Razavi Int J Med. 2015 May; 3(2): e27508. DOI: 10.30483/rijm.2015.118324

Published online 2015 May 2. **Review Article**

Prenatal X-Ray Exposure and Teratogenic Risks: A Literature Review

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Received: January 30, 2015; **Revised:** April 7, 2015; **Accepted:** April 19, 2015

Context: Many women of reproductive age and pregnant women require diagnostic tests involving ionizing radiation. Fetal exposure to radiation worries both the patient and the obstetricians and could lead to inappropriate termination of pregnancy.

Evidence Acquisition: To conduct this review of the literature Pub-med was searched. Retrospective studies, reviews of literature, multicentric epidemiological case control studies were reviewed. Official data base Reprotox and The Teratogen Information System Teris were also consulted.

Results: Standard diagnostic X ray tests including those of the lower abdomen imply that the dose absorbed by the uterus is in any case less than 0.05 Sv (= 5 rad). The majority of the studies in literature estimates that 1-2 rad fetal exposure may increase the risk of leukemia of 1.5 - 2.0 over the natural incidence, meaning that 1 in 2,000 children exposed to ionizing radiation in utero will develop leukemia in childhood.

Conclusions: At present, no single diagnostic procedure is able to cause damage to the embryo or fetus. There are possible harmful effects for doses above 0.2 - 0.25 Gy (20-25 rad).

Keywords: Radiation; Teratogens; Counseling; Prenatal Diagnosis

1. Context

The word radiation indicates the transfer of energy from a source (radiant) to a receiver (radiated). This transfer is brought about by the motion of corpuscular particles or of electromagnetic waves. Radiation is said to be ionizing when it can transfer enough energy to liberate electrons from the atoms of the radiated receiver, therefore producing ionization. Ionizing radiation can consist of electromagnetic waves or radiation (X rays and Gamma rays) and corpuscular particles (alpha, beta, neutrons and protons). As regards electromagnetic radiation, transmission is made through photons (characterized by their frequency and wavelength), whereas, in the case of corpuscular radiation it occurs by means of particles (characterized by their mass, charge and speed). When radiation is transmitted through biological tissue, the transfer of energy can cause biological damage. About 18% of human exposure to ionizing radiation derives from human activity (medical diagnostics: X rays and nuclear medicine, radiotherapy and nuclear reactors) while 82% is caused by natural radioactivity (largely due to the presence of radon) (1). Many women of reproductive age and pregnant women suffer from diseases which require immediate diagnosis and treatment, including diagnostic tests involving ionizing radiation. Fetal exposure to radiation worries both the patient and the family. Often, doctors themselves do not cope with this kind of situation in an appropriate scientific way, thus providing incorrect and highly alarming counseling. A previous study showed that most of the women who called our Teratology Information Service asked for information about drugs (78%); others called for following the exposure to radiation of infections. A small proportion was concerned about homeopathic drugs or cosmetic products (3%) or about professional exposure or vaccinations (1%) (2). X rays and more rarely gamma rays are the most commonly used ionizing radiations in clinical practice, diagnostics (radiodiagnostics, nuclear medicine, bone densitometry) and in treatment (radiotherapy, metabolic therapy). X rays are classified as short electromagnetic waves (below 10 nm). Different units of measure are used for electromagnetic waves. The quantity of energy absorbed by the organism per unit mass is known as absorbed dose or simply dose and is measured in Gray (1 Gy = 1 J/Kg). Absorbed dose used to be measured in Rad (1 Rad = 0.01 Gy). The different kinds of ionizing radiations have the intrinsic capacity to bring about different biological effects with the same dose; therefore, a new magnitude has been introduced, the equivalent dose measured in Sievert (Sv) (1 Sv = 1 Gray), which takes the different capacity of causing biological effects into account. Moreover,

the risks, with the same absorbed dose (or equivalent dose) are different depending on the organ involved. For this reason the effective dose (Sievert), which is the sum of the weighted equivalent doses, has been introduced. The biological effects of ionizing radiation can be divided into two categories: deterministic effects and stochastic effects. The deterministic effects are those caused by the impairment or loss of organ function due to cell damage or death. For these effects there are threshold doses: the functionality of many organs and tissues is not impaired by small decreases of the number of healthy cells. Only a substantial decrease can bring about pathological effects which can be clinically detected in the unborn child. On the other hand, the stochastic effects are those deriving from radiation-induced modifications in the cells, which retain their dividing capacity. These modified cells can sometimes trigger a malignant cell transformation which leads to the development of a malignant clone and a possibly of a clinically manifest cancer. The timespan between the onset and the manifestation of the disease can range from a few years (leukemia, thyroid cancer) to several decades (colon cancer, liver cancer) (3).

2. Evidence Acquisition

To conduct this review of the literature Pub-med was searched using the following terms: ionizing radiation, pregnancy, teratology, X-ray, fetal exposure, malformations, carcinogenetic effects. Retrospective studies, reviews of literature, multicentric epidemiological case control studies were reviewed. Official databases Reprotox and The Teratogen Information System Teris were also consulted (4, 5).

3. Results

Previous nuclear disasters have caused ionizing radiations to be commonly classified as mutagenic agents or causes of malformations; however, few studies have actually supplied proof of this association in humans. Chernobyl suffered the most serious nuclear accident ever. Although although at first there was no evidence of increased cancer risk, by the end of 1994 an increase of thyroid cancer in the pediatric age was recorded in the children exposed to these radiations. No data have been definitely established as regards the increased risk of congenital malformations or reproductive toxicity (6). Between 1950 and 1989 a survey conducted on male workers of the nuclear plant in Sellafield (UK) found a possible association between the risk of stillbirth and malformations in fetuses whose fathers had been exposed to ionizing radiations before conceiving the offspring (7). On the contrary, a similar survey carried out in 2000 on all the nuclear industry male workers in the UK had not found an increased risk of intrauterine death, congenital malformations and neonatal deaths. The only positive correlation identified was the one between pre-conceptional maternal exposure and an increased risk of early miscarriage and stillbirth, but the survey had been carried out on a limited group of women (8). The analysis of the Hiroshima and Nagasaki data carried out by Otake and Schull (9) assessed the prevalence of mental retardation among the 1600 children exposed in utero to the atomic bomb. The study identified a critical period corresponding to the peak period of neuronal proliferation: from 8 to 15 weeks after conception. Otake and Schull evaluated the risk of mental retardation in different gestational ages and for different doses of exposure. No definite threshold dose was found, but no significant increased risks were found below 10 rad exposure (9). Mental retardation rate in the control group was 0.8 percent. A later analysis of the same data, which excluded two cases of Down Syndrome from the cases exposed between weeks 8 and 15 (10), showed an increased risk with a 95% confidence level for exposure ranging from 6 to 31 rad (0.06 - 0.31 gy). A study by Yamazaki and Schull (11) examined the neurological anomalies in offsprings of exposed mothers in Nagasaki and Hiroshima and set the threshold dose for increased risk of mental retardation between 10 and 20 rad (0.1 a 0.2 Gy). The few cases in which autopsy could be performed confirmed the hypothesis of damage caused by erratic neuronal migration. Other studies on human pregnancy have confirmed that the risk of microcephaly and mental retardation is associated with exposure absorbed doses of at least 20 rad between weeks 8 and 15 (12, 13). At any rate, the risk extrapolated from the surveys carried out in Hiroshima and Nagasaki for intrauterine exposure does not apply to the low dose exposure used in diagnostic tests (14, 15). Standard X ray tests carried out in pregnancy, including those of the lower abdomen, imply that the dose absorbed by the uterus is in any case less than 0.05 Sv (= 5 rad). This dose is reached with more than 71.000 chest x-ray, about 50.000 dental X-ray, 1.250 skull X-ray and more than 20 abdomen X-Ray. CT scan results in a higher dose of radiation absorbed by the embryo, in fact only 1 abdomen CT scan or 1 lumbar spine CT scan reaches the alarm dose of 5 rad. On the other hand, more than 100 Skull CT scan and 50 chest CT scan are necessary to achieve 5 rad (16). In a study on 17 pregnant women subjected to ERCP (Endoscopic Retrograde cholangiopancreatography) ionizing radiation exposure was 0.0004 rad (range 0.001 - 0.18 rad) (17). Radiation dose in diagnostic tests of the lumbar column and pelvis is steadily kept below 0.002 Sv (equivalent to 0.2 rad). Secondary radiation to other parts of the body, such as upper abdomen, skull or teeth is insignificant because the dose of radiation absorbed by the embryo is less than 0.0001 Sv (0.01 rad). Longer radiographies, such as urography or intestinal radiography, can cause the uterus to receive an exposure dose of at least 0.039 Sv (= 3.9 rad) (16). Among the diagnostic tests, the CT scan has the highest dose of ionizing radiation, albeit below 0.05 Sv (= 5rad). A 2013 review has assessed the safety of skull radiography during pregnancy and has concluded that if the CT scan is not directed to

the pelvis-abdomen area, the dose absorbed by the embryo or fetus is very low and can be considered harmless. Due to the limited number of studies, this test should be performed in pregnancy only if strictly necessary for the mother. The survey, however, did not specify the dosage of radiation, but the authors assumed that for each radiography test the dose was below 0.05 Gray (5 rad) (18). In the past, a number of studies had hypothesized a correlation between diagnostic radiation exposure and the risk of Down Syndrome, but the available data was not suitable to prove this association (19). A study in 1963 suggested that ionizing radiation exposure could induce iris heterochromia, but this association has not been supported by later more detailed studies (20). Brent in 1999 (13) and De Santis in 2005 (21) reviewed literature and concluded that ionizing radiation from diagnostic procedures during pregnancy do not increase the risk of congenital malformations. Radiation-related growth reduction has been reported, especially for exposure in the first and second trimester of pregnancy (22). In the past, several authors (23) had found an increased risk of low birth weight. In a case-control study in 2004, Hujoel (24) concluded that dental X-rays during pregnancy led to low birth weight probably when exposure was at least 0.4 mGray (0.04 rad) in the thyroid. In a survey of 224 cases of thyroid radiation exposure during pregnancy De Santis (25) found a higher risk of low birth weight when exposure was between 0.4 and 0.8 mGray (0.04 - 0.08 rad). It is nonetheless difficult to establish a cause-effect relationship in these cases, because these doses are not capable of bringing about hypothyroidism (26, 27). Another survey has studied the association between low birth weight and dental ionizing radiation during pregnancy (23). It yielded a limited, albeit statistically significant, association of low birth weight in full term babies and exposure > 0.04 rad, with OR of 3.61 (95% CI 1.46-8.92). The authors ascribed this correlation to radiation-induced thyroid damage. These conclusions were however criticized (28) because literature has already referred that dental pathologies are associated with preterm birth and full term low birth weight. In 2012 a consensus conference of the Oral Health Care during Pregnancy Expert Workgroup sponsored by the American Dental Association and by ACOG concluded that dental radiography is not contra indicated during pregnancy, but they recommended that the abdomen and thyroid should be protected throughout the procedures (29). A prospective study on 62 pregnant women exposed to diagnostic radiography procedures concluded that appropriate counseling is fundamental (30). These women had been subjected to diagnostic procedures at an average gestational period of 7 + 2 weeks, with a fetal dose estimated between 0.01 and 47.9 mGy (0.001- 4.79 rad). Although counseling had been reassuring for these patients, 5 out of the 69 women chose voluntary termination of pregnancy. Among the women who carried on pregnancy, the study group and the control group showed no difference in the rates of live births, birth weight and major malformations. The National Council on Radiation Protection has stated that the risk of malformations for exposure up to 5 rad is insignificant compared to other pregnancy risks (31).

3.1. Tumors

The mutagenic or transplacental carcinogenic risk of ionizing radiations is more difficult to evaluate than the teratogenic risk. Mutagenic effects are stochastic effects, therefore no threshold dose can be established. Point mutations often occur spontaneously. A dose of 100 - 200 rad (1-2 Gy = 1-2 Sv) could induce a doubling of the point mutation rate (12, 31). The threshold dose capable of increasing the cancer risk, in particular the risk of prenatal leukemia has not yet been established. A 1985 study used the data on the incidence of neoplastic diseases in twins to establish whether radiation during pregnancy has carcinogenic effects (32). Before obstetric ultrasound was introduced, twins were often exposed to X rays both to diagnose a twin pregnancy and to assess fetal position during delivery (33). The results reported in the 1985 study were in general agreement with previous investigations of childhood tumors (34, 35) and suggested that intrauterine X ray exposure of at least 0.01 Sievert (1 rad) increases the risk of leukemia and other infantile tumors by about 40%. In a survey on childhood cancer Wakeford 2003 (36) concluded that fetal exposure of 0.01 Sievert (1 rad) increased the risk of childhood cancer. However, this data can hardly allow us to reach a realistic conclusion as to the risk level with such a low dose. Other authors conclude that there should not be any risk for the fetus between 0.02 and 0.05 sievert (2-5 rad) (37). A population survey has not shown an increased risk of childhood brain tumors after prenatal exposure to X rays (38). A British record linkage study has not found evidence of risk of cancer in the offsprings of female workers professionally exposed to ionizing radiation (39). A 2014 review on the carcinogenic risks of prenatal exposure to ionizing radiation has found that procedures using high doses of X rays (> 0.5 Gy) (50 rad) can lead to an increased risk of cancer (40). The risk related to embryonic and fetal exposures < 0.1 Gy (10 rad) has not been established. The review also suggested that the earlier embryonic exposure to radiation the lesser the probability to develop cancer. The 2004 AGOC Committee Opinion (reaffirmed in 2014) estimates that 1 - 2 rad fetal exposure may increase the risk of leukemia of 1.5 - 2.0 over the natural incidence, it means that 1 in 2,000 children exposed to ionizing radiation in utero will develop leukemia in childhood (41).

4. Conclusions

Natural radioactivity causes humans to absorb about 3 mSv radiations a year (a fetus would absorb this dose if the pregnant mother was subjected during pregnancy to about 300 chest radiographies carried out in a single anteroposterior projection over one year) (1). Embryos

and fetuses are sensitive to radiations according to the development stage happening during exposure to other physical and chemical agents (15). Fetal development can be roughly divided into three fundamental stages:

-Before embryo implantation (9th day from fertilization) and in the preimplantation stage (9 – 14 days), the effects of radiation can lead to miscarriage or may not bear consequences on its development.

- The main stage of development (organogenesis) lasts approximately until the eighth week after ovulation (15 – 50 days); in this stage, organs may suffer malformations. The risk of malformations depends on the organogenetic stage at which exposure occurred and is likely to be particularly high during the most active stage of cell multiplication and of differentiation of the developing organs. Experiments on animals have yielded threshold values, estimated for humans as 0.1 Sv (corresponding to 10 rad or 0.1 Gy).

- In the stage of fetal development, from the ninth week of pregnancy to childbirth, the rate and seriousness of malformations decrease, while there is a relevant risk of defective development of the central nervous system, which is radiosensitive throughout most of this period. The fetal brain radiosensitivity is highest between the 8th and 15th weeks after conception and radiation can bring about mental retardation (42). Doses up to 0.1 Sv (corresponding to 10 rad or 0.1 Gy) should not have substantial effects on the intelligence quotient. After atomic bomb explosion in Hiroshima, radiations have been proved to lead to an increased risk of leukemia and different types of adulthood and childhood cancers. Instead the risk of malignant neoplasia in children subjected to pelvimetry in the third trimester of pregnancy (about 0.01 Gy) and followed up for 14 years after birth was 0.064%/0.01Gy (0.064 %/1 rad) higher than natural risk standing at 0.1% (43).

The risk for embryonic/fetal exposure is assumed to be equivalent to the risk of carcinogenic effects in children (44).

The different studies in literature have established the radiation dose supplied to embryo and fetus in diagnostic and therapeutic procedures. No diagnostic procedure currently in use exceeds 0.05 Sv (5 rad), which is not associated with a high risk of congenital malformations (45, 46). Even if we do not consider that a threshold may exist for all these effects, we can act that:

- Patient should be informed that exposure to less than 5 rad (0.05 Sv) has not been associated with increased risk of fetal malformation, abortion or childhood tumors;

- In anyway on no account special measure is required for doses received by the embryo or fetus below 0.1 Gy (10 rad), because there are not real evidence of an increased risk for exposure between 5 - 10 rad;

- If possible, during pregnancy other imaging procedures not associated with ionizing radiation should be considered (eg. ultrasonography, magnetic resonance imaging);

- We advise a constant monitoring of pregnancy for doses between 0.1 and 0.2 Gy (10 - 20 rad)

- Possible harmful effects for doses above 0.2 - 0.25 Gy (20 - 25 rad).

The use of radiation in pregnancy often causes anxiety for patients and obstetricians, but at present, according to the American College of Radiology, no single diagnostic procedure is able to cause damage to the embryo or fetus. Therefore exposure to a single diagnostic procedure using X-ray during pregnancy is never an indication for elective abortion (41).

Acknowledgements

we thank the head of the department of Obstetrics and Gynecology, Prof. G. Scambia, for providing general support.

Authors' Contributions

Study concept and design: Luisa D'Oria, Marcella Pellegrino, Marco De Santis, Angelo Licameli, Carmen De Luca, Daniela Visconti, Laura Donati. Acquisition of data: Luisa D'Oria, Marcella Pellegrino, Marco De Santis. Analysis and interpretation of data: Luisa D'Oria, Marcella Pellegrino. Drafting of the manuscript: Luisa D'Oria, Marcella Pellegrino. Critical revision of the manuscript for important intellectual content: Marco De Santis. Study supervision: Alessandro Caruso, Marco De Santis.

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