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# Review: Influence of Radiation on Female Fertility and Pregnancy

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## Abstract

Radiations made up of non-ionizing and ionizing radiations, this classification is based on the ionizing power and the energy of radiations. In developed and developing communities, people are continually exposed to radiations which are generated from variety sources that are naturally occurring or producing by human. The purpose of this study is to review accessible information on the influence of radiation on female fertility and to discuss the options for fertility preservation. Radiation exposure can result in impairment of tissue integrity and sometimes, leading to organs dysfunction, the impact of radiations on organs depends on site of irradiation, patient age and total radiation dose. Female patients who are treated with radiation have an increased rate of uterine dysfunction, ovaries dysfunction, impaired fertility, incidence of pregnancy complications, premature birth and miscarriage. Pre-pubertal uterus is more vulnerable to the effect of radiation, compared with the pubertal uterus due to arising ovarian estrogen production and uterus enlarges. To reduce the effects of radiations on female reproductive organ, fertility preservation procedures such as ovarian transposition, reproductive gland protection and oocyte cryopreservation should be carried out before and/or during radiotherapy.

**Keywords:** Cancer, Radiotherapy, fertility, pregnancy, ovary dysfunction.

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# مراجعة: تأثير الإشعاع على الخصوبة والحمل عند النساء

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## الملخص

تصنف الاشعاعات الى اشعاعات مؤينة غير مؤينة اعتمادا على قدرة التأين وطاقة الاشعاعات. في المجتمعات المتقدمة والنامية، يتعرض الناس باستمرار للإشعاعات التي تتولد من مصادر متنوعة تحدث بشكل طبيعي أو ينتجها الإنسان. الغرض من هذه الدراسة هو مراجعة المعلومات التي يمكن الوصول إليها حول تأثير الإشعاع على خصوبة الإناث ومناقشة خيارات الحفاظ على الخصوبة. يمكن أن يؤدي التعرض للإشعاع إلى إضعاف سلامة الأنسجة، وفي بعض الأحيان يؤدي إلى خلل في وظائف الأعضاء، ويعتمد تأثير الإشعاع على الأعضاء على موقع التشعيع وعمر المريض والجرعة الإجمالية للإشعاع. تعاني النساء اللواتي يتم علاجهن بالإشعاع من زيادة معدل ضعف الرحم، وضعف المبيضين، ضعف الخصوبة، حدوث مضاعفات الحمل، الولادة المبكرة والإجهاض. يكون الرحم قبل البلوغ أكثر عرضة لتأثير الإشعاع مقارنة بالرحم عند البلوغ بسبب إنتاج هرمون الاستروجين في المبيض وتضخم الرحم. لتقليل آثار الإشعاع على العضو التناسلي الأنثوي، يجب إجراء إجراءات الحفاظ على الخصوبة مثل تبديل المبيض وحماية الغدة التناسلية وحفظ البويضات قبل و / أو أثناء العلاج الإشعاعي.

**الكلمات الدالة:** السرطان، العلاج الإشعاعي، الخصوبة، الحمل، ضعف المبيض.

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## 1. Introduction:

Radiation is energy which could be in the form of waves or particles [1]. In developed and developing communities, people are continually exposed to non-ionizing and ionizing radiations which generate from various of sources that naturally occurring or producing by human. It could be from non-ionizing radiation (e.g., TV, mobile, solar light, and laser therapy device) or from medical applications (e.g., diagnostic imaging and radiotherapy). However, radiation associated with some biological effects, regardless the types and the source of radiation as well as the amount of the dose [1, 2].

Radiations are divided into two groups, ionizing and non-ionizing, this classification is based on energy and capability of radiations to produce ions [3, 4]. Energy of ionizing radiation is above 10 eV, which has sufficient energy to generate ions and have an impact on cellular level. This is a vital distinction because of the substantial difference in injuriousness to organs. Ionizing radiation could be particle such as alpha (α) and beta (β) particles. Alpha (α) particles are a positive charge particle (+2), and their emission can result in decreasing the number of proton and neutrons. Their range is about 5 cell diameters in the mammalian and are considered to have a heavy linear energy transfer (LET). This results in alpha-particle emitters to be less applicable in therapeutic aspects [5, 6].

Beta particles are either negative charge particle (negatrons) or positive charge particle (positrons) [7], which emitted as a consequence of decomposing the nucleus radioactive material. Their emission can result in increasing the number of protons by one or decreasing neutron by one, and their range is much more compared to α particles. They are considered to have very low linear energy transfer (LET). Consequently, beta-particle emitters have high a therapeutic efficacy [6].

Ionizing radiation could be wave form such as X-rays and gamma (γ) rays which have been used in diagnostic imaging and anticancer treatment [5]. γ-rays originating from the nucleus, while x-rays emitted from the electron shell described as characteristic X-ray or continuous X-rays can be produced through the acceleration or deceleration of charged particles. A potential ionization produced as a result of interaction of X-rays with matter. This causes the chemical and biological effects. The capability of penetrating wave forms radiation elevated when the energy increase, decrease with elevating the atomic number of the absorbed material [8, 9]. The purpose of this study is to review accessible information on the influence of radiation on female fertility and to discuss the options for fertility preservation.

## 2. Types of Radiation:

Radiations made up of non-ionizing and ionizing radiations, this classification is based on the ionizing power and the energy of radiations [10].

### 2.1. Non-ionizing Radiation:

Non-ionization radiations have a much longer wave length, when compared to ionizing radiation therefore, Non-ionizing radiations are located at the bottom section of the frequency spectrum, their energy is lower than energy that need to have an impact on electron shell. The energy below the ultraviolet spectrum cannot ionize atoms, and break bonds. However, they can result in vibrations in the bonds [11, 12].

Non-ionizing radiation starts at (0Hz) that is from direct current, rising frequency to (50-60 Hz) that are from electric power. 30 kHz is considered as a very low frequency which followed by radio frequencies, microwave, infrared, visible and ultraviolet light, respectively [3] [13].

### 2.2. Ionizing Radiation:

Ionizing radiation has enough energy to deprive atoms from the cells and convert them into ions. Most ionizing radiation that come from radioactive materials are invisible and undetectable by human senses; thus, different types of detectors are needed to detect them. Ionizing radiations have many practical uses and applications in medicine, but they present a health hazard. Exposing to radiation can result in damaging living tissue. High doses radiation exposure could cause acute radiation syndrome (e.g., hair loss, internal organ failure, and skin burn), while low and moderate doses are more associated with increasing cancer risk and genetic damage such as thyroid cancer that often occurs due to the nuclear accidents and nuclear explosions and the biological tendency of the radioactive iodine(iodine-131) [14], thereby ionizing radiation is generally harmful and potentially lethal.

The two predominant categories of ionizing radiation are (X-Rays and gamma ($\gamma$) rays) that can be used to treat cancer cells, while they are known to cause damage, including, the induction of cancer after years or decades of exposure, also resulting in skin burn and hair loss with high doses [14].

## 3. Biological Effects of Radiation:

Human beings are constantly exposed to radiation from variety of sources that naturally occurring or producing by human. This radiation can affect living cells, leading to ionize molecules and malfunctions in cell processes. The influence of radiation is determined by the type and energy of radiation, the amount of dose, age, sex, and the long-term exposure [15]. The first biological damage of exposure to radiation was observed by Roentgen's discovery of the X-ray in 1895, following years, the impact of radiation was based on the experience of early radiologists and workers in miners [16, 17].

### 3.1. Mechanisms of Radiation Damage:

When radiation exposed to an organ, its damage initiate at the cellular level through absorbing radiation by cells and particularly has the potential effect on DNA. Studies showed that impaired DNA can result in mutation, and can lead to cell death [15, 16].

Through two important mechanisms (direct and indirect effects) radiation can impact on cells:

#### 3.1.1. Direct Effect:

In this interaction, radiation affects DNA molecule directly and resulting in ionizing DNA molecule, often cells may reproduce themselves and survive. However, sometimes cells cannot repair themselves, and leading to improper replicate of chromosomes then cells may be damaged directly. The probability of occurrence of this action is uncommon due to a small diameter of the DNA [16, 17].

#### 3.1.2 Indirect Effect (water radiolysis):

This action occurs in the presence of water, radiation interacts with water, resulting in generation of free radicals, they are characterized by an unpaired electron, which are recognizable as they are chemically highly reactive. They have capability to diffuse distance in the cells and damage DNA. Radiation-induced harm due to indirect action is more frequent compared to those harm that generate as result of direct action. Indirect action is more prominent in low linear energy transfer (LET) radiation (e.g. gamma rays and X-rays) [14, 15]. An ion pair of HOH+ and e- are produced through the interaction of radiation with water, $H_2O + \text{radiation} \rightarrow HOH^+ + e^-$. The electron recombines with HOH+ ion or it may react with another water molecule and forming a free radical that characterized by unpaired electron.

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$H2O + e- \rightarrow HOH-$

The $HOH^-$ attempts to divide into hydroxyl ($OH^-$) and hydrogen free radical (H*).

$HOH^- \rightarrow OH^- + H*$

Free radicals attempt to reconnect with another oxygen, producing hydroperoxyl radicals. The hydroperoxyl radicals may result in biological impair directly or fragment create hydrogen peroxide and oxygen:

$H*+O_2 \rightarrow HO_2*$

$HO_2* \rightarrow H_2O_2+O_2$

A hydroxyl radical OH* and $H_3O$ formed through the interaction of the $HOH^+$ with HOH molecule and ion $H^+$ and a hydroxyl radical producing as result of breaking down $HOH^+$:

$HOH^+ + HOH \rightarrow OH* + H_3O$

$HOH^+ \rightarrow H^+ + OH*$

The hydroxyl radicals interact with other hydroxyl radicals, create $H_2O_2$ (hydrogen peroxide).

$OH* + OH* \rightarrow H_2O_2$

The hydrogen peroxide results in about two thirds of all biological damage [15-17].

### 3.2 Deterministic and Stochastic Effects:

Radiation exposure result in impairment of tissue integrity and function, ICRP has classified such deleterious radiation effects into either stochastic effects or deterministic effects.

#### 3.2.1. Deterministic Effects:

Deterministic effect is function of dose with threshold, which is a point below there is no observable effect. These effects are due to acute exposure. It requires the killing of many cells in the affected organ to occur. This leads to a loss of organ function. Cataracts and infertility are example of deterministic effect [16, 17].

#### 3.2.2. Stochastic Effects:

Stochastic effects results from chronic exposure and have a non-threshold and the probability occurring is a function of dose. Stochastic effects are supposed to result from

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damaging a small number or directly affecting the critical target of the cell (DNA) that result in large number of abnormal cells. These cells can develop as a form of cancer or causing heritable disease. Cancer does not appear immediately after exposure, such as two years for leukemia to thirty years or possibility longer for some solid cancers. Radiation risk from diagnostic imaging of pregnancy women is considered to be stochastic [16, 17].

## 4. Radiotherapy:

Radiotherapy is one of the standard modalities that can kill cancer cells, prevent its recurrence, or reduce symptoms. Radiotherapy uses ionization radiations that can kill cancer cells or halt their ability to reproduce, through deposition energy in the cells of the tissues [18]. Although exposing to radiation can damage normal and cancer cells, the aim of radiotherapy is to expose the maximum radiation dose to cancer cells while the minimum dose to healthy cells. Abnormal cells have fewer capabilities to recover when compared to normal cells [19]. In order to eradicate tumors, patients receive radiotherapy as part of their treatment. Some of them need other treatments, such as chemotherapy or surgery [20].

Radiotherapy use two main approaches to deliver radiation: External or internal in the first method: photons, protons or particle radiation is delivered from outside the body to the location of the tumor, in the second modality: a radioactive source can be placed either inside the lesions or nearby. Selection of the treatment depends on the shape and size of the cancer, where the tumor is located and the type of cancer [21].

## 5. Female Reproductive Organ:

Females are born with nearly 500,000-1000,000 primordial follicles, the number is continuing to reduce with increasing age, primarily through apoptosis and atresia [22], declining to about 1000 at 50 years, which is considered as a time of menopause. Cells with high mitotic activity are more likely to be damaged when exposed to radiation, compared to those which has low mitotic activity [23, 24].

### 5.1. Ovarian Dysfunction

Ovarian follicles are impaired by radiation through damaging DNA, resulting to follicular atrophy and reduced ovarian follicular store. This can cause reduction in follicle numbers and

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decline in producing ovarian hormone. Uterine dysfunction can occur as a result of insufficient estrogen and premature menopause [25].

Patient who underwent pelvic irradiation are more likely to experience ovarian dysfunction [26, 27]. The degree of the ovary damage depends on patient characteristics (e.g., age), amount of dose, exposure time and extent of radiation treatment field. According to Al Ogilvy -Atuart and S m Shalet a dose of 4 Gy can lead to 30% infertility in young female patients, while in female above 40 years, it can cause 100% sterility [25].

Wallace et al., performed a study and indicated that the dose that was necessary to damage half of the immature oocytes should be below 2Gy. In addition, Wallace et al., attempted to estimate the correlation between ovarian failure and age, by accounting radiation dose and age during treatment.

The effective sterilizing dose (ESD) defined as a dose can result in ovarian failure happens instantly after radiotherapy. The results showed that ESD reduced with elevating age. The predictable value of effective sterilizing dose (ESD) was the highest at birth which was 20.3 Gy, reduced to 18.4 Gy at 10 years, and for 16.5Gy, 14.3 Gy at 20 years and 30years, respectively [26-28]. a dose of (20–30 Gy) to whole abdominal, can result in 97% ovarian failure, and a dose of 9.2–15.75 Gy to total body, can lead to ovarian insufficiency in 90% adult patients who treated with radiation during their childhood [29]. Recently, a systematic review showed the effect of the radioactive iodine therapy ($^{131}$I) on ovarian function, most of the articles indicated that the radioactive iodine therapy ($^{131}$I) is not linked with ovarian failure and reduction in pregnancy rate; however, meta-analysis study showed that $^{131}$I can result in decrease the hormones such as anti-Mullerian hormone (AMH) that needed for regular ovarian functions [30]. In 2019, Mantawy and coworkers reported that the premature ovarian failure in the immature female Sprague-Dawley rats that exposed to a dose of 3.2 Gy γ-radiation, and showed that treated rats with chrysin can ameliorate premature ovarian failure as a result of radiation [31]. Similarly, Mahran et al., exposing Wister rats, with a dose of 3.2 Gy *γ*- ray to whole-body irradiation, found that irradiation-induced ovarian damage that approved through histopathological findings and hormonal changes, and showed that administration rat with the carvacrol can protect the ovarian from failure [32]. Likewise, a present study showed that ovaries of irradiated rats can be preserved through Ethinyl estradiol treatment prior to exposing to radiation [33], Table 1.

**Table 1:** Types of radiation and effects on ovary function.

| Author | Types of radiation | Dose | Organs exposed to radiation | Effects |
|---|---|---|---|---|
| **Al Ogilvy - Atuart and S m Shalet [25]** | X-rays | 4Gy | Ovary | 30% infertility in young female patients, while in female above 40 years, it can cause 100% sterility |
| **Wallace et al., [26]** | X-rays | > 2Gy | Ovary | It can damage half of the immature oocytes |
| **LE. Bath et al., [29]** | X-rays | | Whole abdominal irradiation | It can result in 97% ovarian failure |
| **Piek MWet al., [30]** | $^{131}$I(beta particle) | 1110–40,700 MBq | Thyroid | It can decrease the hormones such as anti-Mullerian hormone (AMH) |
| **Mantawy et al., [31]** | γ-radiation | 3.2Gy | Whole-body irradiation | Ovarian failure in the immature female Sprague-Dawley rats |
| **Mahran et al., [32]** | γ-radiation | 3.2 Gy | Whole-body irradiation | Ovarian damage in rat |
| **Mahran et al., [33]** | γ-radiation | 3.2 Gy | Whole-body irradiation | Ovarian damage in rat |

### 5.2 Uterus Dysfunction:

Radiotherapy can have a long-term effect on uterus, this concept comes from those studies that females treated with radiation for childhood cancers [34]. However, this brings limitations for adult women as the uterus vary during puberty [35-36], the impact of radiations that have on uterus depending on site of irradiation, patient age, and total radiation dose [37-38]. Pre-pubertal uterus is more vulnerable to the effect of radiation, compared with the pubertal uterus due to increasing ovarian oestrogen production and uterus enlarges [35-36].

It has been reported that a dose from 14 to 30 Gy of radiation treatment can cause changes in the uterus including, undetectable blood supply, reduced uterine volume and myometrial fibrosis [39]. Holm et al., revealed the effects of total body irradiation (TBI) on both uterine volume and blood using sonography and a dose of 8 Gy and 14 Gy, the results showed a significant decline in uterine volume [40]. In addition, in a review by Critchley et al., indicated that the uterine volume of young women that exposed to radiation, decreased to 40%, and showed that young female patients that exposed to radiation during their childhood as a part of their anticancer treatment were more likely to have deleterious effects on future pregnancies [41].

Larsen et al., reported that, direct and indirect exposing uterus to radiation in young woman can result in decreasing uterine volume, indirect irradiation explained by those that generate due to scattering radiation [42].

Uterine function was assessed in nine females who diagnosed with childhood leukemia. Assessments were performed after 4.0 to 10.9 years after TBI. Uterine volumes significantly reduced, resulted in damaged uterine blood flow, six patients had systolic blood flow, while one patient had diastolic blood flow. In contrast, children without leukemia showed that only thirty-five percentage experienced the diastolic blood flow. This showed that exposing to radiation at time of pre-pubertal can result in an irreparable impact on uterine growth and vasculature [39-40]. Women who received a dose of 45Gy to uterus during adulthood and less than 25Gy in childhood should avoid attempting pregnancy as a uterus start to function irregularly, while pentoxifylline and tocopherol may improve uterine function [43]. In narrative review by Buonomo et al., concluded that patients who received radiation to uterine may experience the endometrium, myometrium, and less elastic uterus. Additionally, they indicated that cancer survivors whose pelvic exposed to a dose of 4–45 Gy radiation and (4–25 Gy if childhood radiation) might become pregnant, but with the increasing risk of pregnancy complications [44]. Furthermore, another study showed that a girl who received radiation at prepubertal age, uterine growth is less and is resistance to hormone therapy. In contrast, female who exposed to radiation at post-puberty age, can take advantage from hormone replacement therapy, as explained by growth uterine volume and function [45]. Ali and Chaudhary indicated that dose of 46Gy to endometrial can result in uterine dysfunction [46].

**Table 2:** Outcomes of radiation on uterus function.

| Author | Dose | outcome |
|---|---|---|
| **EM. Laursen et al., [39]** | 14 to 30 Gy | Reduced uterine volume and myometrial fibrosis |
| **Holm et al., [40]** | 8 Gy and 14 Gy | Decline in uterine volume |
| **The et al., [43]** | 45Gy to uterus during adulthood and > 25Gy in childhood | Uterine function irregularly |
| **Buonomo et al., [44]** | a dose of 4–45 Gy radiation and (4–25 Gy if childhood radiation) | Increasing risk of pregnancy complications |
| **Ali & Chaudhary [46]** | 46 Gy | Uterine dysfunction |

### 5.3 Effects of Radiation on Pregnancy and Newborn:

A number of publications evaluated the deleterious effects of radiation on pregnancy in those females who treated with radiation [47-49]. In addition, several studies on detrimental influence radiation on pregnancy among young cancer survivors that received radiation as a part of their treatment were carried out and showed an elevation in deleterious effects of radiation on pregnancy and newborn in women patients who had received radiation during their childhood [50, 51], including low weight in newborn and detaining the growing up in uterus [52, 53]. Additionally, in two studied by Arrive et al., and Green et al., who pointed out treating young women with the total body irradiation (TBI) can result in premature birth and miscarriage [54, 55].

The impacts of radiation on fertility are dependent on the amount of dose and whether unborn child at an embryonic or a fetal stage, for example exposing to radiation during early gestation (less than two weeks) most often results in pregnancy loss. Additionally, embryo from (2 to 7 weeks) is more likely to be affected by radiation. Also, malformations of body parts and developmental delays can happen, while occurring are based on the radiation dose, whether below or above threshold [56, 57].

There are also very limited data on the increasing risk of congenital anomalies and childhood cancer in children whose parents have been treated with radiation during their childhood [58, 59]. A study by Larsen et al., demonstrated ovum donation in three female survivors of cancer in childhood and Adolescene who were treated with radiotherapy in the form of TBI. First female, treated post pubertally, uterine volume was (41.8 ml) which is considered as a normal uterine volume, had childbirth at thirty-seventh week gestation and the baby was healthy. The second female, treated prepubertally (aged 12.9 years), uterine volume was small (9.4 ml) as severe impairment of uterine growth and miscarried at seventeenth weeks gestation. The third patient, uterine volume was (31.9 ml), treated post pubertally, not became pregnant when Larsen et al., published their article. This study concluded that pregnancy is possible by oocyte donation despite TBI in adolescence [60].

This agrees with the finding of bath et al., who determined the final status of the uterine volume by both age and pubertal [29]. Green et al., focused on the increasing possibility of occurring unnatural birth, miscarriage, and abortion in female survivors. Childhood Cancer Survivor Study (CCSS) performed a questionnaire that filled in and returned by women participant who diagnosed between 1970 and 1986, The questionnaires comprise of achieving pregnancy and outcome of pregnancy. (i.e., live birth, still birth, miscarriage, abortion). 1915 females achieved 4029 pregnancies, among these, the results were; live birth was more than 60%, abortions, and miscarriage were less than 20%, in stillbirth and in gestation had the lowest percentage which were1% and 3% respectively. More importantly, the possibility of occurring miscarriage was increased when ovaries close to radiation area. In contrast, the possibility of miscarriage was not increased when ovaries shielded. Women with pelvic irradiation are more likely to have baby with low-birthweight [54].

**5.4. Measures to preserve fertility:**

Infertility is still one remaining issue that experienced by survivors who were treated with radiation during their childhood [61]. Ovarian transposition is considered as preservation

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measure for childhood cancer survivors [61-63]. Kalapurakal et al., assessed the protection of the abdominal from radiation in those children who had radiotherapy with a dose of 10-20 Gy and results showed that abdominal can be preserved [64]. Women who are about to undergo radiotherapy have different options regarding fertility conservation. For example:

• **Oocyte cryopreservation:** Oocyte undergo artificial hormone therapy and the unfertilized oocytes are then frozen. This technique can be performed prior to radiotherapy [63-66]. Although Oocyte cryopreservation allow female patients to delay reproduction, only 100babies reportedly born from oocyte storage prior to 2004 [67], and over 500live births generating from this technique before 2010 [68].

• **Reproductive gland protection:** During radiation in an area far from the pelvis, carefully placed shields can reduce the exposure of the reproductive organs to the scatter radiation [62].

• **Ovarian transposition (changing the ovary position):** In this procedure, the position of one or both ovaries are surgically altered, thus they are protected from the planned radiation field. However, due to scatter radiation, the ovaries are not always protected. After treatment, the patient may need to change the position of the ovaries again or use in vitro fertilization (IVF) for pregnancy [64] [69]. In addition, several studies have assessed the efficacy of ovarian transposition and the results varied widely [70-72]. This is variation among these studies might refer to the differences in the amount of dose that delivered to patients and age of patients, shielding of ovaries and whether chemotherapy is present or not [73].

Additionally, a retrospective control study showed that ovarian transposition prior to radiotherapy can preserve ovarian in patients aged less than 35 years and there is ongoing debate about the safety and effectiveness of the ovarian transposition in females aged 36-40 years [74].

• **Surgical removal of the cervix (radical removal of the cervix):** when cervical cancer at early stage, this procedure can help preserve the uterus [66]. Furthermore, A systematic review showed that fertility-sparing can be achieved through the radical trachelectomy [75].

## 6. Conclusions:

Radiation has deleterious impacts on the female genital tract including, natural growth or reduce numbers of eggs and destroy hormones that linked to birth. The extent of the damage that occurs to uterus and ovaries depends on site of irradiation, patient age, and total radiation

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dose. Pre-pubertal uterus is more vulnerable to the effect of radiation, compared with the pubertal uterus due to increasing ovarian oestrogen production and uterus enlarges. To reduce the effects of radiations on female reproductive organ, fertility preservation procedures for example; ovarian transposition, oocyte cryopreservation and reproductive gland protection should be carried out before and/or during radiotherapy. It is necessary to counsel and inform patients about available fertility preservation techniques prior to performing producers by fertility specialist. To improve fertility preservation in female cancer patients, more retrospective and prospective studies needed on impact radiation on fertility.

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