What are the reproductive and developmental risks of in utero exposure to ionizing radiation?

1 Birth defects, mental retardation and other neurobehavioral effects, growth retardation and embryonic death are deterministic effects (threshold effects). This indicates that these effects have a NOAEL (no adverse effect level). Almost all diagnostic radiological procedures provide exposures that are below the NOAEL for these developmental effects. Diagnostic radiological studies rarely exceed 10 rad (0.1 Gy), while the threshold for congenital malformations or miscarriage is >20 rad (0.2 Gy) (Table 3.1).

2 In order for the embryo to be deleteriously affected by ionizing radiation when the mother is exposed to a diagnostic study, the embryo has to be exposed above the NOAEL to increase the risk of deterministic effects. This rarely happens when pregnant women undergo x-ray studies of the head, neck, chest or extremities.

3 During the pre-implantation and pre-organogenesis stages of embryonic development the embryo is least likely to be malformed by the effects of ionizing radiation because the cells of the very young embryo are omnipotent and can replace adjacent cells that have been deleteriously affected. This early period of development has been designated as the 'all or none' period.

4 Protraction and fractionation of exposures of ionizing radiation to the embryo decrease the magnitude of the deleterious effects of deterministic effects.

5 The increased risk of cancer following high exposures to ionizing radiation exposure to adult populations has been demonstrated in the atomic bomb survivor population. Radiation-induced carcinogenesis is assumed to be a stochastic effect (non-threshold effect) so that there is theoretically a risk at low exposures. While there is no question that
Table 3.1 Radiation exposure and risk at different gestational phases. There is no evidence that radiation exposure in the diagnostic ranges (<0.10 Gy, <10 rad) is associated with measurably increased incidence of congenital malformation, stillbirth, miscarriage, growth and mental retardation.

<table>
<thead>
<tr>
<th>Stage, gestation weeks</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st and 2nd weeks after 1st day of the last menstrual period (LMP) (prior to conception)</td>
<td>First 2 weeks after 1st day of the last menstrual period. This is a preconception radiation exposure. Mother has not yet ovulated</td>
</tr>
<tr>
<td>3rd and 4th week of gestation (first 2 weeks post conception)</td>
<td>Minimum human acute lethal dose (from animal studies) approx 0.15–0.20 Gy. Most sensitive period for the induction of embryonic death</td>
</tr>
<tr>
<td>4th to 8th week of gestation (2nd to 6th week post conception)</td>
<td>Minimum lethal dose (from animal studies) – at 18 days post conception = 0.25 Gy (25 rad); after 50 days post conception = &gt;0.50 Gy (50 rad). Embryo is predisposed to the induction of major malformations and growth retardation. Minimum dose for growth retardation: at 18–36 days = 0.20–0.50 Gy (20–50 rad) and at 36–110 days = 0.25–0.5 Gy (25–50 rad). But the induced growth retardation during this period is not as severe as during mid-gestation from similar exposures</td>
</tr>
<tr>
<td>8th to 15th week of gestation</td>
<td>Most vulnerable period for irreversible whole body growth retardation, microcephaly and severe mental retardation. Threshold for severe mental retardation is 0.35–0.50 Gy (35–50 rad). Miller indicated that the threshold was &gt;50 rad (1999). Decrease in IQ may occur at lower exposures but is difficult to document. There is probably no increased risk for mental retardation with exposures &lt;0.10 Gy</td>
</tr>
<tr>
<td>16th week of gestation to term</td>
<td>Higher exposures can produce growth retardation and decreased brain size and intellect, although the effects are not as severe as what occurs from similar exposures during mid-gestation. There is no risk for major anatomical malformations. The threshold dose for lethality (from animal studies) from 15 weeks to term is &gt;1.5 Gy (150 rad). Minimum dose for severe mental retardation: at 15 weeks to term = &gt;1.50 Gy, but decrease in IQ can occur at lower exposures</td>
</tr>
</tbody>
</table>
high exposures of ionizing radiation can increase the risk of cancer, the magnitude of the risk of cancer from embryonic exposures following diagnostic radiological procedures is very controversial. Recent publications and analyses indicate that the risk is lower for the irradiated embryo than for the irradiated child, which surprised many scientists interested in this subject.

Evaluating the risks

The responsibility for evaluating risks of environmental toxicants to the pregnant patient and her embryo frequently lies with the obstetrician. When evaluating the risks of ionizing radiation, the physician is faced with several different clinical situations, as outlined below:

1. The pregnant patient presents with clinical symptoms that need to be evaluated. What is the appropriate utilization of diagnostic radiological procedures that may expose the embryo or fetus to ionizing radiation?

A pregnant or possibly pregnant woman complaining of gastrointestinal bleeding, abdominal or back pain, or an abdominal or pelvic mass that cannot be attributed to pregnancy deserves the appropriate studies to diagnose and treat her clinical problems, including radiological studies. Furthermore, these studies should not be relegated to one portion of the menstrual cycle if she has not yet missed her period. The studies should be performed at the time they are clinically indicated whether or not the woman is in the first or second half of the menstrual cycle.

2. The patient has completed a diagnostic procedure that has exposed her uterus to ionizing radiation. Her pregnancy test was negative. She now believes she was pregnant at the time of the procedure. What is your response to this situation?

Explain that you would have proceeded with the necessary x-ray diagnostic test whether she was pregnant or not, since diagnostic studies that are indicated in the mother have to take priority over the possible risk to her embryo, because almost 100% of diagnostic studies do not increase the risks to the embryo (Table 3.1). Second, she must have been very early in her pregnancy, since her pregnancy test was negative. At this time, obtain the calculated dose to the embryo and determine her stage of pregnancy. If the dose is below 10 rad (0.1 Gy, 0.1 Sv), you can inform the mother that her risks for birth defects and miscarriage have not been increased. In fact the threshold for these effects is 20 rad (0.2 Gy) at the most sensitive stage of embryonic development (Tables 3.1 and 3.2). Of course, you are obligated to tell her that every healthy woman is at risk for the background incidence of birth defects and miscarriage, which is 3% for birth defects and 15% for miscarriage. Every woman faces these risks.
Table 3.2 Risk of 5 rad (5 rem, 50 mSv, 5000 mrem) to embryo

<table>
<thead>
<tr>
<th>Risk</th>
<th>0 rad exposure</th>
<th>Additional risk of 5 rad exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of very early pregnancy loss, before the first missed period</td>
<td>350,000/10^6 pregnancies</td>
<td>0</td>
</tr>
<tr>
<td>Risk of spontaneous abortion in known pregnant women</td>
<td>150,000/10^6 pregnancies</td>
<td>0</td>
</tr>
<tr>
<td>Risk of major congenital malformations</td>
<td>30,000/10^6</td>
<td>0</td>
</tr>
<tr>
<td>Risk of severe mental retardation</td>
<td>5000/10^6</td>
<td>0</td>
</tr>
<tr>
<td>Risk of childhood leukemia/year</td>
<td>40/10^6/year</td>
<td>&lt;2/10^6/year</td>
</tr>
<tr>
<td>Risk of early- or late-onset genetic disease</td>
<td>100,000/10^6</td>
<td>Very low risk is in next generation and is not measurable increased with small populations</td>
</tr>
<tr>
<td>Prematurity</td>
<td>(5.6% to 12.4%) 60,000/10^6 pregnancies</td>
<td>0</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>30,000/10^6 pregnancies</td>
<td>0</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>20-2000/10^6 pregnancies</td>
<td>0</td>
</tr>
<tr>
<td>Infertility</td>
<td>7% of couples</td>
<td>0</td>
</tr>
</tbody>
</table>

3 A woman delivers a baby with serious birth defects. On her first postpartum visit, she recalls that she had a diagnostic x-ray study early in her pregnancy. What is your response when she asks you whether the baby's malformation could be caused by the radiation exposure?

In most instances, the nature of the clinical malformations will rule out radiation teratogenesis. At this time, a clinical teratologist or radiation embryologist could be of assistance. On the other hand, if the exposure is below 10 rad (0.1 Gy), it would not be scientifically supportable to indicate that the radiation exposure was the cause of the malformation. As mentioned before, the threshold for malformations is 20 rad (0.20 Gy). Dose, timing, and the nature of the malformation would enter into this analysis.

In order to appropriately and more completely respond to these questions, the obstetrician should rely on the extensive amount of information that has accumulated on the effects of radiation on the embryo. In fact, there is no environmental hazard that has been more extensively studied or on which more information is available.1-9 (See Tables 3.1 and 3.2.)

Radiation risks to the embryo

There is no question that an acute exposure to ionizing radiation above 50 rad represents a significant risk to the embryo, regardless of the stage
of gestation. The threshold dose for low LET (low energy transfer) ionizing radiation that results in an increase in malformations is approximately 20 rad (0.2 Gy) (Table 3.1). Although congenital malformations are unlikely to be produced by radiation during the first 14 days of human development, there would be a substantial risk of embryonic loss if the dose is high. From approximately the 18th day to the 40th day post-conception, the embryo would be at risk for an increased frequency of anatomical malformations if the embryonic exposure is greater than 20–25 rad (0.2–0.25 Gy). Up until about the 15th week, the embryo maintains an increased susceptibility to central nervous system (CNS) effects, major CNS malformations early in gestation, and mental retardation in mid-gestation. Of course, with very high doses, in the 100s of rads, mental retardation can be produced in the latter part of gestation. While it is true that the embryo is sensitive to the deleterious effects of these mid-range exposures of ionizing radiation, the measurable effects fall off rapidly as the exposure approaches the usual exposures that the embryo receives from diagnostic radiological procedures (<10 rad; 0.1 Gy). The threshold of 20 rad at the most sensitive stage of development (20–25 days post-conception) is raised by protraction of the radiation exposure, for example, following several clinical diagnostic radiological procedures occurring over a period of days.

That is why the recommendation of most official organizations, including the National Council on Radiation Protection and Measurements (NCRP), indicates that exposures in the diagnostic range will not increase the risk of birth defects or miscarriage. The risks of radiation exposure to the human embryo when the exposure exceeds the no-effect dose (20 rad) are:

- embryonic loss
- growth retardation
- congenital malformations
- carcinogenesis (the magnitude of the risk is controversial)
- microcephaly and mental retardation
- sterility.

Because all of the above effects are threshold phenomena, except for carcinogenesis, radiation exposure below 10 rad (0.1 Gy) literally presents no measurable risk to the embryo. Even if one accepts the controversial concept that the embryo is more sensitive to the carcinogenic effects of radiation than the child, the risk at these low exposures is much smaller than the spontaneous risks. Furthermore, other studies indicate that Stewart's estimate of the risk involved is exaggerated.

Table 3.2 compares the spontaneous risks facing an embryo at conception and the risks from a low exposure of ionizing radiation (5 rad, 50 mGy, 5000 mrad).
Therefore, the hazards of exposures in the range of diagnostic roentgenology (2000–10,000 mrad; 0.02–0.1 Gy) (0.2 mGy–0.1 Gy) present an extremely low risk to the embryo, when compared with the spontaneous mishaps that can befall human embryos (Table 3.2). Approximately 30–40% of human embryos abort spontaneously (many abort before the first missed menstrual period). Human infants have a 2.75% major malformation rate at term, which rises to approximately 6–10% once all malformations become manifest. In spite of the fact that doses of 1–3 rad can produce cellular effects and the fact that diagnostic exposure during pregnancy has been associated with malignancy in childhood, the maximum theoretical risk to human embryos exposed to doses of 10 rad or less is extremely small. When the data and risks are explained to the patient, the family with a wanted pregnancy invariably continues with the pregnancy.

The difficulty that frequently arises is that the risks from diagnostic radiation are evaluated outside the context of the significant normal risks of pregnancy. Furthermore, many physicians approach the evaluation of diagnostic radiation exposure with either of two extremes: a cavalier attitude or panic. The usual procedures in clinical medicine are ignored, and an opinion based on meager information is given to the patient. Frequently, it reflects the physician’s bias about radiation effects or his or her ignorance of the field of radiation biology. We have records in our files of scores of patients who were not properly evaluated but were advised to have an abortion following radiation exposure. The following case history is a typical example.

Case report

A 27-year-old woman (gravida 3, pars 2, abortus 0) called on a Friday afternoon because she was 8 weeks pregnant and was scheduled for a therapeutic abortion on Monday morning. Her obstetrician and a pediatric genetic counselor had advised her to have a therapeutic abortion because at the time of conception she had had several x-ray examinations of the abdomen, and they were concerned that the embryo would be malformed. Dosimetry had not been performed, and an evaluation had not been initiated. It took about 10 minutes on the telephone to determine that she became pregnant after the diagnostic radiation studies had been completed and that her two previous boys had developmental problems (hemangioma and pyloric stenosis). She canceled the abortion, and she delivered a normal full-term girl. She was adequately warned that we could not guarantee the outcome of the pregnancy – that there are 27.5 serious malformations per 1000 births as a minimum. She had another determining factor in that she had a serious problem with varicose veins and planned
a tubal ligation after either the abortion or the delivery. This case history illustrates the inadequate amount of data that was collected by the physicians before counseling the patient. There was an added feature in this case. The paternal family was religiously devout and the consideration of an abortion was causing much dissension within the family.

**Evaluating the patient**

Case histories similar to this are transmitted to our laboratory frequently. In most instances, the dose to the embryo is <10 rad (0.1 Gy) and frequently is <1 rad (0.01 Gy). Our experience has taught us that there are many variables involved in radiation exposure to a pregnant or potentially pregnant woman. Therefore, there is no routine or predetermined advice that can be given in this situation. However, if the physician takes a systematic approach to the evaluation of the possible effects of radiation exposure, he/she can help the patient make an informed decision about continuing the pregnancy. This systematic evaluation can begin only when the following information has been obtained:

- stage of pregnancy at the time of exposure
- menstrual history
- previous pregnancy history
- family history of congenital malformations
- other potentially harmful environmental factors during the pregnancy
- ages of the mother and father
- type of radiation study, dates and number of studies performed
- calculation of the embryonic exposure by a medical physicist or competent radiologist
- status of the pregnancy: wanted or unwanted.

An evaluation should be made of the information, with both patient and counselor arriving at a decision. The physician should place a summary of the following information in the medical record. It should state that the patient has been informed that every pregnancy has a significant risk of problems and that the decision to continue the pregnancy does not mean that the counselor is guaranteeing the outcome of the pregnancy. The use of amniocentesis and ultrasound to evaluate the fetus is an individual decision that would have to be made in each pregnancy.

**The carcinogenic effects of radiation**

The carcinogenic risk of in utero radiation is an important topic that cannot be addressed adequately in this publication. Alice Stewart published the results of her case-control study indicating the diagnostic radiation from pelvimetry increased the risk of childhood leukemia by 50% (Table 3.2).
Protocol 3

Table 3.3 Follow-up of adults with solid cancers in Hiroshima and Nagasaki who were in utero at the time of detonation of the A-bombs in 1945 (Preston et al. 2008)

<table>
<thead>
<tr>
<th>Dose in Sv (rads)</th>
<th>No. of patients</th>
<th>No. of cancers</th>
<th>Person-years</th>
<th>% with solid cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.005 (&lt;0.5)</td>
<td>1,547</td>
<td>54</td>
<td>49,326</td>
<td>3.5</td>
</tr>
<tr>
<td>0.005-&lt;0.1 (0.5-10)</td>
<td>435</td>
<td>16</td>
<td>14,005</td>
<td>3.7</td>
</tr>
<tr>
<td>0.1-&lt;0.2 (10-&lt;20)</td>
<td>168</td>
<td>6</td>
<td>5,041</td>
<td>3.6</td>
</tr>
<tr>
<td>0.2-&lt;0.5 (20-&lt;50)</td>
<td>172</td>
<td>8</td>
<td>5,496</td>
<td>4.6</td>
</tr>
<tr>
<td>0.5-&lt;1.0 (50-&lt;100)</td>
<td>92</td>
<td>7</td>
<td>2,771</td>
<td>7.6</td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>48</td>
<td>3</td>
<td>1,404</td>
<td>6.2</td>
</tr>
<tr>
<td>Total</td>
<td>2,452</td>
<td>94</td>
<td>49,466</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Table 3.4 Follow-up of adults with solid cancers in Hiroshima and Nagasaki who were in children at the time of detonation of the A-bombs in 1945 (Preston et al. 2008)

<table>
<thead>
<tr>
<th>Dose in Sv (rads)</th>
<th>No. of patients</th>
<th>No. of cancers</th>
<th>Person-years</th>
<th>% of cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.005 (&lt;0.5)</td>
<td>8,549</td>
<td>318</td>
<td>247,744</td>
<td>3.7</td>
</tr>
<tr>
<td>0.005-&lt;0.1 (0.5-&lt;10)</td>
<td>4,528</td>
<td>173</td>
<td>134,621</td>
<td>3.8</td>
</tr>
<tr>
<td>0.1-&lt;0.2 (10-&lt;20)</td>
<td>853</td>
<td>38</td>
<td>25,802</td>
<td>4.4</td>
</tr>
<tr>
<td>0.2-&lt;0.5 (20-&lt;50)</td>
<td>859</td>
<td>51</td>
<td>25,722</td>
<td>5.9</td>
</tr>
<tr>
<td>0.5-&lt;1.0 (50-&lt;100)</td>
<td>325</td>
<td>21</td>
<td>9,522</td>
<td>6.5</td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>274</td>
<td>48</td>
<td>7,620</td>
<td>17.5</td>
</tr>
<tr>
<td>Total</td>
<td>15,388</td>
<td>649</td>
<td>451,031</td>
<td>4.2</td>
</tr>
</tbody>
</table>

That would change the annual risk of childhood leukemia from 4 cases per 100,000 children to 6 cases per 100,000 children in the population of exposed fetuses. This has been a very controversial subject. A recent publication by Preston et al. presented data from the in utero population of the A-bomb survivors which indicated that the embryo was less vulnerable to the oncogenic effects of ionizing radiation than the child. It appears that the embryo is much less vulnerable to the oncogenic effects of radiation than previous investigators have believed. Patients can be told that the fetal risks are extremely small, so small that we cannot measure the risks because such a large exposed population would be necessary (Tables 3.3 and 3.4).

Diagnostic or therapeutic abdominal radiation in women of reproductive age

In women of reproductive age, it is important for the patient and physician to be aware of the pregnancy status of the patient before performing any
type of x-ray procedure in which the ovaries or uterus will be exposed. If the embryonic exposure will be 10 rad or less, the radiation risks to the embryo are very small when compared with the spontaneous risks (Table 3.2). Even if the exposure is 10 rad, this exposure is far from the threshold or no-effect dose of 20 rad. The patient will accept this information if it is offered as part of the preparation for the x-ray studies at a time when both the physician and patient are aware that a pregnancy exists or may exist. The pregnancy status of the patient should be determined and noted.

Because the risks of 10 rad fetal irradiation are so small, the immediate medical care of the mother should take priority over the risks of diagnostic radiation exposure to the embryo. X-ray studies that are essential for optimal medical care of the mother and evaluation of medical problems that need to be diagnosed or treated should not be postponed. Elective procedures such as employment examinations or follow-up examinations, once a diagnosis has been made, need not be performed on a pregnant woman even though the risk to the embryo is very small. If other procedures (e.g., MRI or ultrasound) can provide adequate information without exposing the embryo to ionizing radiation, then of course they should be used. Naturally, there is a period when the patient is pregnant but the pregnancy test is negative and the menstrual history is of little use. However, the risks of 10 rad or less are extremely small during this period of gestation (all-or-none period, first 2 weeks). The patient will benefit from knowing that the diagnostic study was indicated and should be performed in spite of the fact that she may be pregnant.

**Scheduling the examination**

In those instances in which elective x-ray studies need to be scheduled, it is difficult to know whether to schedule them during the first half of the menstrual cycle just before ovulation or during the second half of the menstrual cycle, when most women will not be pregnant. The genetic risk of diagnostic exposures to the oocyte or the embryopathic effects on the preimplanted embryo is extremely small, and there are no data available to compare the relative risk of 10 rad to the oocyte or the preimplanted embryo. If the diagnostic study is performed in the first 14 days of the menstrual cycle, should the patient be advised to defer conception for several months, based on the assumption that the deleterious effect of radiation to the ovaries decreases with increasing time between radiation exposure and a subsequent ovulation? The physician is in a quandary because he may be warning the patient about a very-low-risk phenomenon. On the other hand, avoiding conception for several months is not an insurmountable hardship. This potential genetic hazard is quite
speculative for man, as indicated by the report by the NCRP and BEIR committee report dealing with preconception radiation.\textsuperscript{3,8}

It is not known whether the interval between irradiation of the gonads and conception has a marked effect on the frequency of genetic changes in human offspring, as has been demonstrated in the female mouse. Nevertheless, it may be advised for patients receiving high doses to the gonads (>25 rad, 0.25Gy) to wait for several months after such exposures before conceiving additional offspring.\textsuperscript{3}

Because the patients exposed during diagnostic radiological procedures absorb considerably less than 25 rad, the recommendations made here may be unnecessary, but it involves no hardship to the patient or physician. Because both the NCRP and ICRP have previously recommended that elective radiological examinations of the abdomen and pelvis be performed during the first part of the menstrual cycle (10-day rule, 14-day cycle) to protect the zygote from possible but largely conjectural hazards, the recommendation to avoid fertilization of recently irradiated ova perhaps merits equal attention.

**Importance of determining pregnancy status of patient**

If exposures <10 rad do not measurably affect the exposed embryos, and it is recommended that diagnostic procedures should be performed at any time during the menstrual cycle, if necessary, for the medical care of the patient, why expend energy to determine the pregnancy status of the patient?

There are several reasons why the physician and patient should share the burden of determining the pregnancy status before performing an x-ray or nuclear medicine procedure that exposes the uterus:

1. If the physician is forced to include the possibility of pregnancy in the differential diagnosis, a small percentage of diagnostic studies may no longer be considered necessary. Early symptoms of pregnancy may mimic certain types of gastrointestinal or genitourinary disease.

2. If the physician and patient are both aware that pregnancy is a possibility and the procedure is still performed, it is much less likely that the patient will be upset if she subsequently proves to be pregnant.

3. The careful evaluation of the reproductive status of women undergoing diagnostic procedures will prevent many unnecessary lawsuits. Many lawsuits are stimulated by the factor of surprise. In some instances, the jury is not concerned with cause and effect but with the fact that something was not done properly by the physicians.\textsuperscript{17,18} In this day and age, failure to communicate adequately can be interpreted as less-than-adequate medical care. Both these factors are eliminated if the patient's pregnancy status has been evaluated properly and the situation discussed adequately with the patient. Physicians are going to have to learn that practicing good technical medicine may not be good
enough in a litigation-prone society. Even more important, the patient will have more confidence if the decision to continue the pregnancy is made before the medical x-ray procedure is performed, because the necessity of performing the procedure would have been determined with the knowledge that the patient was pregnant.

In every consultation dealing with the exposure of the embryo to diagnostic studies involving ionizing radiation (x-ray, CT scans, use of radionuclides) in which her reproductive risks or developmental risks for her fetus have not been increased by the radiation exposure, the patient should be informed that every healthy woman with a negative personal and genetic family reproductive history has background reproductive risks which are 3% for birth defects and 15% for miscarriage. We cannot change these background risks, which every woman faces.

References


