In utero exposure to therapeutic radiation for Hodgkin lymphoma

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ABSTRACT

QUESTION One of my patients was incidentally found to be pregnant after completion of radiotherapy for Hodgkin lymphoma. What are the possible effects that I should discuss with her before she makes a final decision regarding continuation of her pregnancy?

ANSWER Radiotherapy might not be an absolute contraindication in pregnant women who are diagnosed with cancer located in areas remote from the pelvis. However, the fetal exposure should be carefully estimated, and the known dose-response information has to be discussed individually to allow informed decisions to be made.

RÉSUMÉ

QUESTION On a découvert par hasard qu'une de mes patientes était enceinte après qu'elle ait suivi une radiothérapie pour la maladie de Hodgkin. De quels effets possibles devrais-je discuter avec elle avant qu'elle prenne une décision finale concernant la poursuite de sa grossesse?

RÉPONSE La radiothérapie n'est pas nécessairement une contre-indication absolue chez les femmes enceintes qui ont un diagnostic de cancer situé dans des régions éloignées du bassin. Par ailleurs, l'exposition fœtale devrait être estimée soigneusement et les renseignements quant à la réponse connue aux doses doivent être discutés individuellement pour permettre une décision éclairée.

While x-rays can be teratogenic in humans, the consequences of in utero exposure to radiotherapy are unclear in terms of dose and duration. Many of the data on the effects of exposure to ionizing radiation during pregnancy have arisen from studies on survivors of the atomic bombs used in World War II. Exposure to high doses of ionizing radiation has been associated with an increased risk of fetal malformations, mental retardation, growth retardation, and, in particular, small head circumference.[1-4] However, only a few cases have been reported of pregnant mothers treated for cancer with radiotherapy applied to the upper body. Although some of these cases have reported normal outcomes, the offspring follow-up was too short to draw ultimate conclusions.

To highlight the complexities involved, we will present the case of the woman introduced in the "Question." She received radiation for 4 weeks during the first trimester of pregnancy and decided to continue the pregnancy to term, as no fetal abnormalities or intrauterine growth restrictions were detected in repeated fetal ultrasounds. A follow-up when the child was 2 years of age showed a decrease in all growth parameters, although child development remained within the normal range. This case was previously reported by de Wildt et al[5] before any delay in growth parameters appeared.

Case description

A 27-year-old woman (gravida 2, para 1, 1 living child) of Jamaican descent presented with stage IIA Hodgkin disease in her mediastinum. The patient underwent both chemotherapy and radiotherapy, and was incidentally found to be pregnant after completion of her treatment. Based on the date of her last menstrual period and the fetal ultrasound measurements, the fetus was exposed to radiation treatment between the gestational ages of 7 weeks and 4 days and 11 weeks and 4 days. During this time the patient received a dose of 3500 cGy in 20 fractions to the chest. The total estimated fetal dose exposure was 12 cGy. The calculated fetal exposure was at least 5 cGy and possibly as high as 18 cGy. Before conception, the patient also underwent 6 cycles of ABVD (doxorubicin hydrochloride, bleomycin sulfate, vinblastine sulfate, dacarbazine) chemotherapy.

The patient had maternal serum screening in the second trimester of pregnancy, which showed a low risk for having a baby with Down syndrome (< 1:50 000) and open neural tube defects (1:26 600). A detailed fetal ultrasound at 19 weeks' gestation showed appropriate fetal growth with no detectable abnormalities. A repeated fetal ultrasound at

24 weeks' gestation showed no fetal abnormalities, although left cerebral ventriculomegaly measuring 9.5 mm (normal up to 10 mm) was detected. Fetal magnetic resonance imaging confirmed asymmetrical ventricles, with the right and left posterior horn measuring 8 mm and 12 mm, respectively. The inferior vermis appeared incomplete, which raised the possibility of delayed development or hypoplasia of the inferior part of the fetal vermis. The patient was counseled, and she decided to have amniocentesis. Maternal serology studies found no indication of an acute infection. Polymerase chain reaction results for cytomegalovirus and *Parvovirus* B19, as well as virology cultures, were negative. The patient remained disease free throughout the pregnancy, and there were no other maternal exposures or complications.

Delivery was vaginal, spontaneous, and uncomplicated at 39 weeks' gestation. A baby boy was born, weighing 2.9 kg (10th percentile); his length was 52 cm (50th percentile), and he had a head circumference of 34 cm (20th percentile). He had an Apgar score of 9 at 1 minute and at 5 minutes. There were no postnatal complications. Results of the head ultrasound completed before discharge were normal, and there were no parenchymal brain abnormalities detected. His cerebellum was normal, and there were no abnormalities of the vermis detected. His early neonatal course was uneventful. He had no feeding difficulties, and his growth and development were normal. He was not admitted to hospital and did not require surgery. At 2 years of age he remained in good health and his developmental milestones were normal; however, his growth was lagging, particularly his head circumference. His weight and length were in the fifth percentile, and his head circumference was in the third percentile. His mother's occipital-frontal circumference was 1 SD above the mean and his father's was 1 SD below the mean.

Discussion

As with all teratogens, the risk to the fetus depends on timing and dose of exposure. Fetal exposure to radiation depends on several factors, including the target dose, the size of the radiation field, and the distance between the edges of the field and the fetus. The gestational age at the time of exposure is another important factor in determining the nature of the adverse effect.

During the preimplantation period (the first 14 days after conception) when the number of cells in the embryo is relatively small, radiation exposure can either be lethal or have no apparent effect ("all or none" period).[1] During organogenesis (between 2 and 8 weeks postconception) the embryo is extremely sensitive to the teratogenic effects of ionizing radiation, mainly resulting in congenital malformations and growth retardation,[6] with the central nervous system (CNS) being the most sensitive. Radiation-induced malformations of other organs are relatively uncommon (eg, hypoplastic genitalia, microphthalmia, cataracts, and skeletal defects).[7-9] Previous reports have suggested that exposure exceeding 10 to 20 cGy during organogenesis is expected to cause malformations,[10] with the CNS being especially radiosensitive at 8 to 15 weeks' gestation,[7,11] causing microcephaly and mental retardation.[12,13] After 25 weeks' gestation, the CNS becomes less sensitive to radiation.

Data from studies on atomic bomb survivors and from animal experiments indicate that microcephaly (ie, a head circumference of 2 SDs below the mean) is the most common finding observed in humans after exposure to a high dose of radiation during pregnancy.[7-9,14-16] No case of severe mental retardation has been observed in any patient receiving in utero a dose of less than 50 cGy.[17]

In this context it is important to stress that mental retardation is not directly related to microcephaly. Many children who survived the atomic bomb and who were exposed in utero to radiation doses between 10 and 150 cGy up to the seventh week postconception developed microcephaly.[18] Among the microcephalic babies, only 10% exhibited confirmed mental retardation.[19]

It is still unclear to what extent small head size is an independent symptom of mental retardation and what mechanism underlines radiation-related damage to the brain.[20]

Otake et al[19] reviewed neurodevelopmental outcomes among prenatally exposed survivors of the atomic bombs in Hiroshima and Nagasaki in Japan. They noted an increased incidence of severe mental retardation, IQ reduction, diminished school performance, and increased seizure disorders among individuals exposed between the eighth and 25th weeks, especially in the 8- to 15-week period—the time of major neuronal proliferation. Analysis of their data has shown that the risk of severe mental retardation is not increased as a result of exposure before the eighth week or after the 25th week. The maximal risk appears to be at 8 to 15 weeks' gestation (with a linear dose-response model), whereas between 16 and 25 weeks' gestation the sensitivity of the CNS is less striking. There was strong evidence of a threshold dose for severe mental retardation of 6 cGy for a fetus at 8 to 15 weeks' gestation and a threshold of about 25 cGy for a fetus at 16 to 25 weeks' gestation.[3]

While individuals exposed in utero to radiation in Hiroshima and Nagasaki presented reduced height, weight, and head circumference,[4,15,21,22] extrapolation from these studies is difficult, as in clinical practice the total fetal dose is given over a long time with much lower fractional doses. Furthermore, there was no comparison to parental measurements in the Japanese data. In a review of 21 previous case reports—which mostly involved radiation treatment of newly diagnosed

Hodgkin disease—all pregnancies resulted in normal neonatal outcomes, and subsequent follow-up of these children showed no delayed effects of the radiation. Moreover, the pregnancies that did result in spontaneous abortion or adverse affects were associated with a much higher dose of radiation and often for a prolonged period of time.[23]

Fetal radiation doses exceeding 20 cGy are rare for cancers that are remote from the pelvis and for cases in which proper shielding has been applied; however, at fetal radiation doses above this value, resulting from accidental exposure or radiotherapy without shielding, fetal damage might occur. If the fetal doses are high (above 50 cGy) and radiation is given during the organogenesis period, the risk of growth retardation and CNS abnormalities (mainly microcephaly, mental retardation, or eye anomaly) is substantial. In the dose range of 20 to 50 cGy, the risk of IQ reduction should be seriously considered if the fetus were exposed between the gestational age of 8 and 15 weeks.

Another concern is that radiation exposure during pregnancy might be associated with a carcinogenic effect, which can include an increased risk of childhood solid tumours or leukemia. The spontaneous incidence is 2 to 3 cases per 1000, and it might increase by 40% over the background (3 to 4 cases per 1000) after prenatal radiation with a fetal dose of 10 cGy. The risk below this dose is considered to be extremely low.[10]

In the case of our patient, the estimated fetal radiation dose was 12 cGy, with the exposure occurring between the gestational age of 7 and 11 weeks (5 to 9 weeks postconception). The child was born with no malformations or growth retardation. His general health was markedly good with no serious illness. By the age of 24 months, he reached his developmental milestone but his growth was lagging, particularly his head circumference. Given his exposure to ionizing radiation at a critical time of organogenesis, and with the lack of other explanation, one needs to consider radiation as a possible etiology. Reduced height, weight, and head circumference were reported following a radiation dose exceeding 50 cGy, given in a single dose at a high-dose rate (nuclear explosions). Our patient's decreased growth rate affecting the head circumference and height is a possible long-term effect of exposure to radiation below 15 cGy, with no effect on the developmental milestones; however, this potential association is uncertain and long-term follow-up is needed to address this issue.

Conclusion

Congenital anomalies and growth impairment have been reported in infants and adolescents exposed in utero to radiation; however, most studies show that delayed growth and malformations occur following high doses of ionizing radiation, mostly greater than 50 cGy. Thus, radiotherapy should not be an absolute contraindication in pregnant patients diagnosed with cancer located remote from the pelvic area (eg, breast cancer, brain tumours, head and neck tumours, and supradiaphragmatic tumours). In such cases, the fetal radiation dose and the predictive effects should be estimated by qualified medical personnel (ie, a radiation physicist or radiation oncologist) and discussed with the woman (or the couple) on an individual basis to allow an optimally informed decision. Close prenatal follow-up of structural abnormalities, as well as of fetal growth and neurodevelopment, is indicated in these cases.

Competing interests
None declared

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MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. **Drs Klieger-Grossmann** and **Djokanovic** are members and **Dr Koren** is Director of the Motherisk Program. **Dr Chitayat** is Head of the Prenatal Diagnosis and Medical Genetics Program at Mount Sinai Hospital in Toronto. **Dr Koren** is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation. He holds the Ivey Chair in Molecular Toxicology in the Department of Medicine at the University of Western Ontario in London.

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