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September 3, 1992

Donna-Beth Howe, Ph.D.
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Washington, DC 20555

Dear Donna-Beth:

I have calculated the radiation dose to the fetus of the 46-yr-old female who was approximately 8 weeks old at the time of the administration of 10 millicuries of ^{131}I sodium iodide to the mother. I used two different sets of assumptions. If none of the activity was taken up by viable "thyroid" tissue and the biological half-time is 6 h, the fetus received an absorbed dose of 2.5 rad from the 10 millicuries. We had some measurements made on a patient without a thyroid after an administration of 100 millicuries of ^{131}I that indicated about 99% of the activity left the body with a biological half-time of 14 h and 0.8% was taken up by viable thyroid tissue and left the body with a biological half-time of 2880 h. Using these assumptions, I estimate the fetus would receive an absorbed dose of 4.1 rad. In neither of these two situations would the fetal thyroid take up enough ^{131}I to be a significant factor in the risk.

Obviously I do not know whether either of these two estimates is the true dose, but I believe they probably bracket the dose if the stage of pregnancy is reasonably accurate. Therefore, I believe the absorbed dose to the fetus would probably not exceed 4 rads.

As to the risk from this radiation dose, I am attaching a paper by Dr. Robert L. Brent who is regarded as an expert in this field. You will notice that in his section on radiation risks to the embryo he states that radiation exposure below 5 rem presents no measurable risk to the embryo. He also references the NCRP Report No. 54, 1977, (see his list of references) which makes a similar statement.

I hope this provides you with the information you need. Please call if you have questions.

Sincerely,

Evelyn E. Watson, Program Director
Radiation Internal Dose Information Center

Enclosure

Ionizing radiation

By Robert L. Brent, MD, PhD

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

1. The patient may be pregnant and present with clinical symptoms that need to be evaluated. We must ask: What is the appropriate utilization of diagnostic procedures that may expose the embryo or fetus to ionizing radiation?

A potentially pregnant woman with bleeding, pain, or a mass that cannot be attributed to pregnancy deserves the appropriate diagnostic studies to diagnose and treat her clinical problems, including x-ray studies. Furthermore, these studies should not be relegated to one portion of the menstrual cycle; they 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. She now believes she is pregnant. What is your response?

Dr. Brent is chairman, department of pediatrics, and director, Stein Research Center, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pa.

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. At this time, obtain the calculated dose to the embryo and determine her stage of pregnancy. If the dose is below 5 rads, you can support her decision to continue the pregnancy.

3. A woman delivers a baby with a serious birth defect. 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 malformation 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 was below 5 rads, it would not be scientifically supportable to indict the radiation exposure as the cause of the malformation. Dose, timing, and 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 about which more information is available.[1,2]

Radiation risks to the embryo

There is no question that exposure to ionizing radiation above 50 rads presents a significant risk to the embryo, regardless of the stage of gestation.[3] Although congenital malformations are unlikely to be produced by 50 rads during the first 10 to 14 days of human development, there would be a substantial risk of embryonic loss. From approximately the 18th day to the 40th day, the embryo would be at risk for major, severe anatomical malformations. Up until about the 15th week, the embryo maintains a 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 hundreds 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 to ionizing radiation, the measurable effects fall off rapidly as the exposure approaches the usual exposures that the embryo receives from diagnostic radiologic procedures (<5 rem). In fact, many studies indicate that the

threshold for most radiation effects on the embryo is in the 15- to 20-rem range and that this threshold is raised by protraction of the radiation exposure as in clinical diagnostic procedures.[3]

That is why the recommendation of most official organizations, including the National Council on Radiation Protection and Measurements (NCRP), indicates that exposures of 5 rads or less present such a low risk to the embryo that these pregnancies should not be interrupted because of the risk of radiation exposure.[2,4] The major risks of radiation exposure in humans include the following:

- embryonic loss;
- growth retardation;
- congenital malformations;
- carcinogenesis[1,5] (this is controversial);
- microcephaly and mental retardation; and
- sterility.

Because all of the above effects are threshold phenomena, except for carcinogenesis, radiation exposure below 5 rem presents no measurable risk to the embryo. Even if one accepts the controversial concept of Stewart and coworkers that the embryo is more sensitive to the carcinogenic effects of radiation,[5] the risk at these low exposures is much smaller than the spontaneous risks. Furthermore, other studies indicate that this estimate of the risk involved is grossly exaggerated.[6] It has been shown that even if one uses the Stewart team's estimate of the risk, the overall spontaneous risk is 1,721 times greater than the radiation risk. If one uses the in utero carcinogenic risk from the Atomic Bomb Casualty Commission in Japan, the ratio is 114,280 to 1.[7]

Therefore, the hazards of exposures of diagnostic roentgenology (20–50,000 mrads) present an extremely low risk to the embryo, when compared with the spontaneous mishaps that can befall human embryos. About 30% to 50% of human embryos abort spontaneously. Human infants have a 2.75% major malformation rate at term, which rises to 6% to 10% once all malformations and genetic diseases become manifest.

Despite the fact that doses of 1 to 3 rads can produce cellular effects and that diagnostic exposure during pregnancy has been associated with malignancy in childhood, the maximum theoretical risk to human embryos exposed to doses of 5 rads or less is extremely small. In my experience, 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 ignorance of the field of radiation biology. We have in our files records of scores of patients who were not properly evaluated but who were advised to have an abortion after radiation exposure. The following case history is a typical example.

Case report

A 27-year-old woman (gravida 3, para 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 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 minor problems (hemangioma and pyloric stenosis). We canceled the abortion, and she was delivered of a normal full-term girl. She was adequately warned that we could not guarantee the pregnancy outcome—that there are 27.5 serious malformations per 1,000 births as a minimum. She had another determining factor: 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 data collected by the physicians before counseling the patient. There was an added feature in this case. The paternal family was Roman Catholic, 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 below 5 rads, and frequently it is below 1 rad. Our experience has taught us that there are many variables involved in exposure to radiation of a pregnant or potentially pregnant woman. Therefore, there is no routine response that can be given across the board in this situation. However, if physicians take a systematic approach to the evaluation of the possible effects of radiation exposure, they can help patients make informed decisions about continuing or aborting their pregnancies. 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;
- history of congenital malformations;
- other potentially harmful environmental factors during the pregnancy;
- ages of the mother and father;
- type, dates, and number of radiation studies performed;
- calculation of the embryonic exposure by a medical physicist or competent radiologist; and
- status of the pregnancy (wanted or unwanted).

> Diagnostic exposures in the range of 20 to 50,000 mrads present an extremely low risk to the human embryo, when compared with the spontaneous mishaps that befall it.

An evaluation should be made of the information, with both patient and counselor arriving at a decision. The physician should place in the medical record a summary of this information, as well as documentation that the patient has been informed that any 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.

Abdominal radiation in women of reproductive age

In women of childbearing 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 5 rads or less, the radiation risks to the embryo are miniscule when compared with the spontaneous risks. 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 5-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, such as 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

5 rads or less are extremely small during this period of gestation (the all-or-none period, or first 2 weeks).[3] 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 are extremely small, and there are no data with which to compare the relative risk of 5 rads 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 or she 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 in the human, as indicated by the report

X-ray studies essential for care of the mother and evaluation of medical problems that need to be diagnosed or treated should not be postponed.

by the NCRP dealing with preconception radiation:

"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 rads) to wait for several months after such exposures before conceiving additional offspring."[4]

Because the patients exposed during diagnostic radiologic procedures absorb considerably less than 25 rads, the recommendations made here may be unnecessary, but they involve no hardship to the patient or physician. Because both the NCRP and ICRP have previously recommended that elective radiologic 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

If exposures up to 5 rads do not measurably affect the exposed embryos, and it is recommended to perform diagnostic procedures 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 an x-ray or nuclear medicine procedure that will expose the uterus is performed:

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

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and won on the basis of the double jeopardy of the defendant.[8] In some instances, the jury is not concerned with cause and effect but with the fact that something was not done properly by the physician.[8] 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 a pregnancy is made before a 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. □

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ADDITIONAL OPERATIONAL EVENTS FOR SEPTEMBER 9, 1992

ITEM #1 - MAYAGUEZ MEDICAL CENTER (Mayaguez, PR) - Unintended radiation dose from sodium iodide to a fetus

On September 1, 1992, RII was notified by the licensee of an unintended radiation exposure to a fetus resulting from the administration of 10 mCi I-131 sodium iodide to the mother. In 1985 the patient was treated for papillary Ca of the thyroid with surgery and 129 mCi I-131 therapy. On February 24, 1992, a routine follow-up whole body scan was performed with 10 mCi I-131. The patient did not know she was pregnant (her LMP was December, 1991, but here cycle was irregular). On May 28, 1992, the Nuclear Medicine Dept. was notified by an ob/gyn physician that the patient was pregnant. The RSO was notified during the first week of June and a meeting was held with the patient present to discuss the possible consequences. The dose to the feuts was considered to be ~10-15 rad whole body and >700 rad to the thyroid. The patient would not consider termination of the pregnancy as an option. An ultrasound was done during the week of August 17 at which time it was determined that the woman was ~34 weeks pregnant. That would indicate that she was 8 - 9 weeks pregnant at the time of administration of the I-131.

NMSS forwarded the case to ORISE for dose calculation. Assuming the fetus was 8 weeks old at the time of the administration and two different sets of assumptions for uptake and biological half-time, ORISE estimated the fetus to have received an absorbed dose of 2.5 to 4.1 rad whole body, with no uptake in the fetal thyroid (not yet developed). This is significantly lower than that estimated by the licensee and presents no measurable risk to the embryo/fetus.

The patient's expected date of delivery is around October 1, 1992. Her obstetrician will notify the Nuclear Medicine Dept. at the time of delivery so that the infant can be followed up for any problems.

ITEM #2 - BETHESDA NATIONAL NAVAL MEDICAL CENTER (Bethesda, MD) - Loss of material

On August 28, 1992, the licensee notified the NRC Operations Center and RII of a loss of 3.6 mCi I-131 MIBG (meta-iodabenzylguanidine). On August 27, 1992, the junior Radiation Safety technician received and signed for the material. He attempted to deliver to the user in the hot lab. As no-one was around, he left the material in the passageway outside the nuclear pharmacy where it was unattended in an unrestricted area. The licensee did have a procedure in place that the user was to sign for any package and it was not to be left there. However, it appears that the junior tech was improperly trained as he had on more than one occasion left the package without delivering it directly to the user. As the pharmacist was out that day, he did not notice the package was missing until he needed it on August 28. At that time he notified the RSO and a complete search of the Nuclear Medicine facility, receiving and the hospital was conducted. It was concluded that the housekeeping staff must have mistakenly thought the package was trash and disposed of it accordingly. The RSO did check the dumpster but the package was not found and it is now assumed to have been taken to the landfill in Montgomery County.

FOLLOW-UP OPERATIONAL EVENTS - NOVEMBER 2, 1992

ITEM #3 - ST. CLARES RIVERSIDE MEDICAL CENTER - (Denville, NJ) - Brachytherapy Misadministration and Possible Worker Overexposure

On October 2, 1992, the licensee notified RI that a patient undergoing brachytherapy treatment was found with the ribbons containing the Ir-192 seeds taped onto the patients abdomen instead of where they had been implanted.

ACTION: IMAB provide status report at next meeting.

STATUS:

A special announced inspection was conducted Oct. 5-9 to review the circumstances surrounding the misadministration. The INEL risk assessment team and Dr. Rathbun accompanied the inpection. Two Ir-192 ribbons, each containing six seeds with a total activity of 48.25 mCi were implanted into 2 catheters inserted in the patient's common bile duct. The patient was to receive 1500 to 2000 rad to an obstructive tumour at the junction of the bile ducts over a 20 to 23 hr period. On the morning of October 2, a routine x-ray of the patient's abdomen was taken to viualize the seeds to verify implant location. The radiologist who read the x-ray film did not see any evidence of the Ir-192 seed in the x-ray film and reported his findings to the oncologist. The dressing on the wound had been changed by a night nurse at ~4:00 a.m. at which time she coiled the ribbons which had dislodged ard taped to the patient's abdomen. The oncologist indicated that she left verbal orders with the day shift charge nurse "not to change the dressing". An earlier changing of the dressing may have caused the iridium ribbons to become dislodged. The oncologist removed the ribbons from the patient's skin where they had been earlier taped by a nurse who was providing care to the patient. The patient and his physician were notified of the incident. No adverse effects to the patient are expected and there was no evidence of skin erythema on October 5.

The LPN who discovered the dislodged sources coiled the ribbons around her hand and taped them to the patient's abdomen. The licensee estimated that patient received 1145 rad to the tumour site over 13.16 hr. The patient's skin exposure over various areas ranged from 1,032 rad to 172 rad. Preliminary dose estimates to the employee calculated by the licensee were ~52,800 rad to a 1 x 2 mm area of her finger. The licensee is recalculating the dose based on regulatory requirements and guidelines and has not yet submitted the results to the NRC. Therefore, the dose to the LPN's hand is considered an unresolved matter pending completion of dose calculations.

Three apparent violations were identified during the inspection: 1) RSO did not provide radiation safety oversight; 2) Failure to provide adequate training; and 3) Failure of the authorized user to prepare a written directive. The licensee had submitted a QM program, prepared by a consultant, which the RSO was unfamiliar with. There was no training provided to the staff on the licensee's QMP. Furthermore, the RSO, a diagnostic radiologist, had no knowledge of the licensee's procedures governing brachytherapy operations including the QM program. There is no Radiation Oncology Department at the facility. However, an authorized user named on the license performs infrequent (about one treatment every two years) brachytherapy implant procedures at this location. Authorized users are not hospital

employees and generally contract their services to the licensee. The RSO did not provide oversight of brachytherapy operations nor was the RSO knowledgeable about approved procedures or regulatory requirements in this area.

An open enforcement conference is schedule in RI for November 5, 1992.

ITEM #5 - MAYAGUEZ MEDICAL CENTER (Mayaguez, PR) - Unintentional Dose to Fetus

On September 1, 1992, the licensee notified RII that a fetus received an unintentional radiation dose when 10 mCi I-131 was administered to the mother on February 24, 1992.

ACTION: IMAB provide status report at next meeting.

STATUS:

The licensee notified RII on October 17, 1992 that the mother delivered a baby girl on October 7, 1992. Height, weight and head circumference were all within normal limits as was thyroid function (T3, T4, TSH). There were some unexplained erthematous lesions over her body with obvious abrasions on both wrists. However, these did not appear to be related to radiation exposure and in fact, are healing well.