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The Effects of Maternal Exposure to Radiation on the Fetus

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Radiation exposure during pregnancy should be avoided for several reasons, including teratogenesis, carcinogenesis, and mutagenesis. However, exposure during pregnancy is often unavoidable because procedures involving radiation are vital for identifying significant maternal and/or fetal complications or trauma. Moreover, women may be exposed to radiation before they are aware of their pregnancy. Radiation exposure through diagnostic and therapeutic procedures is a common concern for pregnant women. Most of their anxiety originates from the general view that any radiation exposure is harmful and can result in adverse effects on the fetus. This anxiety can lead to an unnecessary termination of the pregnancy. Therefore, pregnant women should always be informed of the benefits of the procedures and the risks of radiation exposure to the fetus, and allow them to make an informed decision regarding termination of the pregnancy after radiation exposure. The present report focuses on issues related to radiation exposure of pregnant women and fetuses, specifically in Japanese medical institutions.

Key words: radiation exposure, medical exposure, pregnant women, fetus.

1. Radiodiagnosis

The principal diagnostic radiation exposure during pregnancy occurs during X-ray pelvimetry for detection of cephalopelvic disproportion, chest radiography for preoperative evaluation, and diagnostic X-ray imaging for significant and urgent maternal or fetal medical problems or trauma. The Annals of the International Commission on Radiological Protection (ICRP Publication 84, 2000) reported the following regarding radiodiagnosis: "almost always, if a diagnostic radiology examination is medically indicated, the risk to the mother of not doing the procedure is greater than is the risk of potential harm to the fetus. Radiation doses resulting from most diagnostic procedures present no substantial risk of causing fetal death, malformation, or impairment of mental development. If the fetus is in the direct beam, the procedure often can, and should be, tailored to reduce fetal dose"[1]. The ICRP estimates of the probability of bearing healthy children as a function of radiation dose are shown in Table 1[2].

Table 2 shows typical fetal doses for some common routine examinations in the United Kingdom[3]. The examinations can be tailored to reduce these doses if the pregnancy is recognized prior to exposure. For fetal doses less than 100 mGy, there is no medical justification for terminating a

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Table 1. Probability of bearing healthy children as a function of radiation dose[6)]

Absorbed dose to conceptus, mGy, above natural background	Probability that child will have no malformation, %	Probability that child will not develop cancer (age 0—19), % [1)]
0	97	99.7
0.5	97	99.7
1.0	97	99.7
2.5	97	99.7
5	97	99.7
10	97	99.6
50	97	99.4
100	(close to 97) [2)]	99.1

[1)] Rounded values. Radiation risk for fatal cancer conservatively assumed to be 0.6% per 100 mGy fetal doses, corresponding to about l/17,000 per mGy, and a linear dose-response relationship. Many epidemiological studies suggest that the risk may be lower than that assumed here. Background risk of childhood cancer calculated from NCI-SEER (1994)[33)].
[2)] Although the exact risk in humans is uncertain, animal data suggest that malformations due to radiation are not likely at doses less than 10–200 mGy. Above this malformations would only be observed if exposure were between the 3rd and 25th weeks of gestation. The risk of malformation is low at 10–200 mGy but will increase with increasing dose. Decreased IQ and possible retardation are only detectable when fetal doses exceed 100 mGy during the 8th to 25th weeks of gestation.

Table 2. Approximate fetal doses from common diagnostic procedures in the United Kingdom[31)]

Examination	Fetal doses (mGy) Mean	Maximum
Conventional X-ray		
Abdomen	1.4	4.2
Chest	<0.01	<0.01
Intravenous uro-gram; lumbar spine	1.7	10
Pelvis	1.1	4
Skull	<0.01	<0.01
Thoracic spine	<0.01	<0.01
Fluoroscopic examinations		
Barium meal (UGI)	1.1	5.8
Barium enema	6.8	24
Computed tomography		
Head	<0.005	<0.005
Chest	0.06	1.0
Abdomen	8.0	49
Pelvis	25	80

pregnancy because of radiation exposure. A conservative estimate of the lifetime risk of radiogenic induction of childhood cancer or leukaemia at 100 mGy is about 1 in 170[4)]. Without radiation exposure (apart from natural background) the lifetime risk of contracting cancer is about 1 in 3; for fatal cancer the risk is about l in 5. As pointed out earlier, malformations due to radiation probably do not occur at fetal doses less than l0–200 mGy. The guideline edited by the Japan Society of Obstetrics and Gynecology provides an explanation of the effect of radiation exposure on pregnant women[5)].

A large number of epidemiological studies have been performed to assess the possible effects of prenatal radiation on the incidence of malignant disease. Lowe discusses the oncogenicity of prenatal radiation exposure in his review[6)]. In addition, the ICRP (publication 84) reported that throughout most of pregnancy, the carcinogenic effect of radiation exposure to the embryo/fetus is about the same as that for children[7)].

1.1. X-ray pelvimetry

X-ray pelvimetry was used widely to supplement diagnosis in the early detection of cephalopelvic disportion[8)]. Pelvimetry can be performed by conventional radiography, CT, or MRI[9)]. Although MRI has the theoretical advantage of not using ionizing radiation, the fetal dose from a limited CT pelvimetry study (with a single axial slice through the femoral heads to measure interspinous diameter) is less than 0.001 Gy. Even assuming the worst case scenario that the dose is 0.001 Gy and that such a dose is as dangerous as radiation exposure earlier in pregnancy, the risk of fatal childhood cancer would increase from 1 in 2,000 (baseline risk) to 1.02 in 2,000. Therefore, if pelvimetry is considered clinically appropriate, it is reasonable to perform pelvimetry by CT rather than by MRI. In Japan, X-ray pelvimetry for diagnosis is becoming decrease considering mother and child radiation exposure.

1.2. Chest radiography for preoperative evaluation

The radiation dose from chest radiography is estimated to be less than 0.005 mGy, suggesting this procedure carries a low risk to the fetus. It has been reported that the risk of pulmonary embolism increases 7-fold in the puerperal period after cesarean section[10)]; therefore, chest radiography should be performed before the caesarean section. Chest radiography is essential in cases of pregnancy-induced hypertension where there are multiple births or a possibility of pulmonary edema, or premature delivery requiring treatment with ritodrine hydrochloride and magnesium sulfate.

1.3. Computed tomography

X-ray computed tomography (CT) is a medical imaging method employing tomography created by computer processing[11)]. Digital geometry processing is used to generate a three-dimensional image of the inside of an object from a large series of two-dimensional X-ray images taken around a single axis of rotation[12)]. A CT imaging system produces cross-sectional images or "slices" of areas of the

Table 3. Radioactive pharmaceutical listed in the Radiopharmaceutical Standard of Japan

No.	Nuclide	Radiopharmaceutical	Caution
1	^{18}F	Fluorodeoxyglucose injection	
2	^{51}Cr	Injection	
3	^{59}Fe	Cpd ferric citrate [1)]	
4	^{57}Co	Cyanocobalamin [1)]	
5	^{58}Co	Cyanocobalamin [1)]	
6	^{67}Ga	Citrate injection	
7	^{81m}Kr	Generator	
8	^{89}Sr	Strontium chloride injection	
9	^{90}Y	Yttrium chloride	Contraindication
10	^{99m}Tc	Exametazime injection	
11		Ethyl cysteinate dimer injection	
12		Sodium pertechnetate injection	
13		Sodium pertechnetate injection generator	
14		Galactosyl human serum albumin diethylenetriamine- pentaacetic acid injection	
15		Diethylenetriamine pentaacetic acid injection	
16		Dimercaptosuccinic acid injection	
17		Preparative solution for injection	
18		Tin colloid injection	
19		Preparative solution for injection	
20		Aggregated albumin injection	
21		Human serum albumin injection	
22		Tetrofosmin injection	
23		Preparative solution for injection	
24		HAS diethylenetriamine pentaacetic acid injection	
25		Hydroxymethylene injection	
26		Preparative solution for injection	
27		Methyltryptophan injection	
28		Pyrophosphate injection	
29		Phytic acid injection	
30		Methoxy-2-isobutylisonitrile injection	
31		Methylene diphosphonate injection	
32		Mercaptoacetylglycylglycylglycine	
33	^{111}In	Indium oxine	
34		Chloride injection	
35		Zevalin	Contraindication
36		Anti-human myosin mouse monoclonal antibody (Fab)–diethylenetriaminepenta-acetic acid [1)]	
37		Diethylenetriamine pentaacetic acid	
38	^{123}I	Iomazenil	
39		Iofetamine hydrochloride	
40		Benzyl guanidine	
41		Sodium iodide capsules	
42		Sodium iodohippurate injection [1)]	
43		15-(4-iodophenyl)-3(R,S)-methylpentadecanoic acid	
44	^{131}I	3-Iodo-benzyl guanidine	
45		Sodium iodide solution [1)]	
46		Sodium iodide capsules	
47		Iodinated human serum albumin injection	
48		Sodium iodohippurate injection	Contraindication
49		Norcholesterol iodomethyl	Contraindication
50	^{133}Xe	Xenon gas	
51		Xenon injection[1)]	
52	^{201}Tl	Thallium chloride injection	

[1)] Only prescription in the Radiopharmaceutical Standard of Japan. Not for distribution.

body, like the slices in a loaf of bread. These cross-sectional images are used for a variety of diagnostic and therapeutic purposes[13)]. A recent report from the Radiological Society of North America Scientific Assembly and Annual Meeting (2007) found an increase of 121% over 10 years in the use of imaging tests requiring ionizing radiation (plain film, CT, and nuclear medicine studies) during pregnancy, with CT use increasing by 25% per year[14)]. As shown in Table 2, the fetal absorbed doses from CT vary considerably depending on the examination[6)]. Although Japan has more CT machines than many other countries, the actual number of CT examinations performed on pregnant women has not been investigated. In a study comparing the estimated fetal absorbed dose at different gestational phases, the mean fetal absorbed dose from helical chest CT varied from 0.003 to 0.02 mGy in the first trimester and 0.05 to 0.13 mGy in the third trimester[15)].

1.4. Magnetic resonance imaging

Magnetic resonance imaging (MRI) can provides three-dimensional images of the brain and other soft tissues. Scanned patients and machine operators can therefore be exposed to very high-strength static magnetic fields (SMF). The biological response after exposure to high-strength SMF

Table 4. Radioactive Compounds That Require Temporary Cessation of Breastfeeding[24)]

Compound	Recommended Time for Cessation of Breastfeeding
^{64}Cu	Radioactivity in milk present at 50 h
^{67}Ga	Radioactivity in milk present for 2 wk
^{111}In	Very small amount present at 20 h
^{123}I	Radioactivity in milk present up to 36 h
^{125}I	Radioactivity in milk present for 12 d
^{131}I	Radioactivity in milk present 2–14 d, depending on study
^{131}I	If used for treatment of thyroid cancer, high radioactivity may prolong exposure to infant
Radioactive sodium	Radioactivity in milk present 96 h
^{99m}Tc macroaggregates, $^{99m}TcO_4$	Radioactivity in milk present 15 h to 3 d

Consult nuclear medicine physician before performing diagnostic study so that radionuclide that has the shortest excretion time in breast milk can be used. Before study, the mother should pump her breast and store enough milk in the freezer for feeding the infant; after study,the mother should pump her breast to maintain milk production but discard all milk pumped for the required time that radioactivity is present in milk. Milk samples can be screened by radiology departments for radioactivity before resumption of nursing.

has recently been widely discussed from the perspective of possible health benefits as well as potential adverse effects. Guidelines for patient exposure to MRI are given by the U.S. Food and Drug Administration, International Electrotechnical Commission, National Radiological Protection Board, and International Commission on Non-Ionizing Radiation Protection[16-19)]. A white paper[18)] advises pregnant health care practitioners that they are permitted to work in and around the MRI environment throughout all stages of pregnancy. MRI is useful for assessing the functionality and condition of the placenta and amniotic fluid[20)]. However, the International Electrotechnical Commission (IEC 60601-2-33)[17)] advises caution in imaging pregnant women, and states that there is no conclusive evidence to establish safety. Current recommendations in the UK say that it is advisable not to scan in the first trimester[21)]. In addition, DeWilde et al. recommends performing risk assessment for pregnant staff working in MRI, and advises that there is a clear need for further research into the effects of MRI in pregnancy to provider clear, authoritative advice[20)].

2. Nuclear Medicine

The radioactive pharmaceuticals listed in the Radiopharmaceutical Standard of Japan are shown in Table 3[22)]. The package insert of each radiopharmaceutical comments that it is desirable to not administer radiopharmaceuticals to pregnant women, women who may become pregnant, or nursing mothers, but to administer only when it is judged that the diagnostic utility exceeds the risks of radiation exposure. In the list of 52 radiopharmaceuticals, 4 are specifically contraindicated: yttrium chloride, Zevalin, sodium iodohippurate injection, and norcholesterol iodomethyl. There are some reports of medical administration of radiopharmaceuticals to pregnant women in Western countries[9)]; however, there are no equivalent studies of pregnant women in Japan.

Many previous studies have reported that radioactive pharmaceuticals can migrate to breast milk, which is generally proportional to the drug concentration in the mother's plasma. The mother should discontinue breast-feeding temporarily during treatment, but can resume nursing when the concentration of drug in the breast milk has decreased. However, the use of isotopes with long half-lives (e.g. ^{131}I) and prolonged administration for therapeutic reasons might preclude breast-feeding[23)]. The recommended times for cessation of breast-feeding for several radioactive pharmaceuticals are shown in Table 4[24)]. Mothers should be given the opportunity to make an informed decision as to whether to continue or temporarily abstain from breast-feeding after receiving contrast agents or radioactive pharmaceuticals. The most important requirements for counseling nursing mothers about the risks of the drugs during breast-feeding are compassion and sensitivity to the emotionality of the counseling situation, and avoiding the unnecessary promotion of anxiety[25)].

Annals of ICRP regarding nuclear medicine reported as follows; "when a nuclear medicine examination is proposed for a pregnant woman, care has to be taken to ascertain that the examination is indeed indicated for a medical condition that requires prompt therapy. For these diagnostic examinations, the risk to the mother of not performing the examination is greater than the radiation risk to the fetus. The possibility of reducing the administered activity should be considered. Since radionuclides in maternal tissues contribute to fetal dose, maternal hydration and frequent voiding can reduce the fetal dose after the administration of a number of radiopharmaceuticals. Radioiodine easily crosses the placenta and therapeutic doses can pose significant problems for the fetus, particularly permanent hypothyroidism. Careful estimation of fetal doses is not usually necessary after diagnostic nuclear medicine studies involving ^{99m}Tc radiopharmaceuticals. If there has been inadvertent administration of other radiopharmaceuticals (such as radioiodine or gallium), more attention should be given to calculation of the fetal dose and explanation of potential risks"[26)].

3. Radiotherapy

Maternal cancer is a rare non-specific complication of pregnancy, and as yet, there are no clear estimates of the maternal cancer rate in the Japanese population. Smith et al. reported an overall occurrence rate for cancer during

pregnancy of 0.94 cases per 1,000 births. In addition, they found the most frequent cancers in pregnancy to be breast, thyroid, and cervical cancers[27].

Annals of ICRP regarding radiotherapy reported as follows: "in pregnant patients, cancers that are remote from the pelvis usually can be treated with radiotherapy. This however requires careful planning. Cancers in the pelvis cannot be adequately treated by radiotherapy during pregnancy without severe or lethal consequences for the fetus. Since fetal doses in radiotherapy can be high, it is important to ascertain whether a female patient is pregnant prior to radiotherapy. Teletherapy to non-pelvic fields during pregnancy can be done, but it requires careful estimation of fetal dose and may require additional shielding. Regardless of protective measures, radiotherapy involving the pelvis of a pregnant female almost always results in severe consequences for the fetus, most likely fetal death. After radiotherapy involving a pregnant patient, careful records of the technique and fetal dose estimation should be maintained. Since there may be fetal consequences, careful counseling and follow-up is recommended" [28].

In 2011, the Japan Society of Obstetrics and Gynecology and Japan Association of Obstetricians and Gynecologists published guidelines for obstetrical practice in Japan[5]. They reported that because the radiation dose for diagnostic procedures is generally less than 50 mGy, there should be little affect on the fetus, except under special circumstances due to errors in radiotherapy or accidents at nuclear power plants.

4. Radiation exposure in perinatal care

The influence of radioactivity on the fetus generally depends on the radiation exposure dose and the age of gestation at exposure. Brent et al. has reviewed the effects of embryonic and fetal exposure to radiation, microwaves, and ultrasound[29]. It was suggested that the risks of fetal anomalies, growth restriction, or abortions are not increased with radiation exposure of less than 5 rad, a level above the range of exposure for diagnostic procedures. The fetal dose differs with the radiologic procedure, but in commonly used diagnostics, the radiation dose does not reach 5 rad, the dose considered to be dangerous to the fetus[30, 31]. The estimated fetal exposure from some common radiologic procedures is shown in Table 2 [31].

Regarding the effects of radiation exposure on the fetus, the guidelines for obstetrical practice in Japan 2011[5], edited by Japan Society of Obstetrics and Gynecology and Japan Association of Obstetricians and Gynecologists, posed the question "How should women anxious about the adverse effects of radiation exposure during pregnancy be treated?" To answer, they propose:

1. Before counseling, determine the dose of the exposure and the stage of pregnancy (GW) when the exposure occurred using the last menstrual period, measurement of the conceptus by ultrasonography, or the date of a positive pregnancy test result.
2. Explain that the risk of a fetal anomaly does not increase in cases with exposure within 10 days after conception.
3. Explain that an embryo at stages ranging from 11 days after conception until 10 GW is vulnerable but does not have an increased risk of malformation at doses of < 50 mGy.
4. Explain that the central nervous system of a fetus at 10–27 GW may be affected unfavorably at doses of ≥ 100 mGy.
5. Explain that a dose of 10 mGy is associated with a subtle, but negligible, increase in the risk of childhood cancer.

5. Conclusions

The health of both the mother and fetus should be considered in cases of medical radiation exposure during pregnancy. Radiation exposure throughout pregnancy should be avoided; therefore, it is very important that such medical treatments should be performed in pregnant women only when the benefits exceed the risks. Termination of pregnancy at fetal doses of less than 100 mGy is not justified based on the radiation risk. At higher fetal doses, informed decisions should be made based upon individual circumstances [32]. When X-ray examinations are performed on pregnant women, the precise gestational age should be known and the patient should be provided with clear explanations of the risks to alleviate fear and secure safe perinatal care. To promote an understanding of radiation exposure in the medical field, research is needed on the exposure of pregnant women and fetuses in Japanese medical institutions. In addition, many Japanese residents have been placed at risk by the accidents at the Fukushima nuclear power stations in March 11. These incidents will require long-term follow-up of the health of the residents of Fukushima, especially infants and fetuses, as well as residents of other regions affected by the radioactive material.

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