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Review

Ionizing radiations in pregnancy and teratogenesis A review of literature

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Abstract

The present paper is a review of the data available in the literature concerning the prenatal exposure to radiation evaluating the reported teratogenic effect. We have particularly focused on the fetal effects of maternal ionising radiation exposure, both diagnostic and occupational, particularly in terms of congenital anomalies and birth weight. Ionising radiation represents a possible teratogen for the fetus, but this risk has been found to be dependent on the dosage and the effects correlatable to the gestational age at exposure. Recently, of particularly note is the fact that maternal thyroid exposure to diagnostic radiation has been associated with a slight reduction in the birth weight. Inadvertent exposure from diagnostic procedures in pregnancy doesn't usually increase the natural risk of congenital anomalies but creates a considerable state of maternal anxiety. Diagnostic radiological procedures should be avoided in pregnant women unless the information cannot be obtained by other techniques.

Keywords: Ionizing radiations; Pregnancy; Teratogenesis; Congenital anomalies; Diagnostic radiations; Fetal dose; Fetal exposure; Low birth weight

Contents

1. Introduction

Exposures to potential teratogens are emotionally relevant and cause anxiety in pregnant women. This consideration is particularly true with regard to pre- and post-conception environmental radiation exposure [1,2]. In fact, the term high-energy radiation is generally associated by the general public, physicians and media with the adverse effects of ionizing radiation, such as the atomic bomb tragedy, the Chernobyl reactor accident and an increased incidence of

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cancer [3]. A recent study has shown that physicians who care for pregnant women perceive the teratogenic risk associated with an abdominal radiograph/CT scan to be unrealistically high during early pregnancy which could lead to an increased anxiety among pregnant women and the non prescription of needed medicines [4]. However, in spite of the large amount of epidemiological, clinical and experimental data, the risk of the prenatal exposure to radiation is still unknown.

It is well known that the biological effects of ionizing radiation in humans are due to physical and chemical processes, which occur immediately following the passage of radiation through living matter. These processes involve successive changes at the molecular, cellular, tissue and whole organism levels. The effects of radiation exposure can be classified as deterministic and stochastic. The deterministic occur principally above a threshold dose and are manifested as clinical damage, primarily as a result of cell killing, although damage to individual cells will take place at lower doses [5]. The stochastic effects occur some time after exposure, and consist of damage to the nuclear material in the cell which can cause radiation-induced cancer or mutations that may be transmitted to the descendants of exposed individuals.

Information on radiation-induced cancer is available from many epidemiological studies. These include the survivors of the atomic bombings in Japan and groups that have been exposed to radiation for medical reasons, nuclear accidents or occupationally [6–10]. Most studies have been concerned with the cancer risk in exposed individuals, while in the case of radiation-induced hereditary diseases no studies have been conducted in human populations, so risk estimates have therefore to be based only on the results of animal studies. The doubling dose method is one of those currently used to estimate the genetic risks of ionizing radiation in humans [5]. It can be defined as the amount of radiation that is required to produce as many mutations as those arising naturally in one generation. Experimental procedures have estimated the doubling dose in mice, the quantitative data, however, only available following exposure to intermediate and high doses. This mouse model can not therefore be easily applied to humans who are exposed, in the majority of cases, to low doses of ionizing radiation such as in the home, in the natural environment, in some work places and, in most cases, for diagnostic purposes [11]. Few studies concern the teratogenic effects of low dose radiation in exposed fetuses. For example, the United Nations Scientific Committee on the Effects of Atomic Radiation volumes do not report on the teratogenicity of radiation, but on mutagenicity with respect to Mendelian diseases and cancer risks [10].

The present paper is a review of the data available in the literature concerning prenatal exposure to radiation evaluating the reported teratogenic effects.

2. Ionizing radiation and congenital anomalies

Ionizing radiation is a potential teratogen whose dose dependent action has not been well defined. It is therefore necessary, when evaluating the effects of exposure during pregnancy, to take into consideration above all the dose absorbed at the level of the fetus. Some sizes and units of measurement have been defined in order to evaluate the action of ionising radiation, in particular its intensity and the energy that it transfers to matter and biological tissues, and further to measure the activity of radioactive substances. The exposure dose that is measured in Roentgen, refers specifically to the X- and gamma-radiations and concerns their capacity to produce ionisation. The exposure dose, and in particular its intensity, is taken much more into consideration when evaluating its safety in the case of radioactive contamination. In the International System (IS), the exposure dose is expressed in Coulomb per kilogram. The absorbed dose is the amount of energy that the ionising radiation transfers to tissue by the unit of mass of the irradiated substance, that is to say the relationship between the energy of the radiation absorbed by tissue and the mass of the interested tissue, independently of the type of ionising radiation. The rad is used as a unit of the dose absorbed. In IS the absorbed dose is measured in gray (Gy). The dose equivalent is the dose of ionising radiation that, absorbed by the human body, produces a biological effect equal to that produced in the same tissue by the absorption of X- or gamma-rays. This size is very important because ionising radiation with different characteristics, like the alfa or X-rays, can provoke different biological effects although brought about by the same dose absorbed. The value of the dose equivalent is obtained by multiplying the dose absorbed by a numerical factor characteristic of the type of ionising radiation (quality factor). The dose equivalent is measured in rem (roentgen equivalent man). X- and gamma-rays have a quality factor of about 1, so the absorbed dose in rads is the same in rem. The IS unit of measurement is the sievert (Sv) (Table 1).

The effect of ionising radiation in pregnancy, as for every teratogen, also depends on the gestational age at the time of exposure and not only on the fetal dose absorbed. Data on teratogenicity of a 1 Gy acute dose in rodents during different periods of fetal development are reported in Table 2 [12]. In the pre-implantation period the embryo is less radiosensitive [13,14]. In about the first 14 days after conception, therefore, the effect of the radiation is more frequently the failure of embryo implantation, an early abortion or no other consequences (all or none effect) [15,16]. In fact if a genetic anomaly or a malformation is produced, the possible result

Table 1
Principle units of radiologic measurement

Unit of measurement	International system	Use	Equivalence
Roentgen (R)	C/kg	Used by the exposure dose	$1\,R = 2.58 \times 10^{-4}$ C/kg
Rad (rad)	Gray (Gy)	Used by the absorbed dose	1 rad = 0.01 Gy
Rem (rem)	Sievert (Sv)	Used by the equivalent dose	1 rem = 0.01 Sv

Table 2
Effects of ionizing radiation (1 Gy) prenatal exposure in rodents by gestational period

Effect	Preimplantation	Embryo	Fetus
Lethality	Yes (++)	Yes (±)	No
Malformations	No	Yes (+)	No
IUGR	No	Yes (+)	Yes (+)
Mental retardation	No	Yes (+)	Yes (+)

Modified from ref. [26]. IUGR: intrauterine growth retardation. ±: observed, +: frequent, ++: high incidence.

is thought to be embryo loss or of repair on the part of the embryo and the totipotent cells present at this stage [17–19]. The organogenesis period (from the end of the 2nd to the 8th week post-conception) is however extremely sensitive to the teratogenic effect of ionising radiation and particularly the central nervous system (CNS) even though its main formation period is between the 8th and 15th week of pregnancy, a period in which it is very radiosensitive [20]. In these weeks the neuronal stem cells are subject to a notable mitotic activity and a proliferation along the passage that goes from the ventricular and subventricular zones to the cerebral cortex [21]. From the 16th to the 25th week, there is a reduction in the radiosensitivity of the CNS and in many of the other organs. After the 25th week the central nervous system becomes relatively radioresistent and major fetal malformations and functional anomalies highly improbable [22–26].

Various epidemiological studies have demonstrated that the exposure to high levels of ionising radiation in pregnancy provokes reasonably characteristic congenital anomalies, such as growth retardation of the organs or mental retardation with or without microcephaly. Such biological effects are of a deterministic kind and the incidence and gravity of these anomalies, therefore, acknowledge a dose dependent relationship and a dose threshold, below which they cannot be verified [12,27,28]. The threshold dose of these deterministic effects is sufficiently high (generally >1 Gy, based on the studies of Hiroshima and Nagasaki). They have concluded that doses of ionising radiation below the threshold dose do not produce teratogenic effects (Table 3) [17]. Thirty four percent of 74 neonates who had received radiation for carcinoma of the uterus in pregnancy had congenital malformations. The majority of these malformations were a reduced head circumference or microcephaly (23%), as well as hypoplasia of the genitalia, palatoschisis, hypospadia, micropthalmia, cataracts, strabism, retinal degeneration and optic atrophy. The estimated dose was >1 Gy. It was the first indication of malformations induced by an iatrogenic agent in human beings [29]. Re-examining the data, the authors observed that 70% of the malformed newborns had been exposed before the fifth month of pregnancy [30]. Other studies have tried to establish, on the basis of the available data, a relationship between the dose, the gestational age in which irradiation occurred and the neonatal outcome. They concluded that radiation caused malformations only from the 3rd/4th to the 19th week with the most serious malformations,

Table 3
Ionizing radiations and malformations [16,24,42,43]

Malformations	Estimated threshold dose	Gestational age at greatest risk (weeks p.c.)
Microcephaly	≥20 Gy	8–15
Mental retardation	0.06–0.31 Gy between 8 and 15 weeks[a] 0.25–0.28 Gy between 16 and 25 weeks[a] >0.50 Gy between 8 and 15 weeks[b]	8–15
Reduction of the IQ	0.1 Gy	8–15
Other malformations (skeleton, genitals, eyes)	≥0.20 Gy	3–11

p.c.: Post-conception.
[a] Estimated by Otake et al. [42].
[b] Estimated by Miller [43].

like microcephaly, occurring only after irradiations before the 17th week [31]. In 1968 Dekaban, re-analysing the data of the literature (26 cases), highlighted that these women had been exposed to a dose >2.5 Gy, the effect of the gestational age also being seen as a dependent factor. This resulted from the fact that many cases of mental retardation and also non-CNS malformations were more frequent following exposure between the 3rd and the 11th week of conception. Finally, growth retardation, microcephaly and mental retardation were the only congenital anomalies observed in the period between the 10th and 12th and the 16th and 20th week of conception, no anomaly being reported for exposure after the 20th week [32].

Much of the information on the effects of acute exposure to ionising radiation has been obtained from studies carried out on the survivors of the atomic bomb of Hiroshima and Nagasaki. Their limitation, however, is that they have analysed the effects of a single, relatively high exposure and not of small intermittent or continual doses typical of medical, professional or environmental exposure [33]. These studies have confirmed that the prevalent effects were microcephaly, mental retardation and growth retardation [34–36]. Further limitations are linked to the difficulty of data collection after the atomic bomb attacks and their evaluation both from a methodological and political point of view as a result of taboos on both the victim's and aggressor's side. Many children who survived the tragedy of the atomic bomb and who were exposed in utero to doses between 0.1 and 1.5 Gy developed microcephaly [34,37]. Otake and Schull found that among these subjects, 4.2% (62/1473) had microcephaly and 87% severe mental retardation. It is worth noting that mental retardation is not directly linked to microcephaly and many cases of reduced head size were exposed between the 0 and 7th week after conception [38]. Various studies of the survivors of the atomic bomb have highlighted that mental retardation is one of the most important risks of ionising radiation at high doses [34,39]. A total of 30 cases of mental

retardation were shown among children exposed in utero to the radiations of Hiroshima and Nagasaki; however, 5 of these were successively excluded because they were correlated to other causes, not radiation. The risk of severe mental retardation is not increased as a result of exposure before 8 weeks post-conception, and reaches a maximum between the 8th and 15th week diminishing between the 16th and 25th week. After the 25th week of gestational age (and for exposures of <1 Gy), no cases of mental retardation have been reported [40]. Furthermore, no incidence of mental retardation has been observed among children exposed in utero to a dose of 0.5 Gy. This data initially orientated towards a dose dependent effect without a threshold dose. In particular, the authors have estimated an increase of mental retardation of 0.4% for every rad (0.01 Gy) of irradiation [37,40]. It is still not clear if there is a threshold dose for mental retardation even if Otake et al. have calculated that this value could be between 0.12 and 0.23 Gy between 8 and 15 weeks and about 0.21 Gy between 16 and 25 weeks [41]. A re-analysis of this data has led to the estimation of a threshold dose of 0.06–0.31 Gy for exposure between 8 and 15 weeks and of 0.25–0.28 between 16 and 25 weeks [42]. Miller in 1999 reported a threshold dose >0.5 Gy for severe mental retardation [43]. Otake has also succeeded in finding a correlation between less severe mental retardation and the exposure in utero to ionising radiation. The data were similar to those concerning severe mental retardation, without evidence of effects before 8 weeks and after 26 weeks post-conception. Because the maximum linear dose effect between 8 and 15 weeks was 21–29 IQ points per Gy they were, however, excluded from the sample of subjects with severe mental retardation. In the period 16–25 weeks, the reduction was of 13 and 21 IQ points, respectively. No effect was evident for doses <100 mGy even in the period of maximum sensitivity [44,45]. The question of IQ reduction has also raised discussion concerning the existence of a threshold dose. The present data do not permit the establishment of definitive answers, but if a threshold dose exists, it is probably at 10 cGy [25]. Smith has presented two studies that have shown a 30-point reduction in the IQ for every sievert of fetal dose between 8 and 15 weeks post-conception. A minor reduction was present even for exposures between 16 and 25 weeks [46].

3. Exposure to diagnostic radiation

There is no evidence either in humans or animals that exposure to diagnostic radiation (<0.5 Gy) is associated with an increased incidence of congenital malformations [17,47–51]. In 1977, the NCRP Report 54 affirmed: “The risk of anomalies is considered negligible at 5 rad (0.05 Gy) or less if compared to the other risks of pregnancy, and the risk of malformations is substantially increased only at doses above 15 rad (0.15 Gy). However, the exposure of the fetus to radiations deriving from diagnostic procedures must rarely constitute a reason for the interruption of the pregnancy” [52]. Various studies in the literature have calculated the fetal dose absorbed with regard to the most common diagnostic radiological examinations [53–55]. The majority of the diagnostic procedures give a fetal dose of <0.05 Gy while those associated with a higher fetal dose are: barium enema (0.07 Gy), pelvic and abdomen CT (0.025 and 0.0088 Gy respectively) and the procedures of nuclear medicine. In every case, when possible, it is always advisable to calculate the fetal dose rather than referring to the average dose published in the literature. In fact, the fetal dose of each single procedure could be up to 10 times greater with respect to the average dose on the basis of the weight of the patient and the techniques used. Only for those radio diagnostic procedures that involve areas of the body at a considerable distance from the abdomen can the fetal dose be assumed to be not higher than a few mGy [55]. The threshold doses for the induction of the deterministic effects provoked by radiation are all above the fetal doses estimated for common diagnostic radiation. On the basis of these considerations the risk of deterministic effects from diagnostic radiation is almost identical to the natural risk. Kinlen and Acheson, in the sphere of the Oxford Record Linkage Study, conducted a case control study on 605 children with various malformations without finding differences in terms of congenital malformations and abortions after diagnostic irradiation when compared to the control group [56]. Osei and Faulkner conducted a prospective study on 50 women exposed to diagnostic radiation in early pregnancy. The doses to the embryo/fetus varied between <0.01 Gy (0.0001 rad) and 117 mGy (11.7 rad) and the gestational age at exposure between 2 and 24 weeks. The percentage of major malformations and of intrauterine death were not higher than those of the general population, taking into consideration that even the highest doses were far from the threshold doses estimated for the occurrence of these adverse effects [54]. Even the incidence of mental retardation was not higher than the natural referred to by Mole as 4–10 per 1000 [57]. Indeed, even in this case the highest fetal dose (117 mGy), although administered in the sensitive period (8–15 weeks post-conception) was much lower than the threshold dose of 390–460 mGy (39–46 rad) reported by Otake for serious mental retardation (1991), on the basis of the data from Hiroshima and Nagasaki [42]. If this threshold dose exists, it can be concluded that there is no risk of serious mental retardation from exposure to diagnostic radiation in the sensitive period. However, Servomaa and Paile do not exclude the fact that the risk of severe mental retardation, correlated according to the data from Hiroshima and Nagasaki to exposures above 0.5 Gy between 8 and 15 weeks, could be verified even at lower doses [58]. In the same way, with regard to mild mental retardation, considering the linear dose dependent course of 25–29 IQ points per Gy estimated by Otake, the majority of the diagnostic procedures should lead to a reduction in IQ of about 0.2 points [41,54]. Ornoy et al. found no differences in terms of neurological, motor or cognitive functionality between 112 newborns who had undergone ionising radiation

at low doses in utero (5 rad–50 mGy) and a control group [59]. A study carried out on 1026 children exposed in utero to diagnostic radiation between 12 and 43 mGy showed no differences in terms of a reduction in IQ when compared to a control group of 1191 subjects. The majority of these children (971/1026) were, however, exposed after the 25th week [60]. Jacobsen and Mellemgaard in 1988 hypothetised an association between diagnostic radiation in pregnancy and the risk of ocular anomalies. However, the incidence of malformations (4/215) and the heterogeneity of the ocular anomalies suggest the absence of a cause and effect relationship [61]. A study conducted on 9793 pregnancies exposed to diagnostic radiation of more than 0.003 Gy in the second and third trimester have shown a significant reduction in the circumference of the head at birth. No effect, however, was observed as a result of exposure in the first trimester [62].

4. Occupational exposure

Roman et al. have studied 9208 pregnancies of 6730 radiographers (fathers and mothers), without showing an increase in the risk of malformation in the children of these subjects. A borderline increase with respect to chromosomic anomalies (excluding Down) and of cancer in childhood has been observed in the children of exposed men and women [8]. A survey carried out on personnel in the nuclear industry has analysed 27,181 pregnancies of 13,600 workers and has found a significant association with fetal death. No evidence of an increased risk of malformations was found in this cohort [9]. However, studies carried out in Sellafield, England, near to a nuclear plant, have shown no effect on stillbirths and malformations [63,64]. Various studies on the adverse effects in pregnancy following the Chernobyl incident, conducted both in the areas nearest and farthest from it have shown an increment in congenital malformations, abortions and pre-term deliveries [65–67]. An analysis of the monthly prevalence of Down's syndrome conducted by Berlin between 1980 and 1989 showed an increase in cases of trisomy 21 in 1 month (12 observed versus 2–3 expected) that came to be attributed by the authors to the ionising radiation from the Chernobyl reactor [68].

5. Radiation and low birth weight

Birth height and weight alterations have been reported among adolescents exposed in utero to the radiations of Hiroshima and Nagasaki [69]. Even Dekaban observed that delayed growth was common to all malformed children born to mothers subjected to high doses of ionising radiation in pregnancy [32]. Exposure to high doses of ionising radiation in pediatric age have been correlated to an increased risk of delivering children with a neonatal weight of less than 2500 g [70–72]. It is not clear if this effect is mediated by a vascular and structural damage [73]. Even exposure to diagnostic radiation both in the pre-conceptional period and in pregnancy have been associated with an increased risk of LBW (<2500 g). In women with idiopathic scoliosis exposed in adolescence, an increased LBW risk was found with a dose dependent effect [74,75]. However this effect could be indirect and linked to the severity of the scoliosis with a consequent compression of the uterus and of the pelvic cavity [76]. In addition, in 1984 Hamilton showed that the percentage of exposure to ionising radiation in pregnancy is greater among women that have given birth to LBW children with respect to those with a normal weight [77]. Hujoel et al. 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 radiographies can be associated with an increased risk of having LBW children (OR = 2.27 95%; confidence interval [CI], 1.11–4.66). The etiopathogenetic mechanism of this effect could be due to an alteration of the hypothalamus–hypophysis–thyroid axis of the mother with the existence of a dose threshold effect around 0.4 mGy at the level of the maternal thyroid [78]. Boice et al. have criticised this study and the possible association between maternal thyroid exposures and fetal growth, while De Santis et al., analysing the outcome of pregnancy in 224 women subjected to diagnostic examinations with thyroid exposure in the I trimester of pregnancy, have shown a slight reduction in the birth weight with a dose threshold at the level of the thyroid of and including between 0.4 and 0.8 mGy [79,80].

6. Conclusions

Ionising radiation represents a possible teratogen for the fetus but inadvertent exposure from diagnostic procedures in pregnancy, although creating a considerable state of anxiety, do not in most cases increase the natural risk of congenital anomalies. In fact, the majority of the diagnostic procedures do not involve fetal exposure >0.05 Gy, considered to be the threshold level for risk. The American College of Obstetricians and Gynecologists guidelines states that: "Exposure to X-rays during pregnancy is not an indication for therapeutic abortion." Subsequent evaluation or referral may be deemed necessary for women exposed to radiation higher than a cumulative dose of 0.05 Gy or for those worried about their baby's well-being. Counselling may be provided for patients during which they can be told the estimated dose of radiation to the fetus, calculated by a radiation physicist and made aware that the population risk of congenital birth defects is 2–3%. There should be no concern about ordering X-rays as a diagnostic tool in the case of maternal indication, if adequate diagnostic information cannot be obtained from other methods. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists have brought out guidelines weighing up all these different

factors. Together they state that "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)" [81,82].

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