80.
- Chow, E J, Friedman, D L, Yasui, Y, et al., Timing of menarche among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer* 2008; 50: 854-8.
- Green, D M, Sklar, C A, Boice, J D, Jr., et al., Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. *J Clin Oncol* 2009; 27: 2374-81.
- Mueller, B A, Chow, E J, Kamineni, A, et al., Pregnancy outcomes in female childhood and adolescent cancer survivors: a linked cancer-birth registry analysis. *Arch Pediatr Adolesc Med* 2009; 163: 879-86.
- Reulen, R C, Zeegers, M P, Wallace, W H, et al., Pregnancy outcomes among adult survivors of childhood cancer in the British Childhood Cancer Survivor Study. *Cancer Epidemiol Biomarkers Prev* 2009; 18: 2239-47.
- Langagergaard, V, Horvath-Puho, E, Norgaard, M, et al., Hodgkin's disease and birth outcome: a Danish nationwide cohort study. *Br J Cancer* 2008; 98: 183-8.