DIAGNOSTIC IMAGING PROCEDURES DURING PREGNANCY: WHAT ARE THE FETAL RISKS?

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Abstract

An important facet of health care is the counsel of patients seeking a better understanding of their medical treatment. One of the most challenging scenarios is the management of female patients exposed to ionizing radiation while pregnant. It requires careful consideration of both maternal benefit and fetal risk. Given the increased frequency of diagnostic examinations involving ionizing radiation, this situation has become commonplace. This paper reviews current literature discussing the risk associated with prenatal exposure to ionizing radiation. The fetal dose received during common radiological procedures is reported in order to emphasize that these doses do not exceed threshold levels for deterministic effects. The definitive cancer risk associated with radiation exposure in utero has yet to be established. This paper will also show that physicians who deal with pregnant women are generally uninformed or misinformed of the doses and risks associated with the exams that they prescribe. This lack of information could be leading to inappropriate advice and actions with respect to patient care.

1. Introduction

In 1986, the explosion of one of the reactors at the Chernobyl nuclear facility resulted in the discharge of airborne radionuclides leading to widespread contamination detectable throughout Europe. This resulted in the exposure of many individuals to radiation doses that varied considerably. Emergency workers and reactor personnel were thought to have received upwards of 15 Gy whereas most of the general public in the surrounding regions (Belarus, Russia and Ukraine) received doses only slightly higher that that obtained from natural background radiation [1]. Nevertheless, the possibility of being exposed caused panic among the inhabitants of Western Europe, particularly among pregnant women who feared radiation-induced fetal effects. In the years that followed, a dramatic increase in the number of voluntary pregnancy terminations was observed in the regions closest to the disaster site. A similar pattern was evident in Switzerland, Norway, Denmark, Italy and Greece [2].

The Chernobyl disaster serves as an example of the pregnancy related radiophobia that endures today despite the volume of information available regarding the adverse effects of irradiation in utero. This negative perception rooted in doubt, misinformation and fear, has made women reluctant to undergo crucial medical procedures involving radiation during pregnancy. It has even deterred physicians from prescribing them when appropriate. Advances in diagnostic imaging techniques (multislice CT, PET/CT) only compound this issue as patient dose continues to escalate with increasingly detailed image acquisition techniques. These concerns are addressed here through a critical review of literature reporting the risks associated with irradiation of the fetus. This review serves as a platform to evaluate the fetal risk of diagnostic imaging procedures during pregnancy, which is the central question of this essay. This is followed by a discussion of the perceived fetal risks from such examinations. It should be noted that only the risk of ionizing radiation to the fetus will be assessed here.

2. Fetal risks of radiation

The effect of radiation on the fetus depends on the stage of development at the time of irradiation and the absorbed fetal dose. The entire period of gestation may be divided into 3 distinct periods: implantation, organogenesis and fetal development.

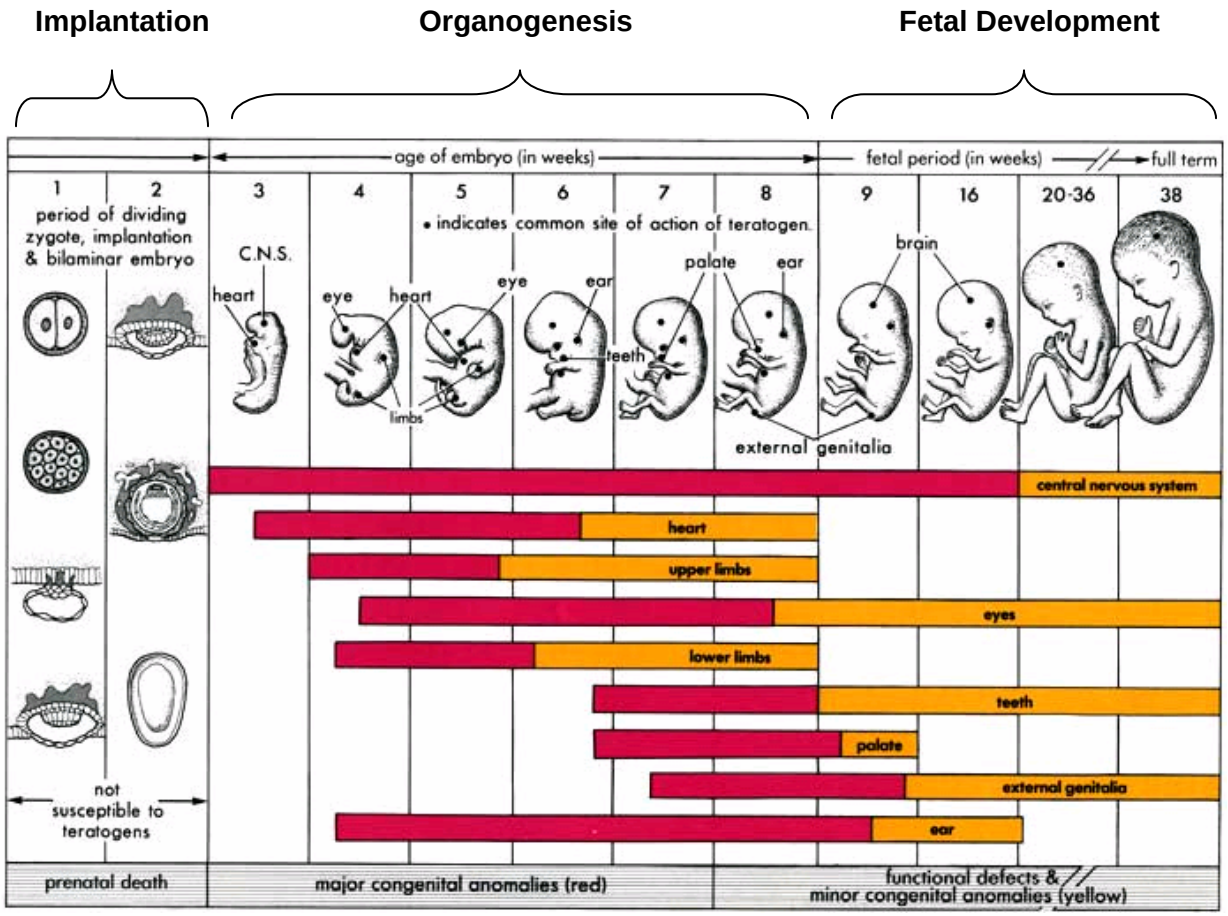

Figure 1 Stages of Prenatal Development [3].

There have been four classes of harmful effects observed as a result of irradiation in utero: intrauterine death, teratogenesis, genetic damage and oncogenesis [4]. Some of these effects are readily apparent at birth (teratogenesis) whereas others could take years to surface (genetic damage, oncogenesis). Figure 2 shows the widely accepted model relating radiation effects to the stage of pregnancy.

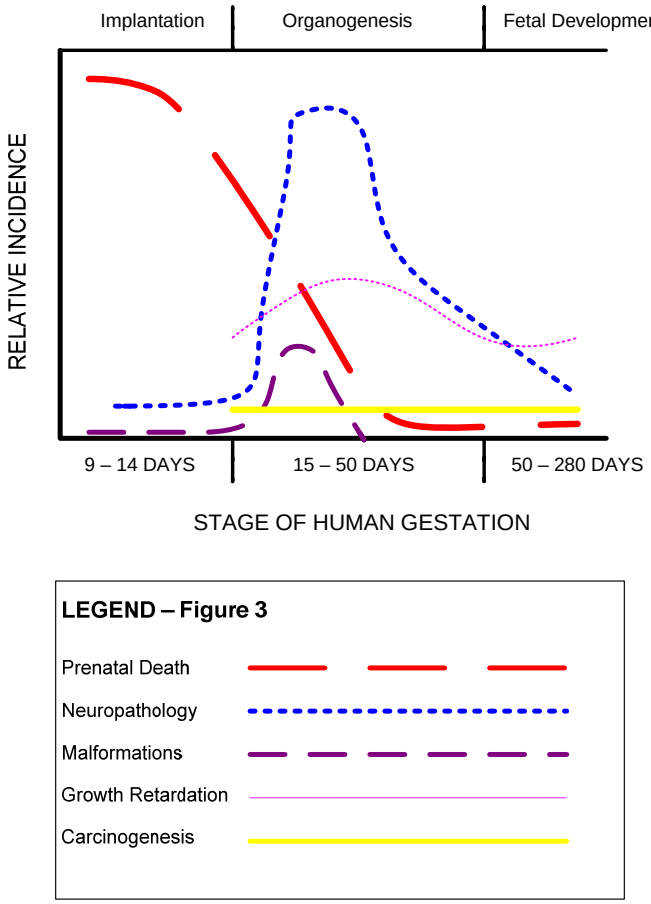

Figure 2 Incidence of adverse effects observed following prenatal exposure to ionizing radiation. These effects vary according to the gestational stage at the time of exposure. Adapted from [5].

Intrauterine death and teratogenesis constitute deterministic effects; there is a threshold value below which the probability of occurrence is not "statistically greater than that of controls" [6]. Increased dose may be correlated with increased severity of these deterministic effects.

2.1 Intrauterine death

The greatest risk associated with the irradiation of the embryo during the period of implantation is intrauterine death. Implantation is a process that occurs 1 week after conception whereby the fertilized egg becomes implanted in the lining of the uterus [7]. At this point, "the number of cells is so small that the effect of damage takes the form of a failure to implant or the undetectable death of the conceptus" [8]. In other words, this is an all or nothing effect. In the event that radiation does not prevent implantation, development and postnatal survival are typically normal. This information has been derived from animal studies because of the difficulty in recognizing this effect in humans. More specifically, in 1965, it was found that the effects x-ray irradiation during pre-implantation in mouse embryos manifested itself primarily by an increased number of dead fetuses**.** This effect was found to occur for maternal x-ray exposures

between 5-25 R [9]. It is important to also consider that the normal incidence of spontaneous abortion in human embryos is as high as 30-50% [5].

2.2 Teratogenesis

The term of teratogenesis refers to the development of non-heritable, congenital abnormalities [7]. The teratogenic nature of radiation was first uncovered in the 1920's at a point when ionizing radiation began to be prescribed for a number of medical conditions including cancer, arthritis and tuberculosis, even in pregnant women [10]. It is estimated that the children of these women had been exposed to an average dose of 2 Gy and were reported having low birth weight, stunted growth, microcephaly, mental retardation, cataracts and genital/skeletal malformations. Since then, a considerable amount of research has been focused on radiation induced malformations.

Many studies [11] have indicated that serious malformations, affecting the central nervous system in particular, are likely to occur following fetal irradiation during the period of organogenesis. As shown in Figure 2, organogenesis is the period during which cells proliferate and differentiate into specialized organs and tissues. According to the Law of Bergonié and Tribondeau [12], the radiosensitivity of cells in the body is known to be proportional to the level of mitotic activity and inversely proportional to the degree of specialization. Each tissue will therefore pass through periods of radiosensitivity according to the stage of differentiation and organization within that tissue.

Two major sources of data have been used to elucidate the teratogenic effects of radiation on the human fetus. The first are murine studies [11] used to associate certain anomalies with the gestational age at the time of exposure. The second are epidemiological studies of human exposures to high doses such as the atom bomb survivor studies. This data has been used to establish threshold values for the anomalies identified in mouse studies. These values are presented in Table 1.

Table 1 Applicable thresholds for radiation induced teratogenesis. This information was obtained via retrospective analysis of high dose accidental exposures in Hiroshima and Nagasaki. Adapted from [13].

Malformations	Estimated Threshold Dose [Gy]	Gestational Period at Risk [weeks]
Microcephaly	≥20	8 – 15 *fetal development*
Mental Retardation	0.06 – 0.31	8 – 15 *fetal development*
	0.25 – 0.28	16 – 25 *fetal development*
Reduction of IQ	0.1	8 – 15 *fetal development*
Other malformations: skeletal, genitals, retinal	≥0.20	3 – 11 *organogenesis*

Interestingly enough, in comparison to the number of studies attempting to extract information from the atom bomb victims, very few studies report on the teratogenic potential of low dose irradiation (characteristic of diagnostic imaging procedures) despite the volume of women who undergo such procedures every year. Perhaps this is because the majority of this original research [14] failed to identify a positive correlation between low doses of radiation (<0.05 Gy) and an increased incidence of teratogenesis.

2.3 Genetic effects/cancer risk

Alterations at the genetic level caused by ionizing radiation are not as obvious to detect as the gross structural malformations discussed previously. This may be part of the reason as to why the risk of childhood cancer following prenatal exposure to radiation remains a matter of great debate. What's more is that there appears to be a divide in the results obtained from major human studies on the carcinogenic potential of exposure to radiation in utero.

The first of these studies deals with children exposed to ionizing radiation during maternal diagnostic procedures. This large scale case control study is referred to as the Oxford Survey of Childhood Cancers (OSCC) and ultimately found that there is a 1.39 increased relative risk of childhood cancer (of all types) following diagnostic radiation in utero [8]. These results provided direct evidence against the idea that there is threshold dose below which no excess risk arises supporting the idea that cancer risk is a stochastic effect. The results of this study were originally reported in 1956.

In the OSCC study, all women whose children had died of cancer under 10 years of age in England and Wales between 1953 and 1955 were asked about the frequency of radiographic examinations during pregnancy among other questions. Detailed medical histories allowed for the selection of control children who had survived (same date of birth, same sex and from the same area). Many other research groups subsequently reported similar findings. The causal relationship however has been questioned for a few reasons. Firstly, it has been suggested that the "women whose children have an increased likelihood of cancer might themselves be more likely to be irradiated during pregnancy for the diagnosis of disease" [5]. Another issue is that no information about the actual fetal dose received was included in evaluating this cancer risk. By assuming 10 mGy per medical exposure, UNSCEAR has estimated that the absolute excess risk of fatal cancer is 0.05-0.06/Gy [15]. Doll [16] later reviewed the OSCC study and other similar research and re-evaluated the risk of childhood cancer following irradiation in utero: it was estimated that an exposure of about 10–20 mGy increases risk by 40%.

In contrast, individuals exposed in utero to ionizing radiation during the bombings of Hiroshima and Nagasaki did not show increased incidence of cancer [17]. It has been discussed that cases of leukemia may not have been registered during that time due to disarray in post-war Japan. Moreover, there is newly emerging data suggesting that while these individuals did not suffer from childhood cancers, there may be an increased incidence of adult cancers. Further studies are required.

2.4 Experimental considerations

For the most part, evidence supporting current risk estimates and thresholds for deleterious effects come from animal studies or epidemiological studies (atom bomb survivors, Chernobyl survivors). These studies however involve experimental conditions that limit the applicability of this data to the practical situations such as low dose exposure of the fetus during diagnostic imaging procedures.

As far as embryonic development is concerned, extrapolating data from murine studies to man raises a few questions. It is thought that these animal studies overestimate the radiation sensitivity of human subjects. The period of gestation in man lasts approximately 270 days whereas that of smaller mammals such as mice or rats lasts 16.5 and 21.5 days respectively. As such, human embryonic cells undergo a comparatively lower rate of cell division, making them less susceptible to radiation induced damage. This increased length of gestation also translates into increased time for repair processes. Moreover, in animals, heterozygotes (humans) exhibit an increased resistance to teratogenic/lethal effects over homozygotes (in-bred lines of mice used in animal studies) [18].

There are even greater limitations associated with studies based on accidental high dose irradiation of the fetus. For one, retrospective analysis of dosimetry carries a 50% margin of error [5]. The exact age of the embryo at the time of irradiation is also rarely known with any kind of precision. Finally, it has also been shown that the fetus is extremely vulnerable to environmental challenges such as increases in maternal stress. Increased levels of maternal stress have been found to induce complications such as miscarriage, pre-eclampsia, preterm parturition, low birth weight and major congenital malformations [19]. Any effects seen in the children exposed to the atom bomb in utero could be due to the stress experienced by their mother rather than the radiation exposure experienced.

3. Fetal doses associated with common diagnostic procedures

Table 2 illustrates that fetal dose during most diagnostic imaging procedures rarely exceeds 50 mGy with the exception of pelvic CT. These values however are only approximations; in some cases, doses may vary by a factor of 30 or more for the same examination. This variability comes from differences in energy, waveform, filtration, grid use, film processing and the possibility of a range of film and screen combinations [8]. Moreover, these values were calculated on the assumption that fetal dose is equal to the dose delivered to the uterus. Fluoroscopy is the most uncertain figure provided in Table 2. Time of exposure, beam positioning, mode of acquisition (conventional or pulsed) are key factors in accurately estimating fetal dose however these parameters were not typically recorded in the medical treatment facilities surveyed to obtain this information [8]. Lastly, the nature of pregnancy dictates that female anatomy change dramatically over the period of gestation. A pelvic x-ray given in the first month of pregnancy will yield a significantly different fetal dose than one taken in the 5th month of pregnancy as a result of changes in the positioning of the uterus and the thickness through which the beam must travel. More generally, the innate variability in size between patients will also cause differences in the absorbed dose to the embryo or fetus.

With advances in imaging techniques, there is a concern that multislice or helical CT used during pregnancy will put the fetus at a more significant risk of adverse effects. An extensive literature search revealed that research focused on this topic has yet to be published.

Table 2 Approximate Fetal Doses from Common Diagnostic Examinations. Adapted from [8] and [20]. * Information not available.

Exam	Average Dose [mGy]	Maximum Dose [mGy]
Conventional X-Rays		
Dental	< 0.01	*
Chest	< 0.01	< 0.01
Skull	< 0.01	< 0.01
Mammography	< 0.05	*
Pelvis	1.1	4
Abdomen	1.4	4.2
Lumbar Spine	1.7	10
Thoracic Spine	< 0.01	< 0.01
Intravenous Urogram	1.7	10
Fluoroscopy		
Barium Meal (Upper GI)	1.1	5.8
Barium Enema	6.8	24
Computed Tomography		
Head	< 0.005	< 0.005
Chest	0.06	0.96
Lumbar Spine	2.4	8.6
Abdominal	8.0	49
Pelvic	25	79

4. Perception of fetal risk from diagnostic imaging during pregnancy

Despite the body of research assessing the risks of ionizing radiation exposure in utero, many individuals remain skeptical. In fact, 2 Canadian studies have shown that the misinterpretation of these risks has been directly responsible for cases of unnecessary pregnancy termination.

The Motherisk program at The Hospital for Sick Children “provides guidance about the safety or risk to the developing fetus or infant, of maternal exposure to drugs, chemicals, diseases, radiation and environmental agents” [21]. A group of 198 pregnant Canadian woman who had been exposed to diagnostic procedures involving ionizing radiation “underwent prospective follow up”[22]. Though the primary goal of this case control study was to establish the frequency of birth defects, numerous details about the radiation exposure itself (type of exam, gestational age at time of exposure, reason for exam, use of shielding) were also recorded. These women were then matched with 198 non exposed controls according to maternal age, gravidity and parity.

The preponderance of women surveyed (77.2%) underwent diagnostic procedures during the first trimester, the average gestational age of exposure being 9.1 ± 0.7 weeks [22]. The frequency of malformation at birth was 2.6% in the exposed group and 3% in the control group. The maximum level of maternal exposure was 5.6 mGy.

The most noteworthy aspect of this study was that 11 women (5.6%) in the radiation exposed group voluntarily terminated their pregnancies whereas none of the women in the control group did. Six of these women (3%) actually admitted to terminating their pregnancy because of their diagnostic exposure to ionizing radiation. There was no other appropriate medical reason for these terminations. These women were even counseled before their abortion on the unlikelihood of fetal harm following diagnostic exposures. It may be concluded that fear of radiation will cause certain women to overestimate the harmful effects of radiation on the fetus regardless of reassuring evidence-based data.

A lack of awareness among health professionals could be exacerbating this issue. Another Canadian study reported that "physicians who care for pregnant women (family physicians, obstetricians) perceive the teratogenic risk associated with abdominal x-rays and abdominal CT to be unrealistically high during pregnancy" [24].

Four hundred family physicians and one hundred obstetricians were randomly selected using the Canadian Medical Directory and sent a questionnaire. This questionnaire included the following 3 questions:

1. *What is the fetal risk of major fetal malformation associated with an abdominal radiograph at 6 weeks gestation?*

2. *What is the fetal risk of major fetal malformation associated with an abdominal CT at 6 weeks gestation?*

3. *Would you recommend therapeutic abortion in either of these 2 cases?*

In this study, the fetal dose from an abdominal radiograph was taken to be 2.5 mGy and 30 mGy for an abdominal CT scan. These values are in agreement with those listed in Table 2. At 6 weeks gestation, the literature generally agrees that no significant increase in teratogenic events is observed in women exposed to 30 mGy of ionizing radiation. Therefore, the increased fetal risk due to abdominal x-rays or CT is 0 at 6 weeks gestation. More importantly, this level of radiation exposure would not be an indication for therapeutic abortion.

Among the respondents, 44% of family physicians and 11% of obstetricians indicated that the risk of teratogenesis following an abdominal x-ray during early pregnancy was increased by at least 5%. An even greater number of physicians (61%) and obstetricians (34%) claimed that an abdominal CT scan during early pregnancy increased the risk of teratogenesis by 5%. Certain physicians (9%) even estimated the increased risk from diagnostic procedures to be as high as 50%. The most disturbing result however was that 6% of physicians and 5% of obstetricians would recommend an abortion to women exposed to radiation from an abdominal radiograph or CT scan during early pregnancy.

This survey demonstrated that, in general, physicians dealing with pregnant women are largely misinformed about the fetal risks of imaging procedures involving ionizing radiation. This research, of course, did not address attitudes regarding any of the other potential effects from irradiation in utero such as cancer risk or intrauterine death. It would seem that consulting a physician about the risks of radiation exposure will only add to a pregnant woman's anxieties and potentially cause the unwarranted termination of pregnancy. This highlights an important aspect of the role of health care providers in the fetal risk/maternal benefit conflict of diagnostic imaging – that "while minimizing radiation exposure is always prudent, it is equally important that inadvertently exposed patients be counseled appropriately" [23].

5. Conclusion

It is estimated that 33,000 women are exposed to diagnostic radiation in early pregnancy each year in the United States [21]. It is also projected that over 50% of pregnancies in the U.S. are unplanned [24]. This means that many women are confronted with the situation of having been exposed to ionizing radiation while unknowingly pregnant. One of the most challenging demands of health care providers is to advise anxious mothers on the appropriate path forward following such exposures. It requires careful consideration of both the maternal benefits and fetal risks. Fortunately, the risks associated with most diagnostic imaging procedures are relatively low, especially when compared to spontaneous rates of perinatal death and congenital malformation (2-3% of live births). As discussed, the doses associated with most diagnostic exams involving ionizing radiation do not exceed threshold levels for teratogenic events. The absorbed fetal doses associated with more complex imaging modalities such as PET/CT however have yet to be examined in detail. Though there is an abundance of studies confirming the radiosensitivity of the fetus to high doses of radiation, analysis of the data regarding low dose exposures reveals that it is inconclusive, particularly in terms in terms of cancer risk. While it may be possible that prenatal exposure to diagnostic levels of radiation increases the risk of cancer, the actual level of increased risk has yet to be agreed on. In any case, the radiation risks associated with most diagnostic levels of radiation fail to justify the termination of pregnancy despite the opinion of many physicians and obstetricians.

6. References

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