

Uterine Function and Reproductive Outcomes in the Female Survivors of Childhood and Adolescent Cancers: Review

Erişkin Yaşa Gelen Çocukluk Çağı ve Adolesan Kanser Hastalarında Uterin Fonksiyon ve Reprodüktif Sonuçlar

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ABSTRACT Uterine functions may adversely be affected by radiation treatments for childhood cancer. The uterine vasculature exposed to radiation therapy may not respond normally to cytotrophoblast, the resulting decrease in fetoplacental blood flow may lead to impaired fetal growth in case of a probable pregnancy. Also as a result of the negative impact of radiotherapy to myometrial layer, uterine elasticity and volume may be reduced. In particular, this effect is more pronounced in patients receiving radiotherapy before puberty. Radiotherapy may injure the endometrium layer and result in disorders of placental attachment, such as placenta accreta or increta. Obstetrical consequences include an increased risk of hypertension, fetal malposition, spontaneous abortion, pregnancy loss, preterm birth, low birthweight. In addition, an increased risk of spontaneous abortion is observed in patients treated with high dose cranial or craniospinal radiation. Other than complications due to radiotherapy, low birth weight can occur in patients undergoing chemotherapy treatment such as doxorubicin or daunorubicin. When comparing patients treated with chemotherapy with those who did not, no significant difference in terms of low birth weight infants, or spontaneous abortion was observed. There was no significant difference considering risk of developing minor anomalies, cytogenetic syndrome or single gene defect in patients with a history of radiotherapy or chemotherapy. In this review, we aim to examine effects of chemotherapy and radiation therapies for childhood cancer on uterine functions.

Key Words: Uterus; reproductive health; radiotherapy

ÖZET Çocukluk çağında radyoterapi uygulanan hastalarda, uterin fonksiyonlar olumsuz etkilenebilmektedir. Uterin damarsal yapılarında oluşan değişiklikler sonucunda, kan akımında azalma ve olası bir gebelik durumunda, sitotrofoblast invazyonunda yetersizlik sonucunda fetal kan akımında bozulmaya bağlı olarak, fetüsün büyümesinde olumsuzluklar görülebilmektedir. Ayrıca radyoterapinin miyometrial tabakaya olumsuz etkisi sonucunda uterin elastisite ve volümde de azalma gelişebilmektedir. Özellikle bu etkilenme, puberte öncesi radyoterapi uygulanan hastalarda daha belirgin olmaktadır. Radyoterapinin endometrial tabaka üzerine de olumsuz etkileri olabilmekte ve bunun sonucunda plasentasyon bozuklukları örneğin plasenta akreata, inkreata gibi rahatsızlıklar gelişebilmektedir. Tüm bu olumsuzluklar neticesinde de gebelik sırasında hipertansiyon, fetal malpozisyon, fetal kayıp ya da spontan abortus, preterm doğum ve düşük doğum ağırlıklı bebek doğumu gibi komplikasyonların gelişme riski artmaktadır. Ayrıca yüksek dozda kranial ya da kraniospinal radyasyon uygulanan hastalarda da spontan abortus riskinde artış olabilmektedir. Radyoterapiye bağlı gelişen bu komplikasyonlar dışında, radyoterapi uygulanmasında bağımsız olarak, doxorubisin ya da daunorubisin gibi kemoterapötik ilaçların kullanımı sonucunda da düşük doğum ağırlıklı bebek doğumu görülebilmektedir. Ancak kemoterapi tedavisi uygulanmış hastalarda, uygulanmayanlarla karşılaştırıldıklarında, ne canlı doğum ne de abortus oranları arasında bir fark görülmemektedir. Radyoterapi ya da kemoterapi kullanma öyküsü olan hastalarda, minör anomaliler, sitogenetik sendrom ya da tek gen defekti gelişme riskinde ise bir farklılık olmamaktadır. Bu derlemede, çocukluk çağı kanserlerinde, kemoterapi ve özellikle radyoterapi uygulanmasının uterin fonksiyonlar üzerine olan etkisi incelenecektir.

Anahtar Kelimeler: Uterus; üreme sağlığı; radyoterapi

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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 delivery.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. Even if the uterus is able to respond to exogenous sex steroid stimulation, a successful pregnancy outcome is by no means ensured.⁶ Endometrium is another target of radiation, which 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 (Figure 1).

UTERINE FUNCTION AND PREGNANCY OUTCOME

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

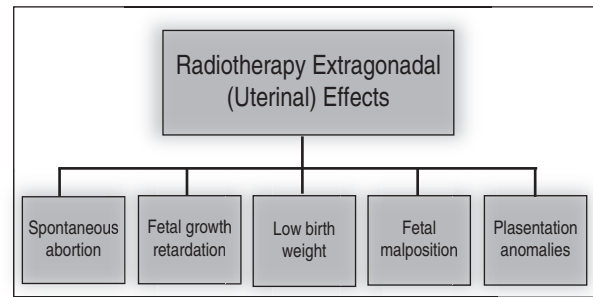


FIGURE 1: Bad reproductive outcomes developed due to radiotherapy.

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 (TBI) 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%, $p=0.02$). Preterm delivery was also higher than the expected population incidence of 8% to 10% ($p<0.001$) and occurred at significantly higher rates in female patients conditioned with TBI compared with those conditioned with cyclophosphamide (63% compared with 18%, $p=0.01$). 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 ($p<0.001$).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; $p<0.001$). 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; $p=0.003$). 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 chemotherapeutic agent in comparison to those who had not been treated with the agent. The cu-

mulative doses of several chemotherapeutic agents were divided into patients. There was no significant difference in the rate of live birth, miscarriage, or medical abortion.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 birth weight 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.

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