

## Counseling patients exposed to ionizing radiation during pregnancy

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### SYNOPSIS

*Health physicists and knowledgeable clinicians have the responsibility to counsel women of reproductive age about the reproductive risks of ionizing radiation exposure before conception or during pregnancy. It is important to realize that lay individuals have many misconceptions about the reproductive risks of ionizing radiation. Many patients who have already had or will undergo some type of radiological test are apprehensive about the reproductive and developmental risks of diagnostic radiological procedures. Epidemiological studies and animal studies indicate that high exposures of ionizing radiation can cause miscarriage, congenital malformations, growth retardation, stillbirth, and cancer. With the exception of cancer, there are threshold exposures for those outcomes, with exposures below certain radiation doses not increasing the reproductive or developmental risks. The threshold exposure for birth defects at the most sensitive stage of development is 0.2 Gy, and the threshold for growth retardation and miscarriage is even higher. However, embryonic loss can occur from low exposures during the preimplantation and presomite stages of development (“the all or none period”). This is a stage when the embryo is more likely to die than survive malformed. The most sensitive period for the induction of mental retardation is from the 8th week to the 15th week of gestation. The threshold for deterministic effects increases after early organogenesis and also as the exposure is protracted, e.g., with radionuclides or multiple radiological procedures. Awareness that the threshold dose for developmental effects increases as the fetus develops complicates counseling because we do not have definitive data on threshold exposures at all stages of gestation. Ionizing radiation exposures prior to pregnancy represent a very low risk for the increased incidence of genetic disease in the offspring of the parents who have had radiation exposures to the ovary or testes. Counseling patients requires knowledge of embryology, genetics, radiation teratology, and the principles of teratology in order for the counselor to provide sympathetic, accurate, scholarly advice.*

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Health physicists and knowledgeable clinicians have the responsibility to counsel women of reproductive age about the reproductive risks of ionizing radiation exposure that occurs either before conception or during pregnancy. Medical personnel need to realize that lay individuals have many misconceptions about the reproductive risks of ionizing radiation. Further, many patients are apprehensive about the reproductive and developmental risks of diagnostic radiological procedures. Counseling patients requires knowledge of embryology, genetics, radiation teratology, and the principles

of teratology in order for the counselor to provide sympathetic, accurate, scholarly advice. This paper will help inform medical personnel about the real risks to the embryo from ionizing radiation, provide suggestions on counseling patients, recommend procedures to follow when evaluating a patient, and offer guidance on when to schedule elective X-ray studies that are needed.

## RISKS TO THE EMBRYO FROM IONIZING RADIATION

There is no question that an acute exposure to ionizing radiation above 0.5 Gy represents a significant risk to the embryo, regardless of the stage of gestation (1–8). The threshold dose for low linear energy transfer ionizing radiation that results in an increase in major anatomical congenital malformations is approximately 0.2 Gy. Although congenital malformations are unlikely to be produced by radiation during the first 14 days of human development, there would be a risk of embryonic loss if the dose were high. From approximately the 18th day to the 40th day postconception, the embryo is at risk for an increased frequency of anatomical congenital malformations if the embryonic exposure is greater than 0.2 Gy. Studies in mice have reported rib variation or other skeletal variations below 0.2 Gy, but these studies cannot be translated to human risks. The embryo maintains an increased susceptibility to central nervous system (CNS) effects, e.g., major CNS malformations early in gestation and mental retardation and microcephaly in midgestation. Of course, with very high doses, e.g., an exposure to a few Gy in the latter part of gestation, there can be a decrease in intelligence. While it is true that the embryo is sensitive to the deleterious effects of these mid-range exposures of ionizing radiation, the measurable effects decrease as the exposure approaches the usual exposures that the embryo receives from diagnostic radiology procedures, which are predominantly less than 0.05 Gy. In fact, many studies indicate that the threshold for most embryonic radiation effects is in the 0.2-Gy range, and that this threshold for deterministic effects is raised by protraction of the radiation exposure (9, 10). For example, following several clinical diagnostic radiological procedures occurring over a period of days, the exposure may be greater than 0.05 Gy (8). In this case, the counselor can more readily reassure the patient that the reproductive risks are not increased because the exposure was protracted. The newer techniques using CT scans have the potential for exposing the embryo or fetus to doses above 0.05 Gy, although there has been a major effort by the radiologists and manufacturers to reduce the exposure from CT scans (11–14).

That is why the recommendation of most official organizations, including the National Council on Radiation Protection and Measurements (NCRP), indicate that exposures of 0.05 Gy or less will not increase the risk of birth defects or miscarriage (3, 7, 8). However, when the exposure exceeds the threshold dose, the risks of radiation exposure to the human embryo include embryonic loss, growth retardation, congenital malformations, microcephaly and mental retardation, infertility, and carcinogenesis (with the magnitude of the oncogenic risk to the fetus being controversial) (15–18).

Except for carcinogenesis, all of those effects are threshold phenomena. Therefore, radiation exposure below 0.05 Gy represents no measurable increased deterministic risks 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 is, the risk at these low exposures is much smaller than the spontaneous risks (Table 1). Furthermore, other studies (16–18) indicate that the estimate of the risk of radiation-induced leukemogenesis made by Stewart et al. (15) is exaggerated.

Table 1 presents the spontaneous risks facing an embryo at conception and the additional risks that would come from a low exposure of ionizing radiation (0.05 Gy). The hazards of exposures in the range of diagnostic radiology (0.2 mGy–0.05 Gy) represent an extremely low risk to the embryo, when compared with the spontaneous mishaps that can befall human embryos. Approximately 15% of clinically recognized pregnancies abort spontaneously, but many more pregnancies do not survive even to the first missed menstrual period. Human infants have a 3% major malformation rate at term, which rises to approximately 6% once all minor and major malformations are recognized. In spite of the fact that doses of <0.05 Gy can produce cellular effects and the fact that diagnostic exposures during pregnancy may have a small risk of malignancy in the child, the maximum theoretical risk to human embryos exposed to doses of 0.05 Gy or less is extremely small. When the risks are explained to the patient, the family with a wanted pregnancy invariably continues with the pregnancy. It is of interest that most mothers who have been exposed to ionizing radiation during their pregnancy are concerned about all congenital malformations. However, if they are concerned about cancer, it is primarily a concern about childhood leukemia. The risk of leukemia following fetal exposures from diagnostic radiological studies is a small fraction of the spontaneous leukemia risk, even when the risk published by Wakeford and Little (18) is utilized, and the risks estimated by other investigators (16–17) are lower than those of Wakeford and Little.

The difficulty that frequently arises is that the risks from diagnostic radiation are evaluated out-

**TABLE 1. Spontaneous risks facing an embryo at conception and the additional risk that would come from a low exposure of ionizing radiation (0.05 Gy)<sup>a</sup>**

| Type of risk  | Spontaneous risks facing an embryo at conception (0 rad exposure) | Additional risk from a 0.05-Gy exposure  |
|---|---|--|
| Risk of very early pregnancy loss, before the first missed period | 350 000/10 <sup>6</sup> pregnancies                               | 0  |
| Risk of spontaneous abortion in known-pregnant women              | 150 000/10 <sup>6</sup> pregnancies                               | 0  |
| Risk of major congenital malformations                            | 30 000/10 <sup>6</sup>  | 0  |
| Risk of severe mental retardation                                 | 5 000/10 <sup>6</sup>   | 0  |
| Risk of childhood leukemia/year                                   | 40/10 <sup>6</sup> /year  | <?1–3/10 <sup>6</sup> /year  |
| Risk of early- or late-onset genetic disease                      | 110 000/10 <sup>6</sup>   | Very low risk; the risk is in the next generation and is not measurably increased with small populations |
| Prematurity   | 40 000/10 <sup>6</sup> pregnancies                                | 0  |
| Growth retardation  | 30 000/10 <sup>6</sup> pregnancies                                | 0  |
| Stillbirth  | 20-2 000/10 <sup>6</sup> pregnancies                              | 0  |
| Infertility   | 7% of couples   | 0  |

<sup>a</sup> Modified from Brent (4) and Brent (5).

side 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. In our consultation records—obtained from the Internet, telephone contacts, and correspondence over the past five decades—we have records of patients who, following radiation exposure from a very low-exposure diagnostic radiological procedure, were not properly evaluated, but were advised to have an abortion.

### COUNSELING PATIENTS ABOUT REPRODUCTIVE AND DEVELOPMENT RISKS

The responsibility for evaluating risks of environmental toxicants to the pregnant patient and her embryo may be that of the family physician, obstetrician, radiologist, or health physicist. When evaluating the risks of ionizing radiation, the counselor can be faced with various clinical situations. Four types of encounters are briefly described in the following paragraphs.

The first situation involves a pregnant or possibly pregnant patient who 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 or pain or an abdominal or pelvic mass that cannot be attributed to pregnancy deserves the appropriate studies—including radiological ones—to diagnose and treat her clinical problems. The studies should be performed in a timely and appropriate manner in order to minimize the exposure and maximize the goal of making the correct diagnosis. 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. Furthermore, these studies should not be relegated to one portion of the menstrual cycle. The first half of the menstrual cycle is a time when the woman is not pregnant. Conception occurs midway during the menstrual cycle. The second half of the menstrual cycle is when the embryo has not yet initiated differentiation and is less sensitive to the teratogenic effects of radiation, although it is more sensitive to the lethal effects of radiation. Animal studies indicate that the threshold for lethality during this very early stage of development is above 0.1 Gy, but one cannot apply these results directly to the human embryo.

In another example of this first situation, if a radiologist has been asked to perform an elective radiological diagnostic study for employment or follow-

up that is not an emergency, then the approach should be different. The radiological study can be postponed until the beginning of the next menstrual period. If the patient and physician are certain the patient is not pregnant or has a negative pregnancy test and has not had intercourse for a lengthy period, then the elective examination can be performed at that time. The situation is complicated when the woman has irregular menstrual cycles. In that situation, the diagnostic study can be performed after the next menstrual cycle begins. However, even in that situation, a pregnancy test should be performed.

A second clinical situation that the counselor may face is that the patient has completed a diagnostic procedure that has exposed her uterus to ionizing radiation, such as a procedure needed to rule out a gastrointestinal disease because of abdominal pain. The examination revealed that the patient had a duodenal ulcer. The procedure was necessary, but the patient now believes she was pregnant at the time of the procedure. If you are the counselor, what is the proper 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 no diagnostic studies increase the developmental risks to the embryo. At this time, obtain the calculated dose to the embryo and determine the woman's stage of pregnancy. If the dose is below 0.05 Gy (that is, 0.05 Sv, or 5 rads), 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 0.2 Gy or greater, thus the 0.05-Gy exposure is far from the threshold exposure.

A third clinical situation that the counselor may face is that a woman delivers a baby with a serious birth defect. On her first postpartum visit, the woman 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 malformation will rule out radiation teratogenesis. Radiation-induced malformations have a confined group of malformations that identifies the radiation teratogenic syndrome, and many malformations have never been reported even following intrauterine radiation exposures that are known to produce congenital malformations. In this situation a clinical teratologist or radiation embryologist could be of assistance. On the other hand, if the exposure is below 0.05 Gy or even 0.10 Gy, it would not be scientifically supportable to indicate that the radiation exposure was the cause of the malformations. As mentioned before, the threshold for major malfor-

mations is 0.20 Gy. Dose, timing, and the nature of the malformation would enter into this analysis. A genetic disease is diagnosed with approximately 15% to 25% of malformed children. If that is the case, the malformations could not have been caused by an intrauterine exposure to ionizing radiation.

For a counselor the most difficult situation of the four possible ones mentioned here is when external radiation therapy or high exposures of radionuclides have been utilized in a pregnant woman or in a woman who became pregnant during the therapy. While this is a serious situation, there are instances when the exposure to the embryo is low. Low exposures to the embryo may occur when radiation therapy is directed toward the head, neck, upper chest, or the extremities. Administered radionuclides are special problems because each radionuclide has a different half-life, metabolism, and excretion. Therefore, each patient needs the expert evaluation of a competent medical or health physicist to determine what the fetal exposure will be or has been, depending on the nature of the radiation exposure. Rarely, the patient may have received the course of therapy or be in the middle of the therapy when the pregnancy is discovered. That can be very upsetting to both the patient and physician. The exposure to the fetus can be calculated and appropriate counseling can be delivered. When the radiation therapist knows that the patient is pregnant, then the situation is much more advantageous, because the fetal exposure can be estimated before the onset of therapy.

In order to appropriately and more completely respond to all these situations, the counselor 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 (2-8).

### Case report

The following consultation occurred by telephone. Unfortunately, it is not an uncommon occurrence among the thousands of consultations that the author has performed. A 27-year-old woman (gravid 3, para 2, abortus 0) called on a Friday afternoon because she was eight weeks pregnant and was scheduled for a therapeutic abortion on Monday morning. The paternal family did not accept abortion as an option, which caused much dissension within the family. 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 the obstetrician and the counselor

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, by taking a reproductive history, to determine that she became pregnant after the diagnostic radiation studies had been completed, and that her two boys had developmental problems (hemangioma and pyloric stenosis). The radiology department was contacted, and they had already calculated a fetal exposure that was  $< 0.01$  Gy. The advice that was given to the patient over the telephone was that the outcome of the pregnancy still had the background risk for reproductive and developmental risks: 30 major malformations per 1 000 births as a minimum, and 15% for miscarriage. She canceled the abortion, and later delivered a normal, full-term girl. This case history illustrates the inadequate amount of data that was collected by the physicians before counseling the patient.

## EVALUATING THE PATIENT

Case histories similar to the case just discussed have been frequently referred to our laboratory at the Thomas Jefferson University or to the duPont Hospital for Children. In most instances the dose to the embryo is  $< 0.05$  Gy, and frequently it is  $< 0.01$  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 and the health physicist take a systematic approach to the evaluation of the possible effects of radiation exposure, they can help the patient make an informed decision about the pregnancy. This systematic evaluation can begin only when the following 10 essential pieces of information have been obtained: (1) stage of pregnancy at the time of exposure; (2) menstrual, medical, and reproductive history; (3) date of conception (sometimes the patient knows when she conceived); (4) previous pregnancy history; (5) family history of congenital malformations and reproductive problems; (6) other potentially harmful environmental factors that occurred during the pregnancy; (7) ages of the mother and father; (8) types, dates, and number of any radiation studies performed; (9) calculation of the embryonic exposure by a medical or health physicist or a radiologist who is familiar with this type of evaluation; and (10) status of the pregnancy (wanted or unwanted).

The information contained in the evaluation should be communicated to the patient so that the family can arrive at a decision. The physician should also place a summary in the medical record stating that the patient has been informed that

every pregnancy begins with a background risk of problems and that the decision to continue the pregnancy does not mean that the counselor is guaranteeing the outcome of the pregnancy. In each pregnancy, the individuals involved will need to make a decision about using amniocentesis or ultrasound to evaluate the fetus.

## 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 0.05 Gy or less, the radiation risks to the embryo are small when compared with the spontaneous risks (Table 1). Even if the exposure is 0.10 Gy, this exposure is below the threshold or no-effect dose of 0.2 Gy for congenital malformations. It is important to discuss the risks of radiation 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 risk of 0.05 Gy is 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. Once a diagnosis has been made, elective procedures, such as employment examinations or follow-up examinations, need not be performed on a pregnant woman, even though the risk to the embryo is very small. If other procedures (e.g., ultrasound) can provide adequate information without exposing the embryo to ionizing radiation, they of course 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 0.05 Gy or less are extremely small during this period of gestation (the "all or none period," that is, the first two weeks post conception) (1) (Table 1).

## Scheduling elective X-ray studies

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 (before ovulation) or during the second half of the cycle (when most women will not

be pregnant, but could be pregnant). Both the genetic risks of diagnostic exposures to the oocyte and the embryopathic effects on the preimplanted embryo are extremely small, especially at low exposures. Also, there are no data available to compare the risk of 0.05 Gy to the oocyte (first half of the menstrual cycle) to the risk of 0.05 Gy to the preimplanted embryo (second half of the menstrual cycle, following fertilization). 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 or she is warning the patient about a very low risk. On the other hand, avoiding conception for several months is not an insurmountable hardship, as indicated in the following quote from the Biological Effects of Ionizing Radiation (BEIR) committee report (2): "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 (> 0.25 Gy) to wait for several months after such exposures before conceiving additional offspring."

Because the patients exposed during diagnostic radiologic procedures absorb considerably less than 0.25 Gy, the recommendations to perform all diagnostic elective radiological studies in the first half of the menstrual cycle may be unnecessary.

### The importance of determining the pregnancy status of the patient

Why expend energy to determine the pregnancy status of the patient if exposures < 0.05 Gy do not measurably affect the exposed embryos, and if it is recommended that diagnostic procedures be performed at any time during the menstrual cycle if necessary for the medical care of the patient?

There are various reasons why the physician and the patient should share the burden of determining the pregnancy status before performing an X-ray or nuclear medicine procedure that exposes the embryo. One key reason is that if the physician includes the possibility of pregnancy in the differential diagnosis, a small percentage of diagnostic studies may no longer be necessary. Early symptoms of pregnancy may mimic certain types of gastrointestinal or genitourinary disease. Another essential reason is that if the physician and the patient are both aware that pregnancy is a possibility, the physician can ex-

plain the necessity of the procedure and answer questions about the risks. It is more likely that the patient will be reassured, having discussed these issues, if she subsequently proves to be pregnant.

Carefully evaluating the reproductive status of women undergoing diagnostic procedures will prevent many unnecessary allegations of malpractice (19). Surprise and anxiety stimulate many lawsuits. In some instances, the jury that considers the lawsuit is not concerned with cause and effect but with the fact that something was not done properly by the physician (20, 21). In this day and age, failure to communicate adequately can be interpreted as less-than-adequate medical care. These factors are eliminated if the patient's pregnancy status has been evaluated properly and the situation has been discussed with the patient. 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 will have been determined with the knowledge that the patient was pregnant.

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### SINOPSIS

#### El asesoramiento de pacientes expuestas a radiaciones ionizantes durante el embarazo

*Los físicos que trabajan en el ámbito de la salud y los clínicos que tienen conocimientos de radiología tienen la responsabilidad de asesorar a las mujeres de edad fecunda acerca de los riesgos reproductivos de la exposición a radiaciones ionizantes antes de la concepción o durante el embarazo. Es importante entender que las personas legas albergan muchas nociones equivocadas acerca de los riesgos asociados con ese tipo de radiaciones. Muchas pacientes que ya se han sometido o serán sometidas a algún tipo de prueba radiológica les temen a los correspondientes riesgos reproductivos y a las posibles consecuencias de estas pruebas diagnósticas para el desarrollo fetal. Según estudios epidemiológicos y con animales, un alto grado de exposición a radiaciones ionizantes puede provocar un aborto, anomalías congénitas, retraso del crecimiento, muerte fetal y cáncer. A salvedad de esto último, hay umbrales de exposición establecidos en relación con cada uno de estos problemas, y una exposición por debajo de ciertas dosis de radiación no se asocia con ninguna elevación del riesgo de sufrir daños reproductivos o del desarrollo. El umbral de exposición asociado con anomalías congénitas durante la etapa del desarrollo de mayor vulnerabilidad es de 0,2 Gy, y el umbral en el caso del retraso del crecimiento y del aborto espontáneo es aun mayor. No obstante, la pérdida de un embrión puede ocurrir incluso a dosis bajas durante las fases del desarrollo que preceden a la implantación o en la fase presomática (el llamado período de "todo o nada"). Esta es la etapa en que un embrión corre un mayor riesgo de morir que de sobrevivir con malformaciones. El período de mayor vulnerabilidad para la inducción de retraso mental dura desde la octava hasta la decimoquinta semana de gestación. El umbral para la aparición de efectos deterministas aumenta después de la embriogénesis temprana y a medida que la exposición se prolonga, sea, por ejemplo, por el uso de radio-*

núclidos o durante una serie de procedimientos radiológicos. El saber que la dosis umbral que afecta al desarrollo aumenta a medida que crece el feto complica el asesoramiento porque no tenemos datos contundentes acerca de los umbrales de exposición para todas las etapas de la gestación. Las exposiciones a radiaciones ionizantes antes del embarazo acarrearán un riesgo muy pequeño de que aumente la frecuencia de enfermedades genéticas en hijos/hijas de madres que han recibido radiaciones en los ovarios o de padres que las han recibido en los testículos. Para ase-

sorar a las pacientes hay que tener conocimientos de embriología, genética y teratología de la radiación y saber los principios de teratología, a fin de poder aconsejar con empatía, exactitud y dominio académico de la materia.

**Palabras clave:** embarazo, resultado del embarazo, radiación ionizante, anomalías, factores de riesgo, teratógenos, aconsejar.

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