

Does Childhood Radiation Lead to Stillbirths or Neonatal Deaths?

Source: Signorello LG, Mulvihill JJ, Munro HM, et al. Stillbirth and neonatal death in relation to radiation exposure before conception: a retrospective cohort study. *Lancet*. 2010;376(9741):624-630; doi:10.1016/S0140-6736(10)60752-0.

Researchers from several US institutions used the Childhood Cancer Survival Study (CCSS) registry to study the impact of cumulative radiation exposure on pregnancy outcomes among childhood cancer survivors. CCSS cohort members who were under age 21 years at the time of cancer diagnosis from 1970 to 1986 at 26 North American centers were included if they survived at least five years after diagnosis. All singleton live births and stillbirths (defined as fetal deaths after week 20) between 1971 and 2002 were included. The cumulative radiation treatment doses absorbed by the testes, uterus, ovaries, and pituitary gland were determined for each patient. Treatment with mutagenic chemotherapy drugs such as cisplatin and dacarbazine was evaluated as a key potential confounder. Other factors adjusted for in multivariable analyses included maternal smoking and alcohol use; pregnancy complications such as diabetes, hypertension, and toxemia; use of medications to aid conception; and time since cancer diagnosis.

The final cohort consisted of 2,805 childhood cancer survivors (1,657 women and 1,148 men) who had 4,853 live births and 93 stillbirths or neonatal deaths during the study period. The 1,774 (63%) survivors who had received radiation therapy accounted for 3,077 (63%) of the live and 60 (64.5%) of the stillbirths and neonatal deaths. Leukemias and Hodgkin's lymphoma accounted for 49% of female and 44% of male cancers.

Irradiation of the testes (mean doses of 0.53 ± 1.4 Gy to 16 men) was not associated with risk of stillbirth or neonatal death (adjusted RR=0.8; 95% CI, 0.4-1.6). There was no increase in risk of stillbirth or neonatal death with any cumulative uterine or ovarian radiation dose received after menarche. However, premenarchal cumulative doses as low as 1.0 Gy increased risk 4.7-fold (95% CI, 1.2-19), while doses of 2.5 Gy or more increased risk 12.3-fold (95% CI, 4.2-36). There were no associations of irradiation of the pituitary gland or exposure to alkylating agents with risk of stillbirth or neonatal death.

The authors conclude that prepubertal uterine and ovarian irradiation can adversely affect birth outcomes of future offspring of females, most likely due to age-related vulnerability to radiation-induced uterine damage rather than a heritable germline genetic event. The authors acknowledge, however, that transmissible mutations could not be totally excluded with current technology as contributory to stillbirth or neonatal death. The analysis revealed no basis for concern about heritable genetic changes from male gonadal irradiation. The key learning is that pregnancies in women who received

high doses of prepubertal pelvic irradiation warrant being managed as high-risk pregnancies.

Commentary by

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Dr Woods has disclosed that he has a research grant from Pfizer. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Patients treated with high-dose radiation and/or certain chemotherapeutic agents may develop somatic mutations that increase risk for later new leukemias or solid tumors. Whether radiation-induced damage to human germline cells can lead to congenital anomalies, offspring with increased risk for cancer, or nonviable offspring has remained an open question. Such mutations have been noted in animals.¹

The current study, in combination with results of other recent studies, provides substantial reassurance that high-dose gonadal irradiation received as part of cancer therapy in childhood does not lead to increased risk of stillbirth, neonatal death, or congenital malformations in the offspring of childhood cancer survivors on a heritable genetic basis. A recent smaller study of 470 first offspring of cohort members from cancer registries in four United States metropolitan areas also found no impact of radiation therapy alone on pregnancy outcomes of children fathered by survivors of childhood cancer.² Another study of 1,715 offspring of 3,963 Danish childhood cancer survivors who received radiation therapy found no increased risk of malformations compared with the offspring of survivors' siblings who did not have cancer.³ The increase in risk of neonatal death or stillbirth found by Signorello, et al, in females who received high-dose pelvic radiation prior to puberty remains noteworthy in terms of patient counseling, but it seems reasonable to reassure affected girls and their parents that the risk is 1) more likely from uterine tissue injury rather than any heritable genetic mutation, and 2) potentially reducible with careful obstetric follow-up.

Radiation doses of abdominal CT scans to the stomach are about 20 mGy in a neonate and 10 mGy in an adult. Exposure doses to children are likely in between, and pelvic CT scans deliver similar doses to reproductive organs. For comparison, the radiation dose to the lungs from posterior-anterior plus lateral chest radiographs is 0.16 mGy and to the breast from screening mammography is 3 mGy.⁴ Diagnostic radiation exposures may slightly increase the risk of subsequent cancer, but these doses are well below the 1 Gy threshold associated with premenarchal uterine damage in the current study and should pose no risk to future offspring.

References

1. Boice JD, et al. *Health Phys*. 2003;85:65-80
2. Chow EJ, et al. *Arch Pediatr Adolesc Med*. 2009;163:887-894
3. Winther JF, et al. *Clin Genet*. 2009;75:50-56
4. Brenner DJ, et al. *N Engl J Med*. 2007;357:2277-2284

Key words: radiation exposure, stillbirth, neonatal death

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Question: Among young adults with significant radiation exposure during childhood, is there an increased risk of stillbirth or neonatal death in their offspring?

Question type: Harm, causation

Study design: Retrospective cohort study