

Case Report

# Dosimetric Evaluation of the Uterus in Patients Receiving Total Body Irradiation with Ovarian Shielding

Keiko Akahane<sup>a</sup> Shinichi Kako<sup>b</sup> Masato Suzuki<sup>a</sup> Yuta Takahashi<sup>a</sup>  
Shogo Hatanaka<sup>c</sup> Masahiro Kawahara<sup>a</sup> Yukari Nakada<sup>a</sup>  
Kazunari Ogawa<sup>d</sup> Satoru Takahashi<sup>d</sup> Yukiko Fukuda<sup>d</sup> Masashi Endo<sup>d</sup>  
Noriko Oyama-Manabe<sup>a</sup> Yoshinobu Kanda<sup>b, e</sup> Katsuyuki Shirai<sup>a, d</sup>

<sup>a</sup>Department of Radiology, Jichi Medical University Saitama Medical Center, Saitama, Japan;

<sup>b</sup>Division of Hematology, Jichi Medical University Saitama Medical Center, Saitama, Japan;

<sup>c</sup>Department of Radiation Oncology, Saitama Medical Center, Saitama Medical University, Saitama, Japan;

<sup>d</sup>Department of Radiology, Jichi Medical University, Tochigi, Japan; <sup>e</sup>Division of Hematology, Department of Medicine, Jichi Medical University, Tochigi, Japan

## Keywords

Total body irradiation · Ovarian shielding · Fertility · Uterus · Radiation dose

## Abstract

Infertility is a well-known late complication in patients receiving hematopoietic stem cell transplantation (HSCT). We previously reported that total body irradiation (TBI) with ovarian shielding reduces the radiation dose to the ovaries to 2.4 Gy – one-fifth of the dose compared to conventional TBI – and preserves fertility without increasing the risk of relapse. Exposure to the uterus and ovaries can reportedly affect pregnancy and childbirth. However, the dose constraint of the uterus that causes infertility remains unknown. Herein, we report the pregnancy and birth outcomes of 2 patients who gave birth following TBI with ovarian shielding and evaluated the dose to the uterus using a dose-volume histogram. Case 1 involved a 30-year-old woman with acute myeloid leukemia who underwent HSCT at 21 years of age with a uterus mean dose ( $D_{\text{mean}}$ ) of 7.0 Gy. She had a natural pregnancy and elective cesarean section at 38 weeks of gestation due to hypertensive disorders of pregnancy. She gave birth to a normal-birthweight infant. Case 2 involved a 32-year-old woman with T-cell acute lymphoblastic leukemia who underwent HSCT at 30 years of age with a uterus  $D_{\text{mean}}$  of 7.6 Gy. Her baby was delivered at full term with normal birthweight. These results indicate that a uterus  $D_{\text{mean}}$  between 7.0 and 7.6 Gy does not have a significant impact on pregnancy and delivery with the ovarian function being preserved for patients who received TBI with ovarian shielding after puberty.

© 2022 The Author(s).

Published by S. Karger AG, Basel

Correspondence to:  
Keiko Akahane, keiko-a@omiya.jichi.ac.jp

## Introduction

Infertility is a well-known late complication in patients receiving hematopoietic stem cell transplantation (HSCT). High-dose (HD) busulfan and total body irradiation (TBI) are known risk factors for fertility impairment in patients treated with HSCT [1, 2]. With improvements in transplantation outcomes, infertility is an important issue for long-term survivors.

TBI is often performed as part of a conditioning regimen before HSCT. Although successful pregnancies after HSCT have been reported, female survivors of TBI are at risk of radiation damage to the uterus and ovaries [3]. To preserve ovarian function in patients with hematologic malignancies, standard care options before HSCT include embryo or oocyte cryopreservation [4]. A future option for fertility preservation in women treated with TBI is uterine transplantation. However, no effective treatment for uterine factor infertility has been established thus far [5].

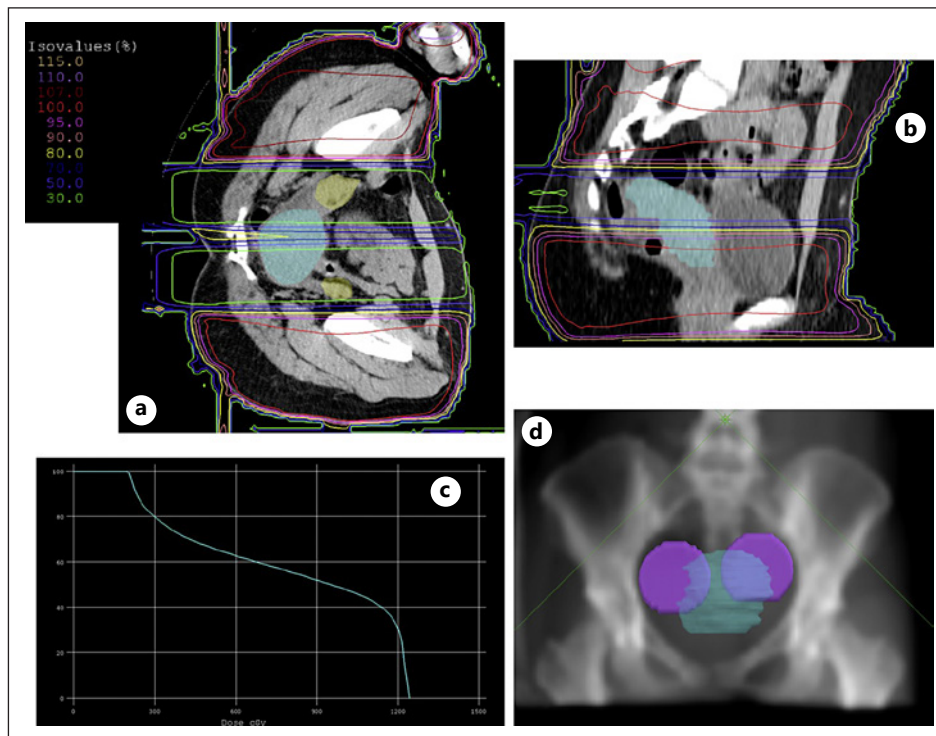
Patients who conceive after TBI have a high rate of pregnancy and birth complications, such as spontaneous abortion, preterm delivery, and low birthweight [2, 6]. Radiotherapy may damage the uterus and compromise fertility independently of ovarian effects. There is a surprising lack of detail in the literature regarding the precise nature and extent of off-target damage to the uterus in response to cancer therapies. Therefore, the dose constraint of the uterus that causes infertility remains unknown [7].

With the aim of fertility preservation, TBI with ovarian shielding has been performed at the Jichi Medical University Saitama Medical Center since July 2007. We previously reported that TBI with ovarian shielding reduced the radiation dose to ovaries to 2.4 Gy, one-fifth of the conventional TBI without ovarian shielding, preserving fertility without increasing the risk of relapse [8]. TBI with ovarian shielding was performed as previously described [9]. Briefly, for ovarian shielding, a pair of cylinder-type blocks (diameter: 5 cm; thickness: 8 cm) were created using low-melting lead and fixed to the acrylic board of the treatment bed. The patients were irradiated in the lateral position using the long source-surface distance (SSD) method from anterior–posterior and posterior–anterior directions, and source-surface distance was 400 cm. When the ovaries were shielded with a pair of blocks (diameter: 5 cm, thickness: 8 cm) to reduce the dose to the ovaries, a part of the uterus was shielded simultaneously. Among the 20 patients enrolled in the previous study, two had pregnancies and deliveries. To the best of our knowledge, there has been no study evaluating the dosimetric evaluation of patients undergoing TBI with ovarian shielding and childbirth using a dose-volume histogram (DVH) to calculate the dose delivered to the reproductive organs. Herein, we report the pregnancy and birth outcomes of 2 patients who gave birth following TBI with ovarian shielding and include an evaluation of the radiation dose to the uterus in these 2 patients.

## Case Presentation

### Case 1

A 19-year-old Japanese woman was diagnosed with acute myeloid leukemia of the French-American-British subtype M2. The patient achieved first complete remission after two courses of induction chemotherapy (daunorubicin and cytosine arabinoside [AraC]). She subsequently underwent consolidation chemotherapy (etoposide and mitoxantrone) and consequently developed chemotherapy-related myocardial dysfunction. Therefore, the last course of consolidation therapy was changed to HD AraC. Nineteen months after the initial diagnosis, bone marrow aspiration indicated a relapse. After reinduction chemotherapy (AraC, etoposide, vincristine, and vindesine), she achieved a second complete remission, and two courses of HD AraC were administered as consolidation therapy. The cumulative dose of

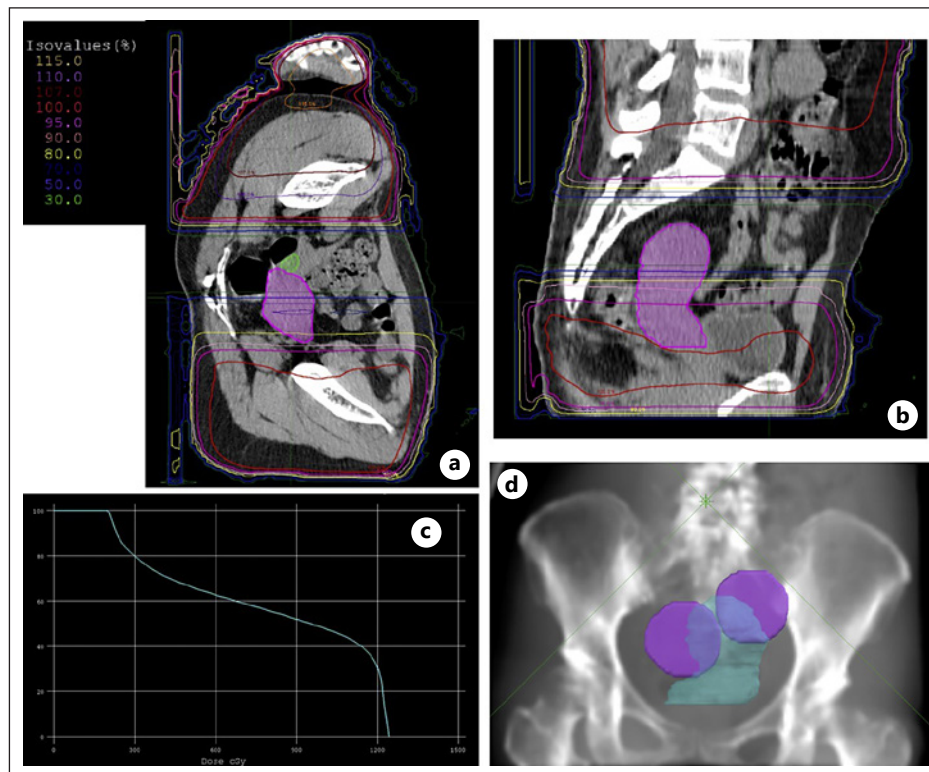


**Fig. 1.** Case 1. **a** Dose distribution in axial slice; light blue mass represents the uterus, and yellow masses represent the ovaries. **b** Dose distribution in sagittal slice. **c** DVH of the uterus. **d** Digital reconstructed radiography; light blue mass represents the uterus, and columnar lead blocks were placed at the purple circles.

anthracycline was 378.9 mg/m<sup>2</sup> (calculated as a doxorubicin-equivalent dose). Although bone marrow (BM) transplantation was planned as the next treatment, she desired to preserve fertility and was referred to our hospital to undergo HSCT using TBI with an ovarian shielding-based regimen. The conditioning regimen was a combination of AraC 2 g/m<sup>2</sup> twice per day for 4 days instead of cyclophosphamide owing to cardiac toxicity and TBI at 2 Gy d/2 x for 3 days. The mean radiation doses ( $D_{\text{mean}}$ ) to the ovaries and uterus were 2.3 Gy and 7.0 Gy, respectively. The irradiation field, dose distribution, and DVH of the uterus are shown in Figure 1. She underwent allogeneic HSCT from a fully human leukocyte antigen-matched donor at 21 years of age. Sustained remission was confirmed after HSCT and acute graft-versus-host disease grade 1 was observed. Menstrual recovery was observed 10.5 months after the HSCT. Thereafter, remission was confirmed using bone marrow aspiration at regular intervals. She was diagnosed with essential hypertension 8 years after HSCT, and antihypertensive medication was initiated. At 30 years of age, 9 years after HSCT, she conceived naturally. No abnormalities in uterine volume, placenta, or fetal growth were noted during pregnancy. At 35 weeks, her blood pressure elevated, and she was admitted to the hospital for blood pressure control. Due to hypertensive disorders of pregnancy, she delivered a baby boy through selective cesarean section at 38 weeks of gestation. Intraoperative and postoperative complications were not observed, and the infant had a normal birthweight.

#### Case 2

A 29-year-old Japanese woman was diagnosed with acute T-cell lymphoblastic leukemia. The patient received induction chemotherapy based on the JALSG ALL202-O protocol [9], but remission was not achieved. Therefore, she subsequently underwent reinduction chemo-



**Fig. 2.** Case 2. **a** Dose distribution in axial slice; pink mass represents the uterus, and green masses represent the ovaries. **b** Dose distribution in sagittal slice. **c** DVH of the uterus. **d** Digital reconstructed radiography; light blue mass represents the uterus, and columnar lead blocks were placed at the purple circles.

therapy based on the GRAALL2005 protocol and achieved hematological CR. Consolidation chemotherapy was also administered based on the GRALL2005 protocol [10]. The cumulative anthracycline dose was 205.2 mg/m<sup>2</sup> (calculated as doxorubicin-equivalent dose). Allogeneic HSCT from a human leukocyte antigen-DRB1-mismatched donor was performed at 30 years of age. The conditioning regimen was a combination of cyclophosphamide 60 mg/kg for 2 days, TBI at 2 Gy d/2 x for 3 days, and anti-thymocyte globulin 2.5 mg/kg for 2 days. The  $D_{\text{mean}}$  to the ovaries and uterus were 2.2 Gy and 7.6 Gy, respectively. The irradiation field, dose distribution, and DVH of the uterus are shown in Figure 2. Sustained remission was confirmed after HSCT, and acute graft-versus-host disease grade 1 was observed. Menstrual recovery was observed 8.9 months after HSCT. Twenty-two months after HSCT, she conceived naturally at the age of 32 years. No abnormalities in uterine volume, placenta, or fetal growth were noted during pregnancy. She had a vaginal, full-term delivery. She conceived again, more than 2 years after her last delivery.

### Discussion/Conclusion

In the abovementioned cases, normal pregnancies and deliveries were observed after TBI with ovarian shielding as a myeloablative conditioning regimen, prior to HSCT. Ovarian shielding reduced the radiation dose to not only the ovaries but also the uterus, and the uterus  $D_{\text{mean}}$  was reduced to 7.0–7.6 Gy, approximately 60% than that of conventional TBI. The reduction in dose to the reproductive organs may have contributed to normal pregnancy and birth outcomes.

Infertility is an important issue for young, long-term cancer survivors. TBI, often used as a conditioning regimen for HSCT, is classified as a high-risk group for gonadal toxicity [11]. Socié et al. [1] reported that recovery of gonadal function occurred in only 10–14% of patients with myeloablative TBI-based conditioning regimens. Additionally, the risk of adverse events during the perinatal period increases in women who previously received TBI. Salooja et al. [6] reported that women who had received TBI were more likely to have an increased risk of preterm delivery (45% vs. 6%) and low birthweight (50% vs. 6%) than the general population. Sanders et al. [2] reported an increase in spontaneous miscarriage (38% vs. 4%) and preterm delivery (63% vs. 18%) among those who received TBI with HD alkylating agents, compared to those who received alkylating agent treatment alone. These results suggest that pregnancy is possible but with lower fertility and more complications in patients with a history of TBI even when gonadal function is restored, and it is expected to be caused by irradiation of the uterus as well as the ovaries during TBI. In pregnancy after TBI, the radiation effects of the ovaries and the uterus cannot be completely separated. However, it has been reported that the risk of preterm delivery in women with abdominal/pelvic radiotherapy or TBI history who conceive after treatment with egg donation greatly exceeds that of women without a history of radiation who undergo similar treatment [12]. Therefore, in female patients who wish to preserve their fertility, it is important to consider the radiation effects on the uterus.

In contrast, it has been reported that TBI with ovarian shielding could preserve ovarian function better than conventional TBI [8, 13]. With the development of assisted reproductive technology, there are more opportunities for oocyte or embryo cryopreservation prior to HSCT. However, applying these methods can be difficult when treatment is initiated in emergency, during critical situations. In such cases, TBI with ovarian shielding is a useful option for preserving fertility. In the 2 patients who gave birth in this study, it was found that shielding the ovaries partially shielded the uterus in close proximity, reducing the dose to the uterus, but the dose constraint of the uterus that affects pregnancy and delivery has not been fully elucidated. Sudour et al. [14] reported that the most important factor endangering a successful pregnancy after radiotherapy is the total dose to the ovaries and uterus in female patients who had received abdominal and/or pelvic radiation in childhood. They found an ovary and uterus dose of <4 Gy had no negative impact on fertility, whereas a uterus dose of 4–15 Gy put patients at risk of subfertility [14]. Studies of childhood cancer survivors have found that the risk of delivering low-birthweight infants and preterm delivery is increased when the uterus is exposed to doses >5 Gy [15], and the risk of stillbirth and neonatal death is increased when the uterus is exposed to doses >10 Gy in cancer survivors exposed to radiotherapy when compared with survivors unexposed to radiotherapy [16]. Critchley et al. [17] reported that a dose of 14–30 Gy could impair uterine function, such as reduced uterine volume, reduced elasticity of the uterine musculature, and uterine vascular damage. These findings suggest that the reason for subfertility in patients receiving TBI is related to the dose to the uterus at approximately 12–14.4 Gy, which is often used in TBI as a myeloablative conditioning regimen. Although the findings of the childhood cancer survivor study indicated that a dose lower than the aforementioned dose might impact fertility, it may be related to differences in uterine maturity related to age. In this study, the uterine dose was reduced to 7–7.6 Gy, suggesting that uterine dose reduction does not affect the course of pregnancy and delivery for patients who received TBI with ovarian shielding after puberty. Recent advances in TBI using intensity-modulated radiation therapy have enabled the radiation dose to the reproductive organs to be reduced to the idealized dose [18]. As more and more TBI using intensity-modulated radiation therapeutic techniques are expected to be performed in the future, further studies with a larger number of patients are warranted to determine the radiation dose to the reproductive organs to maintain normal pregnancy and childbearing processes in female survivors who have undergone TBI. However, extramedullary relapse risk in the

uterus, associated with a reduced radiation dose to the uterus, should also be taken into consideration. Hence, we must carefully select patients who are suitable for TBI with ovarian shielding and exclude those with active malignancies.

Regarding the limitations of the present study, this is a single-institution retrospective study with a small sample size, lacking an evaluation of radiation dose by uterine site. If different parts of the uterus have different extensibility, there may be extreme pressure on one part of the uterus when internal pressure is applied during pregnancy. In addition to the mean dose of the entire uterus evaluated in this study, it may be useful to evaluate the dose separately for the cervix and body and to evaluate the maximum and minimum doses in more detail. We usually use noncontrast computed tomography images for treatment planning, and it is difficult to distinguish the cervix from the body of the uterus in these images. Therefore, we could not evaluate the dose to the cervix and body of the uterus separately in this study. We would like to consider a site-specific evaluation in the future when magnetic resonance imaging for treatment planning becomes available.

In conclusion, we report successful pregnancy and birth outcomes in 2 patients who gave birth following TBI with ovarian shielding. The uterine  $D_{\text{mean}}$  was reduced to 7.0–7.6 Gy by shielding a part of the uterus in proximity to the ovaries. These results suggest that a uterine  $D_{\text{mean}}$  of 7.0–7.6 Gy does not have a significant impact on pregnancy and delivery for patients who received TBI with ovarian shielding after puberty.

## Acknowledgments

We would like to thank Editage ([www.editage.com](http://www.editage.com)) for English language editing.

## Statement of Ethics

Written informed consent was obtained from the patients for publication of this case report and accompanying images. This study protocol was reviewed and approved by the Jichi Medical University Saitama Medical Center Clinical Research Ethics Committee, approval number S18–045.

## Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

## Funding Sources

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

## Author Contributions

Keiko Akahane and Katsuyuki Shirai designed this study. Masato Suzuki, Yuta Takahashi, and Shinichi Kako were involved in patients' management. Shogo Hatanaka, Masahiro Kawahara, Yukari Nakada, Masashi Endo, Yukiko Fukuda, Kazunari Ogawa, and Satoru Takahashi

contributed to the analysis of the results. Noriko Oyama-Manabe, Yoshinobu Kanda, and Katsuyuki Shirai supervised this project. All the authors approved the final manuscript.

### Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

### References

- 1 Socié G, Salooja N, Cohen A, Rovelli A, Carreras E, Locasciulli A, et al. Nonmalignant late effects after allogeneic stem cell transplantation. *Blood*. 2003;101(9):3373–85.
- 2 Sanders JE, Hawley J, Levy W, Gooley T, Buckner CD, Deeg HJ, et al. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. *Blood*. 1996;87(7):3045–52.
- 3 Diesch-Furlanetto T, Rovó A, Galimard JE, Szinnai G, Dalissier A, Sedlacek P, et al. Pregnancy and pregnancy outcomes after hematopoietic stem cell transplantation in childhood: a cross-sectional survey of the EBMT Pediatric Diseases Working Party. *Hum Reprod*. 2021;36(11):2871–82.
- 4 Loren AW, Senapati S. Fertility preservation in patients with hematologic malignancies and recipients of hematopoietic cell transplants. *Blood*. 2019;134(9):746–60.
- 5 Jones BP, Kasaven L, Vali S, Saso S, Jalibrant M, Bracewell-Milnes T, et al. Uterine transplantation: review of livebirths and reproductive implications. *Transplantation*. 2021;105(8):1695–707.
- 6 Salooja N, Szydlo RM, Socie G, Rio B, Chatterjee R, Ljungman P, et al. Pregnancy outcomes after peripheral blood or bone marrow transplantation: a retrospective survey. *Lancet*. 2001;358(9278):271–6.
- 7 Griffiths MJ, Winship AL, Hutt KJ. Do cancer therapies damage the uterus and compromise fertility? *Hum Reprod Update*. 2020;26(2):161–73.
- 8 Akahane K, Shirai K, Wakatsuki M, Suzuki M, Hatanaka S, Takahashi Y, et al. Dosimetric evaluation of ovaries and pelvic bones associated with clinical outcomes in patients receiving total body irradiation with ovarian shielding. *J Radiat Res*. 2021;62(5):918–25.
- 9 Sakura T, Hayakawa F, Sugiura I, Murayama T, Imai K, Usui N, et al. High-dose methotrexate therapy significantly improved survival of adult acute lymphoblastic leukemia: a phase III study by JALSG. *Leukemia*. 2018;32(3):626–32.
- 10 Huguet F, Chevret S, Leguay T, Thomas X, Boissel N, Escoffre-Barbe M, et al. Intensified therapy of acute lymphoblastic leukemia in adults: report of the randomized GRAALL-2005 clinical trial. *J Clin Oncol*. 2018;36(24):2514–23.
- 11 American Society of Clinical Oncology. 2013. Available from: [www.asco.org/sites/www.asco.org/files/fp\\_data\\_supplements\\_012914.pdf](http://www.asco.org/sites/www.asco.org/files/fp_data_supplements_012914.pdf).
- 12 Marklund A, Nasiell J, Berger AS, Fagerberg A, Rodriguez-Wallberg KA. Pregnancy achieved using donor eggs in cancer survivors with treatment-induced ovarian failure: obstetric and perinatal outcome. *J Womens Health*. 2018;27(7):939–45.
- 13 Kanda Y, Wada H, Yamasaki R, Kawamura K, Ishihara Y, Sakamoto K, et al. Protection of ovarian function by two distinct methods of ovarian shielding for young female patients who receive total body irradiation. *Ann Hematol*. 2014;93(2):287–92.
- 14 Sudour H, Chastagner P, Claude L, Desandes E, Klein M, Carrie C, et al. Fertility and pregnancy outcome after abdominal irradiation that included or excluded the pelvis in childhood tumor survivors. *Int J Radiat Oncol Biol Phys*. 2010;76(3):867–73.
- 15 Signorello LB, Cohen SS, Bosetti C, Stovall M, Kasper CE, Weathers RE, et al. Female survivors of childhood cancer: preterm birth and low birth weight among their children. *J Natl Cancer Inst*. 2006;98(20):1453–61.
- 16 Signorello LB, Mulvihill JJ, Green DM, Munro HM, Stovall M, Weathers RE, et al. Stillbirth and neonatal death in relation to radiation exposure before conception: a retrospective cohort study. *Lancet*. 2010;376(9741):624–30.
- 17 Critchley HO, Wallace WH, Shalet SM, Mamtara H, Higginson J, Anderson DC. Abdominal irradiation in childhood; the potential for pregnancy. *Br J Obstet Gynaecol*. 1992;99(5):392–4.
- 18 Dibs K, Sim AJ, Peñagaricano JA, Latifi K, Garcia GA, Peters JA, et al. Gonadal-sparing total body irradiation with the use of helical tomotherapy for nonmalignant indications. *Rep Pract Oncol Radiother*. 2021;26(1):153–8.