Birth Defects Research (Part C) 81:177–182 (2007)

REVIEW

Radiation Effects on Development

Marco De Santis,* Elena Cesari, E. Nobili, Gianluca Straface, Anna Franca Cavaliere, and Alessandro Caruso

It has been widely reported that prenatal exposure to ionizing radiation can interfere with embryonic and fetal development, depending on dose and gestational age in which exposure occurs. According to several studies on animal models, different well-defined stages during prenatal life can be distinguished in relation to teratogenic effects. During the preimplantation stage, elevated doses of radiation can result in abortion, while lower doses may produce genomic damage that is usually repaired. On the other hand, during the organogenesis stage in mice (embryonic day 6.5 [E6.5] to E13.5), irradiation is associated with increased incidence of malformation and intrauterine growth restriction (IUGR). Later exposure is linked to brain damage. Doses used in animal studies are generally higher than those used for diagnostic procedures in humans. Usually, radiation exposure to diagnostic range (<0.05 Gy = 5 rads) is not associated with an increased risk of congenital anomalies. In human studies, elevated doses produce adverse outcomes, depending on stage of development, as in animal studies. Blastogenesis (up to two weeks) is associated with failure to implant or no significant health effects. An increased risk of malformation and growth retardation can be observed for two to seven weeks exposure (organogenesis stage), while exposure at later stages (fetogenesis) is mainly associated with brain damage. In this review we focus on the relevance of estimating the cumulative dose of radiation to the fetus and the gestational age in which exposure occurs, to provide appropriate counseling to pregnant women. **Birth Defects Research (Part C) 81:177–182, 2007.** © 2007 Wiley-Liss, Inc.

Key words: radiation; development; animal; human; dose; gestational age

INTRODUCTION

Many women are affected by pathologies that require immediate diagnosis and treatment, including radiographic diagnosis using ionizing radiography. Exposing the fetus to radiation creates alarm for the patient and her family. These same physicians often confront this situation incorrectly and unscientifically, providing inadequate therapy and insufficient counseling.

X-rays are classified as short wave electromagnetic radiation (less than 10 nm) and are commonly used for diagnostic and therapeutic purposes. Both the gray (Gy) and the rad are units of absorbed dose and reflect the amount of energy deposited into a mass of tissue (1 Gy = 100 rads). X-rays can alter the normal structure of cellular biochemical compounds through direct and indirect mechanisms. The damaging effects of radiation on living organisms can be of two types. The first type is related to the dose and is apparent in clinical damage, most often linked with dead cells. Cell damage can also occur with lower doses. However, stochastic effects appear some time after exposure and consist of genetic injury to the cell. These can cause cancer or cell mutation transmittable to descendants.

ANIMAL STUDIES

There is extensive literature about radiation exposure in the experimental animals. Various well-defined stages during prenatal life can be distinguished from the effects after irradiation (Schull and Otake, 1999) (Table 1). Elevated dose exposure during the preimplantation stage can result in abortion. Lower dosages produce genomic damage that is repaired (Jacquet, 2004). Radiation exposure during later stages results in growth retardation and in different types of congenital anomalies, whose type and severity depend on the radiation dose. Russell (1950) studied irradiation with doses of 100 to 400 rads in the pregnant mouse: preimplantation irradiation tended to be lethal or to have no effects. Exposure between embryonic day 6.5 (E6.5) and E13.5 was shown to be associated with growth retardation and abnormalities related to dose and time of administration. In particular the authors found a correlation between E7.5 through E9.5 exposure and eye defects (coloboma and microphthalmia), E9.5 exposure and renal anomalies, and E9.5 through E12.5 exposure and

Marco De Santis, Elena Cesari, E. Nobili, Gianluca Straface, Anna Franca Cavaliere, and **Alessandro Caruso** are from the Telefono Rosso-Teratology Information Service, Department of Obstetrics and Gynecology, Catholic University, Rome, Italy.

*Correspondence to: De Santis Marco, L.go Agostino Gemelli 1, 00135 Rome, Italy. E-mail: marcodesantis@rm.unicatt.it

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/bdrc.20099

TABLE 1. Effects of Prenatal Irradiation (1 Gray) in Different Stages of Development in Mice

Effects	Pre-implantation	Embryo	Fetus
Lethality	Yes (++)	Yes (±)	No
Malformations	No	Yes (+)	No
IUGR	No	Yes (+)	Yes (+)
Mental retardation	No	Yes (+)	Yes (+)

Modified from Schull and Otake, 1986. IUGR: intrauterine growth retardation. ± : observed. + : frequent. ++ : high incidence.

skeletal anomalies (Russell, 1950). Also, Kuno et al. (1994) confirmed eye defects for E8 mass radiation exposure during the 8th day of development. Thereafter (>E14.5), anomalies were sporadic, but the mice developed cataracts, hydrocephalus, and skin defects in later life (Russell, 1950). Recently Devi and Hossain (2001) confirmed that 14 days postcoitus is a critical period for radiation-induced impairment of postnatal growth that occurred with a dose of 0.3 Gy, but not for congenital anomalies.

Jacquet et al. (1995) confirmed that preimplantation irradiation is associated mainly with prenatal loss and stated that for subsequent exposure the increased risk of congenital anomalies is significant for the doses of 10.5 and 100 Gy. In contrast, Hillerbrand et al. have stated that irradiation during the preimplantation stage is associated with increased risk of gastroschisis in a specific mouse strain at the dose of 1 Gy. The hypothesis is that a particular genomic instability of that strain is responsible of the increased risk of gastroschisis (Hillebrand et al., 1996). At molecular levels it can be observed that deficiency of a specific enzyme can result in a major sensitivity to radiation. The gene responsible for ataxia telangiectasia (AT) encodes the AT ataxia teleangectagio mutated (ATM) protein, which plays a major role in the network of a signal transduction initiated by double-strand DNA breaks (Hall et al., 2005). Thus, this sensitivity in the preimplantation period is due to a susceptible genomic trait (Undarmaa et al., 2004).

Many authors have focused on brain damage due to radiation exposure. Later exposure (15–16 days postconception) is associated with brain damage. Several studies demonstrated that developing brains exhibit a higher level of radiosensitivity in comparison to mature neurons, due to the elevated number of multipotent dividing precursor cells (Minamisawa et al., 1980; Shirai et al., 2006). Early events after irradiation consist of altered neuronal migration and laminar formation in the cerebral cortex (Verheyde and Benotmane, 2007). Devi et al. (1999) showed that in the exposed mice at E17 a dose lower than 0.3 Gy can impair brain function. Irradiation of mice on E9 or E17 to an acute dosage levels of 0.6 Gy is associated with altered postnatal growth and psychophysiologic development at three behavioral tests (Jensh, 1985). Later the same authors confirmed that between 0.75 and 1.5 Gy in the late gestational period (E14 to E18) can cause low birth weight (LBW) and delay in acquisition of several reflexes (Jensh and Brent, 1988). A specific study on the development of cortical cortex was done in the irradiated mice. Prenatal exposure during E15 at a dose of 1.5 Gy causes severe microcephaly and affects the development of local circuits and the axonal projection of cortical neurons to the thalamus (Funahashi et al., 1997). Li et al. (2005) confirm that X-ray irradiation on E14 (1 Gy) causes multiple defects due to the formation of cavities that transiently interrupted both cortical afferent and efferent axons.

Different studies had stated that irradiated mice are at risk also for their fertile life: These studies suggest that ionizing radiation can induce DNA damage in the germ cells of exposed individuals and lead to teratogenic effects in the progeny, such as miscarriage, LBW, congenital anomalies, and cancer (Jacquet, 2004). Pils et al. (1999) showed that in mating mice exposed during the zygote stage to 1 Gy with an unexposed male, an increased risk of malformation and of prenatal mortality could be observed (Pils et al., 1999). Sanová et al. (2005) demonstrated that irradiation of rat males with sublethal doses (3 Gy) for 25 days (spermatids stage) before mating with control females affects brain development in the subsequent progeny. They found an increase in occurrence of chromosomal aberrations (chromosomal bridges) in embryos and brain (hemispheres and little brain) of offspring. These aberrations were still present in the postnatal period. On the other hand, irradiation 80 days before mating (spermatogonia stage) results in significant low presence of chromosomal abnormalities. The radiation used in these studies is markedly higher than doses of radiation diagnostics, but they are similar to doses that can occur in radiotherapy.

HUMAN STUDIES

The embryo and the fetus are particularly sensitive to ionizing radiation, and the developmental consequences can be quite serious. These can be teratogenic, mutagenic, or carcinogenic in nature. As with almost all known teratogens, the dose of ionizing radiation is one of the determining factors for reproductive toxicity in embryonic/fetal development. Although the embryo and the fetus are protected to some degree by the uterus, the dose of radiation tends to be lesser compared to that to which the mother is exposed. Various studies have set the dose of the most commonly used diagnostic and therapeutic procedures for the embryo and the fetus. The current consensus is that exposure to radiation of <5 rads during pregnancy is not related to an ele-

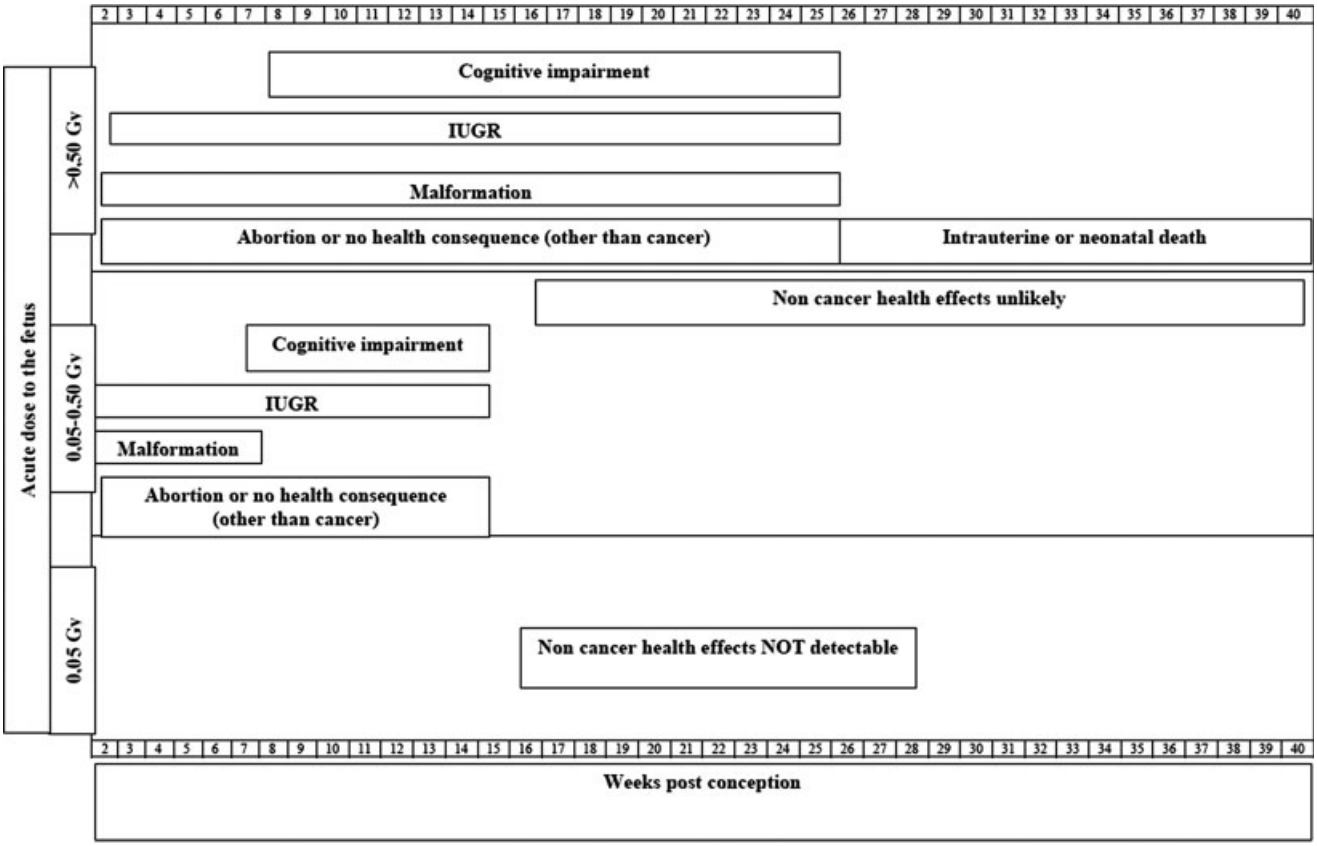

Figure 1. Possible effects (other than cancer) on development for prenatal radiation exposure. [Modified from Prenatal Radiation Exposure: A Fact Sheet for Physicians. CDC 2006 (http://www.bt.cdc.gov/radiation/prenatalphysician.asp)].

vated risk of malformation (Tabuchi et al., 1967; Kinlen and Acheson, 1968; Nokkentred 1968; Vilumsen, 1970; Brent, 1999) Currently, no diagnostic procedures in use today reach a dose of 5 rads, the dose considered to be dangerous to the product of conception (Wagner et al., 1997; Sharp et al., 1998; Osei and Faulkner, 1999).

Apart from the dose of radiation, the developmental age of gestation is important in determining the noncarcinogenic effects on development (Fig. 1). Up to approximately the second week of gestation, the effects on the product of conception in exposure to >0.1 Gy or 10 rads translates into embryonic death. If the embryo survives, it is unlikely that it will suffer damaging effects (Russel et al., 1959; Jankowski, 1986; ICRP, 1997; Brent, 1999).

No damaging effects may be observed in fetal exposure to 0.05 Gy (5 rads) at any period of gestation. In clinical practice the threshold dose in congenital anomalies to the human embryo and fetus is probably around 0.10–0.20 Gy (10–20 rads). Between the 16th week and the end of pregnancy, the noncarcinogenic effects caused by radiation are unlikely below 0.50 Gy (50 rads). Although some authors suggest that a low possibility of alterations in intellectual abilities exists from doses up to 0.10 Gy (10 rads) between the 16th and the 25th weeks, a number of studies have shown that after the 16th week the threshold dose for the occurrence of congenital malformations is approximately 0.5–0.70 Gy (50–70 rads) (Blot and Miller, 1973; Otake and Schull, 1984; Schull and Otake, 1986; Schull et al., 1988; Otake et al., 1996).

The effects of radiation on the embryo and the fetus can thus manifest themselves in the form of spontaneous abortion, growth retardation, and effects on neurological development (severe mental retardation and/or reduction in intelligence quotient [IQ]) and major malformations (De Santis et al., 2005a). The teratogenic effects of radiation have been known since 1929, when Goldstein and Murphy (1929) observed a high evidence of neonatal malformation (34%), particularly microcephaly and reduced cranial circumference, in 74 women who had undergone radiation treatment for uterine cancer during pregnancy. The estimated doses of exposure were >1 Gy (100 rads). Moreover, the majority of those children had been exposed prior to the fifth month (Goldstein and Murphy, 1929b). A few years later, a further analysis of the data revealed that the radiation had caused the malformations only when exposure occurred between the third to fourth week and the 19th week

and that the most severe malformations, such as microcephaly, were related to exposures occurring earlier than the 17th week (Russell and Russell, 1954). The information regarding doses dangerous to the embryo or the fetus remained inaccurate and for many years the generic proposition prevailed that high enough doses of radiation to the pelvic region in the most sensitive periods would cause damage to the fetus. The first studies on the survivors of the atomic bombs in Japan demonstrated that newborns exposed in utero to doses between 0.1 and 1.5 Gy (10–150 rads) developed microcephaly and 87% suffered severe mental retardation. The most sensitive period to the effects of radiation on the central nervous system is between the eighth and the 15th week of gestation. The available data on the survivors of the atomic bomb indicate that during this phase of pregnancy the risk of severe mental retardation above 0.1 Gy (rads) is about 40% per Gy (100 rads). Prior to the eighth and after the 25th weeks and for exposure <1 Gy, no cases of mental retardation were cited. Moreover, no cases of severe mental retardation were observed in infants exposed in utero to 0.5 Gy (50 rads) (Plummer, 1952; Miller, 1969; Kato, 1971; Blot and Miller, 1973).

The sensitivity of the nervous system is reduced in the 16th to 25th weeks. Overall, effects similar to those observed between the eighth and the 15th week, but with higher doses of exposure, are seen in this phase of pregnancy. In particular, in the same doses the percentage of risk of severe mental retardation is 9% (Rakie, 1975; Mole, 1991; ICRP, 2001; Timins, 2001; Streffer et al., 2003). After the 25th week the central nervous system becomes relatively radioresistant and major fetal malformations and functional anomalies highly improbable (Schull and Otake, 1999).

In 1991, Otake et al. (1991) identified the threshold dose for severe mental retardation as being between 0.12 (12 rads) and 0.23 Gy (23 rads) between the eighth and the 15th weeks and approximately 0.21 Gy (21 rads) between the 16th and the 25th week. These values were also reevaluated by Otake et al. (1996): the threshold dose should be 0.06–0.31 Gy (six to 31 rads) between the eighth and the 15th weeks and 0.25–0.28 Gy (25–28 rads) between the 16th and the 25th weeks. However, Miller (1999), established a threshold dose for severe mental retardation to be >0.5 Gy (50 rads).

Effects similar to those of severe mental retardation have been observed in the reduction of IQ. There also seems to be in this case a maximum effect between the 16th and the 25th weeks of 21–29 points per Gy (100 rads). In the period between the 16th and the 25th weeks the reduction should be of 13–21 points. No effect appears in doses of <100 mGy (10 rads) even during the most sensitive period (Schull et al., 1988; Smith, 1992). The probable threshold dose for this type of effect should be approximately 10 cGy (10 rads) (Streffer et al., 2003).

The threshold dose for the induction of effects of this nature provoked by radiation is all above the fetal dose estimated for common diagnostic procedures. Also for severe mental retardation the highest fetal dose administered by diagnostic procedures is still lower than the threshold dose of 0.06–0.31 Gy (six to 31 rads) established by Otake et al. (1996). With regard to slight mental retardation, considering the dose-dependent linear response of 25–29 points per Gy (100 rads), the major part of diagnostic procedures should cause a reduction of 0.2 points in IQ (Otake et al., 1991; Osei and Faulkner, 1999).

Alterations in height and weight were recorded in adolescents exposed in utero to radiation from an atomic bomb (Mole, 1982). It was also noted that exposure to high doses of radiation in pediatric age increases the risk of low birth rates <2500 gm (Chiarelli et al., 2000; Green et al., 2002). Women exposed to radiation during adolescence for idiopathic scoliosis have a higher risk of LBW dose-dependent effects. A study by Hamilton et al. (1984) revealed a higher percentage of radiation exposure during pregnancy in women who gave birth to LBW babies. Hujoel et al. (2004) conducted a case control study on 1117 LBW children, comparing them to a control group of 4468 babies with normal weight. The results of this study have demonstrated how exposure in pregnancy to dental radiography can be associated with an increased risk of having LBW children (odds ratio [OR] = 2.27). The alteration of the mother's hypothalamus-hypophysis-thyroid axis seems to be the etiopathogenetic mechanism of this effect, with the existence of a dose threshold effect around 0.4 mGy at the level of the maternal thyroid. Other authors (Boice et al., 2004; Brent, 2005) have criticized this study and the possible association between maternal thyroid exposures and fetal growth. In a previous study, we showed a slight reduction in the birth weight with a dose threshold at the level of the thyroid of from 0.4 to 0.8 mGy, analyzing the outcome of pregnancy in 224 women exposed to diagnostic examinations with thyroid exposure in the first trimester (De Santis et al., 2005b).

In conclusion, evaluation of the need to undergo a radiodiagnostic exam during pregnancy and counseling of women inadvertently exposed to radiation during pregnancy must take into consideration the dose of the embryonic/fetal exposure. In fact, it is only the dose of radiation that reaches the uterus and consequently the fetus that is relevant.

No necessary radiodiagnostic examination that is clinically justifiable should be avoided due to pregnancy. On the other hand, no radiological examination that is not absolutely necessary should be performed during pregnancy. Protective measures to ensure the health of the mother should be the priority, not the theoretic risk to the unborn fetus. If there are other diagnostic procedures that

are equally as sensitive but not as dangerous to the fetus, these should be the preference. Correct behavior would be to comply with the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) guideline: ''Diagnostic radiologic procedures should not be performed during pregnancy unless the information to be obtained from them is necessary for the care of the patient and cannot be obtained by other means (especially ultrasound)'' (ACOG, 1995).

REFERENCES

ACOG. 1995. American College of Obstetricians and Gynecologists (ACOG), Committee on Obstetric Practice. Guidelines for diagnostic imaging during pregnancy. ACOG Committee Opinion no. 158. Washington, DC: ACOG. 1995 pp 647–651.

Blot WJ, Miller RW. 1973. Mental retardation following in utero exposure to the atomic bomb of Nagasaki and Hiroshima. Radiology 106:617–619.

Boice JD Jr, Stovall M, Mulvihill JJ, et al. 2004. Dental X-rays and low birth weight. J Radiol Prot 24:321–323.

Brent RL. 1999. Utilization of developmental basic science principles in the evaluation of reproductive risks from pre- and post-conception environmental radiation exposures. Teratology 59:182–204.

Brent RL. 2005. Commentary on JAMA article by Hujoel et al. Health Phys 88:379–381.

Chiarelli AM, Marrett LD, Darlington GA. 2000. Pregnancy outcomes in females after treatment for childhood cancer. Epidemiology 11:161–166.

De Santis M, Straface G, Cavaliere AF, et al. 2005a. First trimester maternal thyroid X-ray exposure and neonatal birth weight. Reprod Toxicol 20:3–4.

De Santis M, Di Gianantonio E, Straface G, et al. 2005b. Ionizing radiations in pregnancy and teratogenesis: a review of literature. Reprod Toxicol 20:323–329.

Devi PU, Hossain M. 2001. Effect of early fetal irradiation on the postnatal development of mouse. Teratology 64:45–50.

Devi PU, Hossain M, Bishi KS. 1999. Effect of late fetal irradiation on adult behavior of mouse: Dose-response relationship. Neurotoxicol Teratol 21(2): 193–8.

Funahashi A, Darmanto W, Inouye M. 1997. Cortical fiber distribution in the somatosensory cortex of rats following prenatal exposure to X-irradiation. Environ Med 41:37–39.

Goldstein L, Murphy DP. 1929a. Microcephalic idiocy following radium therapy for uterine cancer during pregnancy. Am J Obstet Gynecol 18:189–195, 289–303.

Goldstein L, Murphy DP. 1929b. Etiology of ill health in children born after maternal pelvic irradiation. Part 11. Defective children born after postconceptional maternal irradiation. Am J Roentgenol 22:322–331.

Green DM, Peabody EM, Nan B, et al. 2002b. Pregnancy outcome after treatment for Wilms tumor: a report from the National Wilms Tumor Study Group. J Clin Oncol 20:2506–2513.

Hall EJ, Brenner DJ, Worgul B, et al. 2005. Genetic susceptibility to radiation. Adv Space Res 35:249–253.

Hamilton PM, Roney PL, Keppel KG, et al. 1984. Radiation procedures performed on U.S. women during pregnancy: findings from two 1980 surveys. Public Health Rep 99:146–151.

Hillebrand SJ, Lambooy E, Veerkamp CH. 1996. The effects of alternative electrical and mechanical stunning methods on haemorrhaging and meat quality of broiler breast and thigh muscles. Poult Sci 75:664–671.

Hujoel PP, Bollen AM, Noonan CJ, et al. 2004. Antepartum dental radiography and infant low birth weight. JAMA 291:1987–1993.

ICRP. 1997. International Commission on Radiological Protection (ICRP) Publication 73. Radiological protection and safety in medicine. Ann ICRP 26:1–31.

ICRP. 2001. Doses to the embryo and fetus from intakes of radionuclides by the mother. A report of the International Commission on Radiological Protection. Ann ICRP 31:19–515.

Jacquet P, de Saint-Georges L, Vankerkom J, et al. 1995. Embryonic death, dwarfism and fetal malformations after irradiation of embryos at the zygote stage: studies on two mouse strains. Mutat Res 332:73–87.

Jacquet P. 2004. Sensitivity of germ cells and embryos to ionizing radiation. J Biol Regul Homeost Agents 18:106–114.

Jankowski CB. 1986. Radiation and pregnancy. Putting the risks in proportion. Am J Nurs 86:260–265.

Jensh RP. 1985. Ionizing radiation and the conceptus: neurophysiological effects of the prenatal X-radiation on offspring. Ann Clin Lab Sci 15:185–194.

Jensh RP, Brent RI. 1988. The effects of prenatal X irradiation on the appearance of reflexes and physiologic markers in the neonatal root. Radiol Res 116(3):416–426.

Kato H. 1971. Mortality in children exposed to the A-bomb while in utero. Am J Epidemiol 93:435–442.

Kinlen LJ, Acheson ED. 1968. Diagnostic irradiation, congenital malformations and spontaneous abortion. Br J Radiol 41:648–654.

Kuno H, Kemi M, Matsumoto H. 1994. Critical period for induction of ocular anomalies produced by soft x ray irradiation (4,6 Gy) in the rat F1 offspring. Exp Anim 43:115–119.

Li HP, Honma S, Miki T, et al. 2005. Multiple defects in the formation of rat cortical axonal pathways following prenatal X-ray irradiation. Eur J Neurosci 21:1847–1858.

Miller RW. 1969. Delayed radiation effects in atomic-bomb survivors. Science 166:569–574.

Miller RW. 1999. Severe mental retardation and cancer among atomic bomb survivors exposed in utero. Teratology 59:234–235.

Minamisawa T, Yamamoto K, Tsuchiya T. 1980. Long-term effects of moderate X-ray doses on the averaged evoked potentials in the rabbit. Electroencephalogr Clin Neurophysiol 50:59–70.

Mole RH. 1982. Consequences of prenatal radiation exposure for postnatal development. A review. Int J Radiat Biol Relat Stud Phys Chem Med 42:1–12.

Mole RH. 1991. Detriment in humans after irradiation in utero. Int J Radiat Biol 60:561–564.

Nokkentred K. 1968. Effect of radiation upon the human fetus. Copenaghen: Munksgaard. p 28.

Osei EK, Faulkner K. 1999. Fetal doses from radiological examinations. Br J Radiol 72:773–780.

Otake M, Schull WJ. 1984. In utero exposure to A-bomb radiation and mental retardation: a reassessment. Br J Radiol 57:409–414.

Otake M, Schull WJ, Yoshimaru H. 1991. A review of forty-five years study of Hiroshima and Nagasaki atomic bomb survivors. Brain damage among the prenatally exposed. J Radiat Res (Tokyo) 32(Suppl):249–264.

Otake M, Schull WJ, Lee S. 1996. Threshold for radiation-related severe mental retardation in prenatally exposed A-bomb survivors: a reanalysis. Int J Radiat Biol 70:755–763.

Pils S, Müller WU, Streffer C. 1999. Lethal and teratogenic effects in two successive generations of the HLG mouse strain after radiation exposure of zygotes—association with genomic instability? Mutat Res 11; 429:85–92.

Plummer G. 1952. Anomalies occurring in children exposed in utero to the atomic bomb in Hiroshima. Pediatrics 10:687–693.

Rakie P. 1975. Cell migration and neuronal ectopias in the brain. Birth Defects Orig Artic Ser 11:95–129.

Russell LB. 1950. X-ray induced developmental abnormalities in the mouse and their use in the analysis of embryological patterns. J Exp Zool 114:545–602.

Russell LB, Russell WL. 1954. An analysis of the changing radiation response of the developing mouse em-

bryo. J Cell Physiol 43(Suppl 1):103–149.
Russel LB, Badgett SK, Saylors CL. 1959. Comparison of the effects of acute, continuous and fractionated irradiation during embryonic development. Conference in Venice. London: Taylor & Francis. pp. 343–359.
Sanová S, Bálentová S, Slovinská L, Russel LB. 2005. Effects of preconceptional gamma irradiation on the development of rat brain. Neurotoxicol Teratol 1:145–151.
Schull WJ, Otake M. 1986. Learning disabilities in individuals exposed prenatally to ionizing radiation: the Hiroshima and Nagasaki experiences. Adv Space Res 10(2):223–32.
Schull WJ, Otake M, Yoshimaru H. 1986. Effects on intelligence test score of prenatal exposure to ionizing radiation in Hiroshima and Nagasaki: a comparison of the old and new dosimetry systems. Technical Report. Hiroshima, Japan: Radiation Effects Research Foundation. pp. 3–88.
Schull WJ, Otake M. 1999. Cognitive function and prenatal exposure to ionizing radiation. Teratology 59: 222–226.
Sharp C, Shrimpton JA, Bury RF, et al. 1998. Diagnostic medical exposures. Advice on exposure to ionising radiation during pregnancy. National Radiological Protection Board, College of Radiographers and Royal College of Radiologists. Available on www.hpa.org.uk/radiation/publications/misc_publications/advice during-pregancy.htm/24K, Rome 30 August 2007.
Shirai K, Mizui T, Suzuki Y, et al. 2006. Differential effects of x-irradiation on immature and mature hippocampal neurons in vitro. Neurosci Lett 15; 399:57–60.
Smith H. 1992. The detrimental health effects of ionising radiation. Nucl Med Commun 13:4–10.
Streffer C, Shore R, Konermann G, et al. 2003. Biological effects after prenatal irradiation (embryo and fetus). A report of the International Commission on Radiological Protection. Ann ICRP 33:5–206.
Tabuchi A. 1964. Fetal disorders due to ionising radiation. Hiroshima J Med Sci 13:125–173.
Timins JK. 2001. Radiation during pregnancy. N J Med 98:29–33.
Undarmaa B, Kodama S, Suzuki K, et al. 2004. X-ray-induced telomeric instability in Atm-deficient mouse cells. Biochem Biophys Res Commun 27, 315:51–8.
Verheyde J, Benotmane MA. 2007. Unraveling the fundamental molecular mechanism of morphological and cognitive defects in the irradiated brain. Brain Res Rev 53:312–320.
Vilumsen A. 1970. Environmental factors in congenital malformations. Copenhagen: FDAL's Forlag. p. 130.
Wagner KL, Lester RG, Saldana LR. 1997. Exposure of the pregnant patient to diagnostic radiations: a guide to medical management. Madison, WI: Medical Physics Publishing.