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CONTENTS

Guideline for Justification of Diagnostic Radiology

JMAJ 44(11): 469–472, 2001

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Abstract: Availability of medical imaging equipment in our country is the highest in the world and far beyond the world average, but at the same time, the radiation exposure of the population is unfortunately far beyond the international standard. A guideline for diagnosis with minimal radiation to the patients and with minimal examination cost and in minimal time interval was needed. Because of the differences of imaging equipments and differences of personal experiences among the institutions, it is not possible to make a guideline to satisfy every one involved in the imaging diagnosis, but it is possible to make a proper diagnosis in reasonable time reducing the radiation dose to the patients after reviewing each diagnostic modality and their combination. The most fundamental point for the diagnostician is to reconsider the efficacy of the examination in the viewpoint of the patients.

Key words: Diagnostic imaging; Efficient combination; Guideline

Introduction

Fortunately, availability of medical imaging equipment in Japan is the highest in the world and far beyond the world average, but at the same time, the radiation exposure of the population is unfortunately far beyond the international standard. We have to admit that a large portion of the exposure is abuse and could be cut down. Now is the time to create a practical guideline for diagnostic radiology, not only in the view of radiation reduction, but also in the view of the new medical insurance system, similar to the Diagnosis Related Group (DRG) system in the United States of America, which already started partially in Japan.

In the medically advanced countries such as European countries and the United States of America, guidelines for imaging diagnosis using medical radiation have been made many years ago and clinically applied,[1,2] but in Japan such a guideline for the efficient usage of imaging examinations associated with radiation has not been made.

The guideline should not be fixed permanently and should be modified according to the swift changes of the medical system. Steps to perform various imaging modalities for diagnosis

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are directly influenced by changes of imaging equipments. They are also influenced by other factors of the institutions such as number of staff and social status surrounding the institution.

As a part of the research group of the Ministry of Health and Welfare: *A study of optimization of the usage of medical radiation and protection, Report of the study for optimization and clinical judgment of radiation medicine* was finalized in 1998.[3] This paper is a part of the summary of the report.

Characteristics of the Imaging Modalities

1. Plain radiography

Plain Radiograph can be obtained in any medical institution and is the most un-expensive imaging test. The International Commission on Radiological Protection (ICRP) had analyzed radiation from plain radiography,[4] and it has been concluded that no serious dose would be emitted unless extremely overused. Information obtained from plain radiography is very valuable and especially for the chest, abdomen, and extremities, it is performed as the initial modality for screening of various diseases.

In diagnosis of diseases of the head, information obtained by plain radiography is limited and it is rarely considered as the modality of first choice, but it is obtained frequently in many institutions.

2. Contrast radiography

Contrast studies have been performed to compensate the weak points of plain film studies. Especially, angiography is still performed as the gold standard in many diseases. In recent years, interventional radiology (IVR) has been prevailed as the modality for treatment using the technique of angiography (Seldinger's technique). However, in performing IVR, it sometimes takes hours in fluoroscopic and radiographic procedure. Recently there are many reports of cutaneous ulcers,[5,6] which could never been imagined to happen in this modern age of radiology.

Contrast studies of the gastrointestinal tract have been widely replaced by endoscopy but they are still frequently performed as screening. Intravenous urography has been performed as the basic study for screening of urinary tract diseases. Although it could be replaced by ultrasonography or computed tomography but IVU is still performed as the routine examination in urology.

3. Computed tomography (CT)

Nearly 30 years have passed since the CT was introduced into the field of clinical examination and became one of the most important clinical tools. Especially due to the recent development of the helical system, hemodynamic information and three-dimensional demonstration of the organs and diseases can be obtained. Virtual endoscopy using helical system is now clinically used after years of experimental application. Detection of small ureteral stone by CT is now drawing attention as the CT urography in clinical practice.

The most recently developed CT unit with multiple detectors (multidetector or multi-slice CT) would be the main modality for imaging diagnosis in the future. It has a capability of examining the whole body in a single study and it is called "one stop shopping", eliminating need for the rest of the studies. However, when the economical situations such as the health insurance system is taken into consideration, the ideal diagnostic strategy (decision tree) cannot be fully practical.

Radiation dose to the patients by the modern powerful CT is also becoming a new problem.

4. Ultrasonography (US)

As there is no radiation associated, the ultrasonography has become one of the most important imaging modality. It has been established as a diagnostic tool replacing the classical stethoscope, and moreover it can replace the manual palpation skill of physicians. It is clear that this simple tool can help the physician at the clinical

practice.

Significant improvement in the quality of the images has been made. Hemodynamic information of the lesion is now easily obtained with the Doppler system. Improvement in the computer technology brought the three dimensional images of ultrasonography. The ultrasonography can be performed by the physician, nurse, clinical radiology technician, and by clinical laboratory technician. The imaging quality, however, depends on the clinical skill and the experience of the examiner significantly. The use of US is limited in some anatomical sites because of the presence of gas and bones, which reflect the ultrasonic wave.

5. Magnetic resonance imaging (MRI)

As with US, there is no radiation to the patient with MRI. The scanning technique is improving very rapidly and scanning time is remarkably shortening, some of which being as short as the conventional X-ray exposure for film. Voluntary slice level can be selected and different information is obtained using a variety of imaging factors. Fine detailed angiography (MR angiography) is also obtained and conventional angiography can be avoided in many cases. Using NMR spector, MR spectroscopy (MRS) is obtained and the tissue characteristics is estimated for more precise imaging diagnosis. Differentiation between malignancy and inflammation could be made in some instances.

Common Items for Consideration to Reduce Radiation Exposure

1. Strict indications for examination

1) **Alternative examination**

Prior to performing the imaging examination with radiation to the patients, it is necessary to consider whether the alternative examinations without radiation such as US or MRI can be done.

2) **Comparison films**

When previous examinations are available for comparison, unnecessary study can be avoided in some cases. Previous examinations performed at other institutions should also be obtained for review. Due to advancement and prevailing of the computer, the new picture archive and communicating system (PACS) is available to convey the images to the remote institution.

2. High performance X-ray units

When taking radiographs, it is preferable to use the machine of higher performance, so that shorter exposure time could be selected, which is advantageous especially for pediatric patients to reduce the artifact on the radiographs due to body movement.

Accurate collimation is also possible with the high performance machine.

3. Fast film/screen combination

Faster film/screen combination is preferable. Radiation dose is significantly reduced by the use of rare earth screen.

4. Digital system

Digital imaging system is now used widely instead of film/screen system. Not only reduction of the radiation to the patient, application of the PACS system become possible by the digital system.

5. Cautions to be marked on the fluoroscopy

(1) Full use of fluoroscopic collimation is important to keep the gonads out of the direct radiation field.
(2) Dead man type on-off switch is ideal to reduce the un-necessary radiation dose to the patient.
(3) Recording system such as Video significantly cut down the fluoroscopy type.
(4) Only personnel needed to perform the examination should be arrowed to stay within the examination room.
(5) When the personnel must stay within the examination room during the fluoroscopy, he or she should ware a lead apron or should be behind the lead protective screen.

6. Storage of images

Images should be filed properly to be utilized effectively. Digitalized images can be more easily filed. It is a necessity for the medical institution that all images could be readily reviewed whenever needed, whether the images are digitalized or not. This rule is, however, not kept at many institution in Japan.

Decision Tree for Effective Diagnosis

Plain film is still the modality of first choice in diagnosis of diseases in many organs because of its simplicity and low radiation dose to the patients. It is important to decide which examination to combine with plain film, US, CT, MRI or nuclear medicine. The combination is different in various organs and also among the institutions and among the physicians of different experiences. Supposing the institution is equipped with the newest diagnostic tools, the ideal decision tree can be established.

To reduce the expanding medical expenses, unnecessary examination should be spared. In medically advanced countries such as the United States of America or United Kingdom, study has been done to establish the ideal diagnostic decision tree. Excessive simplification should not, however, disturb the process of making diagnosis.

Now, ideal guideline for diagnosis suited for Japanese medical situation especially for the medical insurance system is needed. The human body was divided according to the anatomical regions, the head, neck, chest, gastrointestinal system, hepatobiliary and pancreatic system, genitourinary system, extremities, spine, breast, and cardiovascular system and interventional radiology was added. In each of these regions and categories, a guideline was made with the example of representative cases or representative symptoms.

Conclusion

A guideline for diagnosis with minimal radiation to the patients and with minimal examination cost and in minimal time interval was needed. Because of the differences of imaging equipments and differences of personal experiences among the institutions, it is not possible to make a guideline to satisfy every one involved in the imaging diagnosis, but it is possible to make a proper diagnosis in reasonable time reducing the radiation dose to the patients after reviewing each diagnostic modality and their combination.

The most fundamental point for the diagnostician is to reconsider the efficacy of the examination in the viewpoint of the patients.

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Patient Exposure Doses During Diagnostic Radiography

JMAJ 44(11): 473–479, 2001

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Abstract: The exposure doses received by patients during diagnosis in Japan were surveyed. Five nationwide surveys were conducted by the same method between 1974 and 1997. Thirteen sites in the body (17 directions) were the subject of the survey. The dose evaluations were made according to the methods described in the International Basic Safety Standards (BSS) of the International Atomic Energy Agency (IAEA), and calculations were made from the irradiation conditions based on actual measured data. With the exception of mammography and CT examinations, the basic dose evaluations were performed with absorbed doses at the entrance surface. Mammography was evaluated by mean breast absorption doses. The CT examinations were evaluated by the absorbed dose at the center of rotation of a cylindrical water-equivalent substance simulating the head and abdomen and the computed tomography dose index (CTDI). When the values in 1974 were set equal to 100%, with the exception of films of the thorax, the doses decreased to 50% or less. The decrease in values for mammography were particularly marked, falling to less than 10%. A comparison with the 1997 survey and BSS showed decreases of 50% or less at all sites in the body in Japan. Comparison of the film-intensifying screen system (F/S system) with computed radiography (CR) using an imaging plate showed that the values with the latter were lower, except when imaging the thorax.

Key words: Patient exposure; Diagnostic radiography; Entrance surface dose; Guidance level

Introduction

Radiation doses received by patients during diagnostic radiography, especially x-ray radiography, have been reported by the United Nations Science Committee,[1] but there are not many data from Japan. Consequently, we shall report the results of earlier surveys[2–6] and the recent state of affairs regarding exposure during x-ray diagnosis. We shall also attempt to compare the data with the standards published by the International Atomic Energy Associa-

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tion (IAEA).

The IAEA published *Safety series* No. 115[7] in February 1996. It lists doses for representative adult diagnostic radiography examinations, CT examinations, and mammography and dose rates for fluoroscopy examinations published as guidance levels for radiography examinations in the diagnostic area. These guidance levels have been interpreted as the minimum doses that do not compromise the quality of diagnosis. In other words, standard values according to the IAEA recommendations for doses received by patients in the diagnostic area are shown. With the exception of mammography and CT examinations, the dose evaluations are entrance surface doses. The doses at the entrance surface are the largest doses in the diagnostic area.

I have used these doses as the exposure doses in this report, except for mammography and CT examinations. I will explain the dose evaluation methods for mammography and CT examinations in a concise manner later.

This report estimates the doses received by patients in the diagnostic x-ray area in Japan. As regards mammography, the author was responsible for the exposure dose evaluations in the Geriatric Welfare Research Project, "Study on the system for conducting breast cancer examinations that include mammography" (principal investigator: K. Ouchi, which was partially subsidized by the 1997 Geriatric Health Project Fund. The data for the year 1997 utilized these data. For CT examinations, we show the actual measurements made at 38 institutions in the Chubu District. In addition, computed radiography (CR) that uses imaging plates (IPs) instead of the conventional film/screens (F/S) is now being used at many medical institutions. Radiation dose comparisons between F/S and CR were also conducted.

Methods

1. Questionnaire surveys

Nationwide questionnaire surveys on the same items were carried out at medical institutions throughout the country where medical radiological technologists were employed. The surveys have been conducted a total of 5 times, the first time in 1973, and again in 1979, 1989, 1994, and 1997. From the first to third times, 200 institutions were randomly selected by 2-stage sampling from the membership list of the Japan Association of Radiological Technologists, and the fourth and fifth times, 1000 institutions were selected in a similar manner by 2-stage sampling from the membership list of the Japan Society of Radiological Technology. The valid reply rate was about 65%. The 1997 mammography data were obtained from the 782 institutions in which dose calculations were possible among the 2380 institutions that were initially targeted.

In addition to the 1997 survey, CR was surveyed at 200 institutions where equipment had been introduced in the Chubu District in 1999.

2. Dose evaluation

Doses were evaluated based on the actual measured values at 47 institutions in the Chubu District. The entrance surface doses were calculated by classifying the values obtained by actual measurement from the exposure conditions for each of the generator types and filter thicknesses. Whenever the generator type was unknown, it was assumed to be 3-phase 12-peak, and whenever total filtration was unknown, it was assumed to be 3 millimeters aluminum equivalent.

Mammography was evaluated by the average mammary glandular dose.[8] The breast glandular and adipose tissue ratio to the air dose in the entrance surface area was calculated as 50%–50%, and the mammary glandular dose was calculated by multiplying this value by the mammany glandular absorbed-dose conversion coefficient for middle-aged women.

Doses in the CT examinations were evaluated[7] by the dose at the center of rotation (inside the body) when routine examinations of the head and abdomen (14 scans or more) was performed.

Table 1 Exposure Sites Surveyed in 1997 and Dose Comparisons

Exposure sites	No. of institutions calculated	75% dose	Mean	Standard deviation	Guidance level
Head, frontal view	642	2.68	2.28	1.67	5
Head, lateral view	636	1.96	1.62	1.14	3
Cervical spine, frontal view	640	0.83	0.71	0.68	—
Thoracic spine, frontal view	620	3.68	3.10	2.32	7
Thoracic spine, lateral view	617	7.70	5.86	4.47	20
Chest, low voltage	321	0.37	0.38	0.63	—
Chest, quasi-high voltage	312	0.33	0.29	0.34	—
Chest, high voltage	523	0.18	0.18	0.20	0.4
Lumbar spine, frontal view	617	4.15	3.63	3.10	10
Lumbar spine, lateral view	622	13.50	11.08	10.50	30
Pelvis, frontal view	632	2.87	2.42	1.96	10
Femur, proximal	631	1.97	1.68	1.32	—
Forearm bones	639	0.16	0.15	0.17	—
Ankle	646	0.22	0.21	0.19	—
Guthmann	355	8.63	6.49	7.50	—
Martius	341	8.97	6.95	7.21	—
Hip, small child	500	0.15	0.13	0.15	—
Chest, small child	525	0.13	0.18	0.13	—
Chest, child	544	0.13	0.12	0.14	—
*Mammography	782	1.63	1.42	1.58	**1, 3

Units: mGy

*Nationwide Mammography Survey, Ministry of Health and Welfare study group (Ouchi group), 1997 data.
**Without grid: 1 mGy; with grid: 3 mGy (not classified according to whether a grid was used or not).

Table 2 CR (F/S) Use Rate at 5 Representative Exposure Sites in the 1997 Survey and Dose Comparisons

	CR use rate (%)	CR	F/S	CR/(F/S)
Head, frontal view	16.1	1.96	2.23	0.88
Chest, high voltage	14.1	0.20	0.17	1.20
Lumbar spine, frontal view	15.7	2.29	3.59	0.64
Lumbar spine, lateral view	15.7	9.29	10.90	0.85
Pelvis, frontal view	14.4	2.28	2.33	0.98

Units: mGy

Results of the Surveys

Table 1 shows the numbers of institutions used to make the calculations, the 3/4 quantile doses (75% doses), means, standard deviations, and IAEA guidance levels. The 75% dose is the dose at the institution in the 75% position, and it means that 75% of the institutions are at or below that dose. Except for "chest, high voltage", "chest, low voltage", and "chest, young child", the 75% doses were higher than the mean dose. Particularly at sites where the dose was large, i.e., the thoracic spine lateral view, lumbar spine lateral view, Guthmann, and Martius sites, the 75% dose was about 2 mGy larger than the mean. Comparisons with the guidance levels showed that all 8 sites were 1/2 to 1/3.

The CR use rates in the 1997 survey were about 14-16% (Table 2). With the exception of "chest, high-voltage", the higher exposure dose

was higher with F/S. It was particularly higher in the "lumbar spine, frontal view", where the exposure dose was 36% greater than with CR. The histogram for "lumbar spine, lateral view" showed a wider distribution of F/S doses than with CR (Fig. 1). In the 1999 survey, in which the Chubu District was the subject, differences in doses occurred according to whether a technologist was present or not (Table 3).

The changes in doses at 10 representative sites in the body between 1974 and 1997 are shown in Table 4. The changes are shown by letting "100" represent the dose (%) at each site in 1974. During the 23-period the dose de-

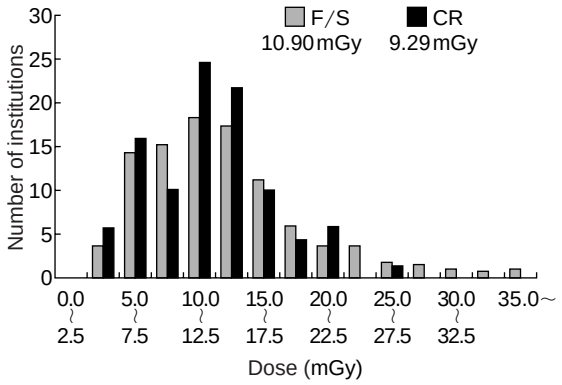

Fig. 1 CR and F/S dose histograms for lumbar spine lateral view radiography in the 1997 survey

Table 3 Dose Comparison According to Whether a Technician was Present According to the 1999 Survey

	Dose according to the conditions recommended by the manufacturer	Clinical radiological technologist		None present/ Full-time
		None present	Full-time	
Head, frontal view	0.69	2.25 ± 2.40	1.60 ± 0.91	1.41
Chest, high voltage	0.16	0.24 ± 0.11	0.33 ± 0.55	0.73
Lumbar spine, frontal view	1.71	4.93 ± 3.52	3.17 ± 2.72	1.56
Thoracic spine, lateral view	7.49	14.17 ± 9.03	9.67 ± 8.04	1.47
Pelvis, frontal view	1.37	3.69 ± 2.96	2.35 ± 2.26	1.57

Units: mGy

Table 4 Exposure Doses for Imaging at 10 Sites in the Body —Changes between 1974 and 1997—

	1974	1979		1989		1994		1997	
	Dose	Dose	(%)	Dose	(%)	Dose	(%)	Dose	(%)
Head, frontal view	7.11	5.34	(75)	3.84	(54)	2.49	(35)	2.28	(32)
Lumbar spine, frontal view	8.21	5.99	(73)	4.19	(51)	3.61	(44)	3.63	(44)
Lumbar spine, lateral view	22.30	15.61	(70)	9.37	(42)	10.48	(47)	11.08	(50)
Pelvis, frontal view	6.74	5.12	(76)	3.10	(46)	2.49	(37)	2.42	(36)
Chest, high voltage (100 kV or more)	0.23	0.18	(77)	0.13	(55)	0.13	(56)	0.18	(77)
Ankle	0.44	0.31	(71)	0.21	(49)	0.17	(39)	0.21	(49)
Hip, small child	0.50	0.37	(74)	0.23	(46)	0.12	(25)	0.13	(27)
Thorax, small child	0.56	0.39	(69)	0.24	(43)	0.12	(21)	0.18	(31)
Guthmann	24.26	16.74	(69)	7.28	(30)	5.58	(23)	6.49	(27)
Mammography	22.50	10.35	(46)	4.28	(19)	1.80	(8)	1.42	(6)

Units: mGy

Table 5 Doses for CT Examinations of the Head and Abdomen in the 1998 Survey

		Mean	Standard deviation
Head CT	Center	40.40	±10.80
	Upper portion	45.43	±12.15
	Lower portion	40.15	±11.55
Abdominal CT	Center	10.94	±3.13
	Upper portion	19.74	±5.93
	Lower portion	17.09	±5.18

Units: mGy

*Measurement with a cylinder of tissue-equivalent substance, 16 cm in diameter for the head and 30 cm for the abdomen

creased 23% for "chest, high voltage", 50% for "lumbar spine, lateral view", 51% for "ankle", and 56% for "lumbar spine, lateral view". The dose for mammography decreased to 6%, less than 1/10 the dose in 1974. No large changes in doses were observed between the 1994 survey and the 1997 survey.

The doses for routine CT examinations (head, abdomen) are shown in Table 5. They are internal doses measured with a human body substitute (tissue equivalent) substance on a bed. The mean dose at 38 institutions was 40.40 mGy for the head and 10.94 mGy for the abdomen.

Discussion

The doses that have been published internationally as guidance levels were used for the exposure dose evaluation in this study. The doses are expressed as mean breast doses for mammography, center of rotation doses for CT examinations, and as the entrance surface doses for other x-ray examinations. Entrance surface doses are treated as exposure doses in the general diagnostic area.

The survey spanned 23 years. Because it was anticipated that rapid changes in equipment and digitalization had progressed, the goal of determining how exposure doses had changed was in the background of the 1997 survey. It was obvious that inverter-type high-voltage generators had come into widespread use. In this situation, the exposure did not decrease even though the irradiation time became shorter. It is important to be sufficiently aware that sometimes the exposure dose does not increase despite lower irradiation conditions as a result of improvements in the equipment.

Examination of the dispersions of the doses at each site exposed in the 1997 survey for Japan as a whole shows that there is a great deal of room for an assessment. Even when the error of the questionnaire survey is included, they are not very small. The results are generally consistent with the results of a similar survey conducted by Mori[9] in 1995. There was a great difference between the changes in doses in the surveys up to 1994 and the changes since 1994, with not as much fluctuation in the two most recent surveys. This does not appear to have occurred because there has been a lack of effort to reduce the doses, but because the optimal doses have been established to ensure the quality of diagnosis. This is clear even from the example of mammography.

The CT examinations were evaluated by a method similar to the guidance levels. The mean results of the measurements were below the guidance levels in both the head and the abdomen. However, there were 5 institutions (13%) where the measurements in the head exceeded the guidance level. CT examinations have evolved considerably, and since these results represent the doses in ordinary examinations, it will be necessary to assess the doses for examinations by different modes (helical scanning, multi-scanning, etc.) again.

It appears that in the future there will be a transition from examinations that use x-ray film to those that use digital images. Under the present circumstances, the doses are on the same level as those used for film, but since digital image quality increases with the radiation dose, the likelihood of the exposure dose exceeding the dose used for film is a problem. This cannot be resolved by technology alone, and the manufacturers also must make an effort. The differ-

ences in dose from F/S were not very great in the 1997 survey, but the doses were higher at institutions where there was no clinical radiological technologist (i.e., where physicians, or dentists took the films). It will be necessary to further increase the physicians' and dentists' concern about exposure.

With the exception of mammography,[8] the standard doses for each of the exposure sites shown by the IAEA have not been clearly shown in Japan. First the standards should be decided, and then some form of advice should be given to institutions that exceed the standards and to institutions that are far below the standards. Improving both should ultimately make it possible to define the most appropriate dose that ensures image quality. Confronted with this situation it is necessary to immediately set the radiation doses that patients receive in radiological examinations in Japan and the guidance levels.

Conclusion

I have reported on the current situation regarding the doses received by patients who undergo diagnostic radiography examinations in Japan based on the results of surveys conducted over a 23-year period. Reductions in the doses were observed, but there is still a good deal of room for improvement. Physicians, dentists, and radiological technologists who are responsible for radiation therapy carry a heavy burden. Faced with the prospect of digitalization in the future, efforts must be made to decrease exposure so that the doses do not become even higher than they are now. I hope that this report has served as an opportunity for you to learn about the current situation regarding the radiation doses to which patients are exposed during diagnostic radiography.

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Optimization and Guidance Levels for Radiation Protection in Diagnostic X-ray Examinations

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Abstract: Although dose limits for medical exposure have not been established in law, it is necessary to confirm that the use of radiation will benefit the patient, and at the same time, to endeavor to reduce the patient's exposure. The fundamental principles for putting this into practice are *justification of actions* and *optimization of protection*, which were proposed by the International Commission on Radiological Protection. *Optimization of protection* means that all exposure should be kept as low as can be rationally achieved, taking economic and social factors into consideration. Upon this proposal, the International Atomic Energy Agency provided guidance levels, which are standards for the *optimization* of medical exposure. Indicating standards for radiopharmaceutical doses and for exposure doses in patients undergoing various radiological examinations, these guidance levels serve as a yardstick by which to evaluate the amount of exposure associated with a patient or facility. As new technology is introduced for cancer screening and the like, it is necessary to consider *optimization* from the viewpoints of image quality and exposure reduction.

Key words: Radiation protection; Optimization; Guidance level; X-ray examinations

Introduction

Radiation exposure can be classified as occupational, medical, or public. In the medical institution, *occupational exposure* refers to the exposure received by physicians, nurses, technicians, and others who are involved in the medical use of radiation; *medical exposure* refers to the exposure received by patients when they undergo radiodiagnosis or radiotherapy, and the exposure received by persons who accompany those patients; and *public exposure* refers to the exposure received by staff members who are not involved in the medical use of radiation, and the exposure received by patients that is not part of their medical care.

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Dose limits for occupational exposure and public exposure have been established in law. In existing law, the effective dose limit for occupational exposure is 100 millisievert (mSv) per 5 years (with exposure in any one year not to exceed 50 mSv). The limit for public exposure is 1 mSv per year.

For medical exposure, however, there are no dose limits. The reason for this is that radiodiagnosis, interventional radiology (IR), radiotherapy, and the like are of direct benefit to the exposed individual (patient), and applying dose limits to such medically necessary actions could result in harm to the patient. For this reason to be a valid, however, the physician must confirm that the use of radiation will clearly benefit the patient, possess sufficient knowledge of radiation protection, and constantly endeavor to reduce the patient's exposure. The fundamental principles for putting this into practice were proposed by the International Commission on Radiological Protection (ICRP)[1]; those principles are *justification of actions* and *optimization of protection*.

Justification and Optimization

In its 1990 recommendations, the ICRP advanced 3 principles as a system of general radiation protection for reducing exposure and making effective use of radiation: 1) Justification of actions, 2) optimization of protection, and 3) dose limits for individuals. In regard to medical exposure, *justification* and *optimization* must be considered, since dose limits for individuals are not appropriate, as was explained above.

Justification of actions means that no action involving exposure to radiation should be performed unless the benefits to the exposed individuals and public from the exposure exceed any harm they will suffer from it. It is proper, of course, that the clinical need for an x-ray examination be confirmed before such an examination is performed on a patient. For example, before performing an abdominal computerized tomography (CT) examination, the clinical necessity and reliability of the diagnostic information expected to be obtained in the examination should be considered. Then as the next step, the use of other diagnostic imaging techniques that do not involve radiation, such as ultrasonography and MRI, should be considered, and the decision to employ CT should be made based on the conclusion that CT will be the most useful technique.

Optimization of protection means that all exposure should be kept as low as can be rationally achieved, taking economic and social factors into consideration. That is, it is necessary to endeavor to keep exposure as low as possible for the patient who needs (or is justified) for radiotherapy such as radiodiagnosis, IR, or other medical use of radiation. So that such optimization could be applied to some common diagnostic procedures, the ICRP recommended the use of dose constraints, or investigation levels, selected by appropriate professional organizations or regulatory agencies.

Guidance Levels for Medical Exposure

Upon the recommendations of the ICRP, the International Atomic Energy Agency (IAEA) provided guidance levels for medical exposure in the 1994 Basic Safety Standards (BSS).[2] These guidance levels — which indicate standards for radiopharmaceutical doses and for exposure doses in patients examined by simple roentgenography, CT, fluoroscopy, or nuclear medicine — can be used to assess whether the exposure associated with a patient or facility is large or small (Table 1 to 4). When exposure of patients in a facility exceeds a guidance level, an investigation is conducted so that doses can be reduced to appropriate levels. Thus, using guidance levels, patients and facilities with high exposure can be identified and measures can be promoted.

It is thought that some IAEA guidance levels were set so that based upon the results of actual measurements in about 20 hospitals in the United Kingdom the guidance levels would

Table 1 Dose Guidance Levels for Radiodiagnosis

Site examined	Direction	Entrance surface dose (mGy/exposure)
Lumbar spine	AP	10
	Lateral	30
Lumbosacral spine	AP	40
Abdomen, urinary tract, gallbladder	AP	10
Pelvis	AP	10
Hip joint	AP	10
Chest	PA	0.4
	Lateral	1.5
Thoracic spine	AP	7
	Lateral	20
Teeth	Root apex	7
	Frontal	5
Skull	AP	5
	Lateral	3

Table 2 Dose Guidance Levels for CT

Site	Mean dose per examination* (mGy)
Head	50
Lumbar spine	35
Abdomen	25

*By measurement of water phantom at the rotation axis

Table 3 Dose Guidance Levels for Mammography

Mammary tissue dose by craniocaudal exposure*
1 mGy (without grid)
3 mGy (with grid)

*By dedicated mammography system with molybdenum target and molybdenum filter

Table 4 Guidance Levels for Fluoroscopy

Operation	Entrance surface dose rate (mGy/min)
Usual	25
High level*	100

*High-dose-rate mode option used in intervention

Table 5 Mean Dose per Capita from X-ray Examinations in Different Countries

Country	Year	Effective dose (mSv)
Japan	('89)	2.2
France	('82)	1.6
Russia	('90)	1.1
West Germany	('88)	1.0
United States	('80)	0.4
United Kingdom	('89)	0.35

include 75% of all the patients. Thus, these guidance levels were set for typical European or American adults. In Japan, discussions related to the establishment of guidance levels that consider such factors as technological progress and the size of Japanese bodies are under way, mainly by the Japan Radiological Society (JRS).

The Present Condition and Future of Medical Exposure in Japan

According to a study by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), medical exposure from diagnostic x-ray examinations in the Japanese people was 2.2 mSv per person (1989), which was the highest in the world (Table 5). Furthermore, this exposure value increased 1.7 fold over a 10-year period.[3] The reason for this situation is the high per capita number of x-ray examinations in Japan, and the fact that many of those examinations are ones in which the patient receives a high dose each time the examination is done, such as upper gastrointestinal study and CT. Background for this could be such phenomena as differences in insurance medical systems and the spread of medical equipment associated with advances in medicine. Medical exposure accounts for 90% of exposure to man-made radiation. The necessity of reflection of the benefits associated with increased medical exposure in the Japanese people as a whole in increased health of the Japanese, who have achieved the world's greatest longevity, must be recognized.

Table 6 Exposure Doses (mGy) from Simple Roentgenography in the Japanese

Site	Mean value	75% value	Guidance level
Chest PA	0.16	0.19	0.4
Abdomen AP	2.3	3.1	10
Pelvis AP	2.3	2.8	10
Lumbar Spine AP	3.7	4.3	10
Lumbar Spine Lateral	9.3	11.5	30

The Protection Committee of the JRS recently conducted a survey of the exposure doses associated with 5 representative kinds of simple roentgenography in approximately 200 hospitals registered as training facilities for radiologists.[4] The results of this survey revealed that the values that included 75% of all the patients (75% values) were all low, ranging from 28% (pelvis) to 47% (chest) of the IAEA guidance levels (Table 6). Considering these results, there is a need for further discussion of the advisability of establishing values for Japan that are lower than the IAEA guidance levels, and a need for discussion of the advantages, costs, etc. associated with the lowering of guidance levels.

On the other hand, new problems are arising as diagnostic imaging technology progresses; for example, doses are significantly greater in facilities using computed radiography (CR) than in facilities using conventional film and intensifying screens. Of the collective effective dose equivalent of overall medical exposure in the Japanese, 6% is attributable to upper gastrointestinal study for gastric cancer screening, and 2.6% to chest roentgenography for screening of lung cancer and tuberculosis.[3] At present, mammography for breast cancer screening is being introduced in Japan. In addition, the introduction of lung cancer screening by CT is also being discussed. As these new technologies are introduced, *optimization* from the viewpoint of reduction of exposure must be considered as well as the image quality control necessary for early detection of cancer.

Conclusion

In performing radiological examinations, it is necessary to make an effort to keep exposure as low as possible while maintaining clinically satisfactory image quality. Guidance levels are the standards for this *optimization*, but in them, conditions such as the patient's physique should be considered. Furthermore, guidance levels should be revised as technology advances.

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Radiological Protection of Patient and Operator in Interventional Radiology

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Abstract: Although marked progress has been made in interventional radiology (IVR), radiation exposure is on the increase among both patients and operators. The number of IVR cases is also increasing yearly and the exposure time has become prolonged due to recent sophisticated and complex techniques. Recent reports cite increasing dermatological disorders in patients after PTCA and stenting. No limits have yet been placed on patients' exposure, but doses must be reduced to minimum necessary levels by enhancing protective efforts. Operators' exposure levels depend on whether the fluoroscopy device employed is of the under-tube type or the over-tube. When an under-tube type is used and the operator always wears a protective garment during the procedure, exposure is expected to remain below the annual effective dose limit. On the other hand, operators working with an over-tube fluoroscopy are advised to wear protective goggles, since without them there is a risk of exposing the lens to doses in excess of the annual equivalent dose limits. To reduce the exposure, it is important for operators to have sufficient knowledge of radiological protection and always be on guard while conducting the procedure. It is also necessary to employ an X-ray device equipped with optimal protective functions.

Key words: Interventional radiology; Exposure of patient; Exposure of operator; Prevention from exposure

Introduction

Interventional radiology (IVR) is an effective treatment method that achieves steady result with less invasion. However, the problem of radiation exposure is attracting attention along with a marked increase in the corresponding cases. To be more precise, the skin injuries in the patient and lens disorder in the operator have been reported. In this respect, FDA (Food & Drug Administration) of USA issued a recommendation in relation to IVR. Furthermore, ICRP (International Commission on Radiological Protection) is also compiling a draft of

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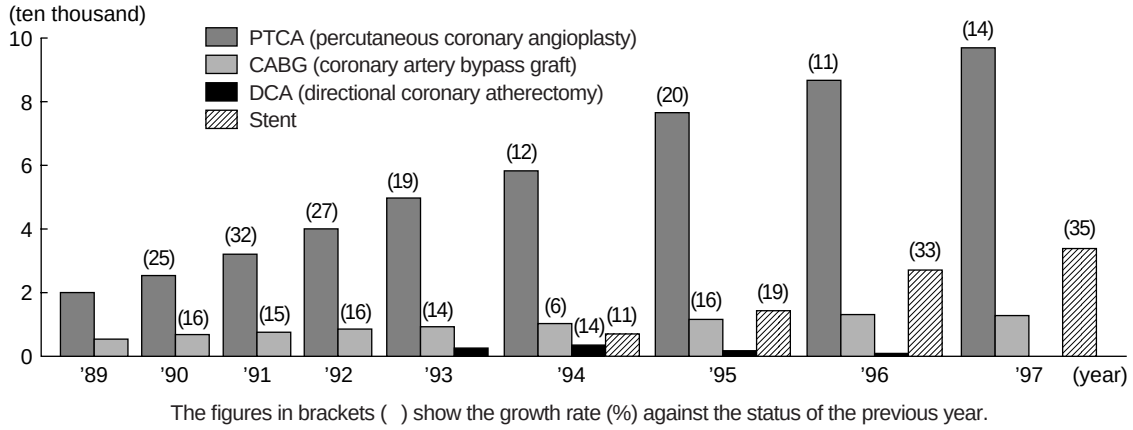

Fig. 1 Annual changes in the number of PTCA, CABG, DCA, and stent cases in Japan (quoted from Reference 2)

recommendation in relation to the exposure.

The facts about the exposure during IVR and the protective measures are described in the following.

Reasons for Increased Exposure

The term "interventional radiology" was used for the first time by Prof. Alexander R. Margulis at University of California San Francisco in his editorial that appeared in AJR 1967. The radiological exposure was already mentioned in this article[1] as in the following.

According to Prof. Margulis, "the techniques in the category of IVR had been practiced since the time before 1967 but there was a hazard called "radiation exposure". For example, an operator who treated fractures or luxations under direct fluoroscopy suffered radiological disorder. However, thanks to the recent progress of radiological devices, the exposure is on the decrease. As a result, therapeutic techniques that depend on fluoroscopy have been aggressively used. It is expected that IVR will be established as a subspeciality of radiology and will be developed increasingly more in the future." In reality, IVR has been improved and developed more than Prof. Margulis predicted but the radiation exposure is again causing a problem.

The reasons for increased exposure during IVR are:

(1) An increase in the number of cases due to the development of new techniques and increased scope of application;
(2) Prolonged duration of treatment due to advanced techniques and complicated treatment.

For example, the cases of PTCA (percutaneous coronary angioplasty) against coronary diseases are showing a marked increase each year while cases of CABG (coronary artery bypass graft) are leveling off. Due to the use of stent in coronary artery, the cases of stenting are also showing a sharp increase (Fig. 1).[2]

The catheter manipulating time in the TAE (transcatheter arterial embolization) was short in the initial stage because the embolization was conducted in the proper hepatic artery or the right and left hepatic artery at most. However, in the recent subsegmental TAE, the catheter goes through the tortuosity of hepatic artery into the subsegmental artery or its periphery. As a result, the fluoroscopic exposure time is prolonged. The use of microcatheter and microwire increased the frequency of conducting fluoroscopy at a high dose such as magnification fluoroscopy, which also increases the exposure.

Exposure of Patient

Reports on the radiation-induced skin injuries caused by IVR have been made since 1994,

Table 1 Threshold Dose in Skin Disorders and the Duration up to the Onset

	Threshold dose	Duration up to onset
Early transient erythema	2 Sv	Several hours
Transient epilation	3 Sv	3 weeks
Main erythema	6 Sv	10 days
Permanent epilation	7 Sv	3 weeks
Dry desquamation	10 Sv	4 weeks
Wet desquamation	15 Sv	4 weeks
Dermal necrosis	18 Sv	10 weeks or more
Secondary ulceration	20 Sv	6 weeks or more

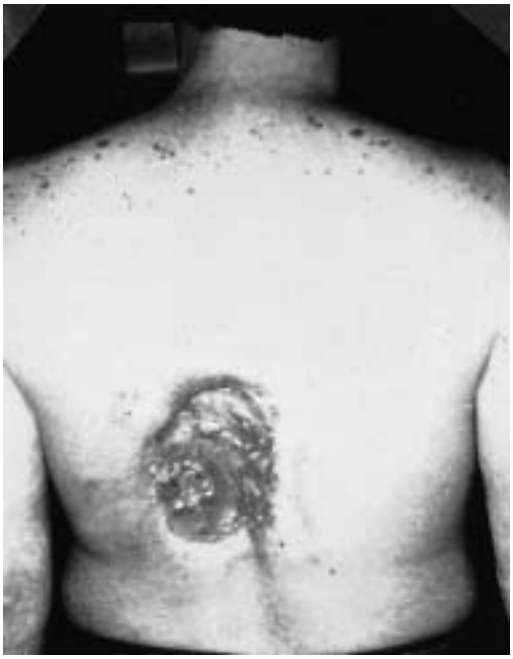

Fig. 2 Case of skin necrosis caused by coronary angiography (2 times) and PTCA (quoted from Reference 4)

and the number of reports on this subject is showing a tendency to increase each year.[3–5] Depending on the absorbed dose to the skin, the injuries range from mild and transient erythema, alopecia, etc. to severe symptoms such as necrosis of skin. Table 1 shows the relation between the dose and skin injuries, and the latency[6] up to the onset. These injuries are called deterministic effects and occur when the dose exceeds a threshold. The severity of symptom in such case is dose-dependent. Accordingly, the dose irradiated can be estimated on the basis of severity of skin injury. The patient shown in Fig. 2 is considered to have been exposed to a dose of 20 Sv or more.

The exposure of patient is classified as medical exposure and the dose is not limited in such case because the patient is expected to receive direct benefit from the medical deed (even if associated with radiation exposure) (the justification of a practice). Needless to say, however, maximum efforts should be made to protect the patient and the exposure should be reduced to the minimum (the optimization of protection).

Exposure of Operator

The exposure of operator is one of the occupational exposures, and the ICRP recommendation regulates the annual dose. According to the recommendation made in 1990, the limit of effective dose was 20 mSv/year (mean of 5 years) and the dose limit a year was 50 mSv (Table 2). The level is based on the high incidence of malignant tumors at 200 mSv or more in those exposed to the atomic bomb. The influence of this type has simply to do with the increased probability and has no threshold level. Accordingly, it is termed as "stochastic effects". Stochastic effects include genetic effects but it has not been confirmed in human.

As the deterministic effects that the operator suffer are disorders in the lens and skin (especially the fingers of hand). In this regard, the

Table 2 Dose Limit in Those Engaged in Radiological Work (Recommendation of ICRP in 1990)

Effective dose:	20 mSv or less per year in 5 years running (50 mSv or less a year)
Annual equivalent dose:	
· Lens of the eye	150 mSv
· Skin	500 mSv
· Hands and feet	500 mSv

Equivalent dose: The dose obtained by taking account of the dose quality into absorbed dose (Gy). Indicated in Sv. For X-ray, Gy = Sv.

Effective dose: The dose obtained by taking account of the sensitivity of each organ and tissue into the equivalent dose. Indicated in Sv.

dose limit is 150 mSv/year for the lens and 500 mSv/year for the skin.

Dose the Patient is Exposed in IVR

The essential element that determines the exposure dose in IVR is the fluoroscopy time. When the mean fluoroscopy time in vascular IVR conducted at Osaka University Hospital was compared with that of DSA (digital subtraction angiography) conducted for diagnosis, the IVR related to the heart took 43 minutes (26 minutes for diagnosis only) and that related to abdomen took 32 minutes (14 minutes). More than twice longer fluoroscopy time was required in the latter case. In the case of the former, the frequency of radiography was more than twice higher than that for diagnosis only, and the estimated exposure dose of the patient was mean 1.14 Sv.

Fluoroscopy longer than 60 minutes was conducted in 51 cases (7.2%) for the abdominal vascular IVR in 1997. TAE (39 cases) against hepatocellular carcinoma accounted for the largest number of these 51 cases, followed by catheter placement cases (9 cases) against metastatic liver cancer. There were also 1 case each of peripheral arterial angioplasty, stenting, and TIPS (transjugular intrahepatic portosystemic shunt). Including the radiography dose, the skin of these 51 patients was exposed to a mean dose far exceeding 3 Gy. Furthermore, 6 of them (0.85%) required the fluoroscopy time of 120 minutes or more, resulting in the mean dose of 6 Gy to which their skin was exposed. However, skin disorder was not reported as a problem in these cases. It was mainly because different sites of skin were irradiated, though the disorder may have been overlooked.

Difference in Exposure of the Operator by Under-tube or Over-tube

Whether an under-tube type or over-tube type fluoroscopy device is used makes a difference in the exposure dose, that is, whether the source is underneath or above the patient's table (Fig. 3). In general, an under-tube is used in the vascular type IVR including TAE and PTA (percutaneous transluminal angioplasty) while an over-tube is frequently used in the non-vascular type IVR (biliary intervention etc.).

According to the data reported by Hayashi *et al.* who used phantom at Fukui Medical University, the exposure doses at the same position as the patient's, at a position 50 cm higher than that of the patient's and at a position 50 cm lower than that of the patient's after 30 minutes of fluoroscopy were 0.75 mSv, 0.25 mSv, and 0.95 mSv, respectively in the case of the operator using an under-tube device. That is, the exposure dose after 30 to 60 minutes of fluoroscopy is 0.25–0.5 mSv at a 50 cm higher position with consideration to the exposure of eyes and thyroid gland. Assuming that each case requires mean 45 minutes of fluoroscopy, the dose does not reach the 150 mSv/year level unless more than 400 cases are handled. At the same position as that of the patient and at a 50 cm lower position, no problem occurs because the abdomen and lower half of the operator's body are shielded by a protective garment.

On the other hand, the exposure doses were 0.65 mSv, 1 mSv, and 0 mSv, respectively at the above mentioned positions (the same as the

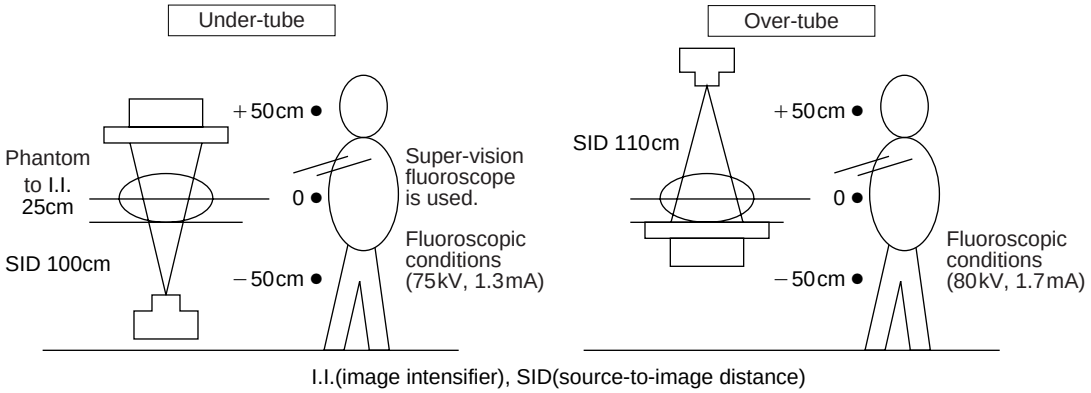

Fig. 3 Exposure of the operator in under-tube and over-tube fluoroscopy

patient, +50 cm, −50 cm) when an over-tube fluoroscopy was used. The 1 mSv at the eye level is a critical dose because the dose exceeds the limit if 30 minutes of fluoroscopy is conducted 150 times a year. Since the fluoroscopy time of non-vascular type IVR takes mean 15 minutes or so at Osaka University, there is still some allowance. However, when the vascular type IVR is conducted using an over-tube device, it is possible that the dose exposure exceeds the limit when 2 cases a day are handled twice a week. It is advisable to wear protective goggles when operating an over-tube fluoroscopy.

As to the exposure of fingers of hands, a survey in which the operator wore a film ring (4th finger of left hand) was conducted at Osaka University Hospital for 2 months. The result indicated the highest exposure in the IVR related to the heart. The operator was exposed to mean 0.755 mSv a case. And, the operator who handled a largest number of abdominal IVR cases was exposed to mean 0.556 mSv per case that is a dose far below the limit of 500 mSv/year.

For Reducing the Exposure

Apart from the IVR that uses ultrasonography and MRI, the exposure in IVR is unavoidable to some extent so long as a radiological device is used. Accordingly, the operators engaged in IVR and medical staff should make an all-out effort to reduce the exposure. In this regard, the following two points should be stressed.

1. The operator should have sufficient knowledge of radiological protection and conduct the procedure always paying attention to prevent the staff including himself/herself and the patient from exposure

Operators' lack in knowledge is a serious problem. The required knowledge was also lacking before I became a member of ICRP. Even a radiologist does not necessarily have sufficient knowledge. For example, I happened to witness the following scene: The operator was concentrating on the catheter and the wire, and was not paying attention to the distance from the source. He shouted angrily and turned off the fluoroscopy when a staff came into the room without protection. The distance between the source and the staff was more than 2 m but the operator did not know that it was a safe distance. Even though he seemed very attentive in avoiding exposure, he didn't seem to mind using an over-tube fluoroscopy without protective goggles.

Probably, the problem lies in the medical care system itself in Japan. Whatever his/her specialty is, a physician, is allowed to handle a

fluoroscopy device and there is no penalty for being absent from the training course for protection from radiation exposure.

The second point to be stressed is that the operator is not necessarily conscious of the danger of exposure even if he/she has sufficient knowledge about it. If the operator is conscious of the exposure of the patient, the frequency of unnecessary radiography and fluoroscopy will be decreased and at the same time more attention will be paid to the irradiation field of the patient by always using collimation. If conscious of the exposure, the operator himself/herself will try to keep as much distance as possible from the source, not to mention of the protector and goggles. Even a distance of 10 cm further from the source makes a difference. Furthermore, a knowledgeable operator will try to improve his/her skill and to reduce the fluoroscopy time.

2. To improve X-ray devices, equip the device with exposure-reducing measures and to indicate the dose by real time

First of all, the use of an under-tube type fluoroscopy device should be encouraged even in the non-vascular IVR cases. At our institution, devices (Shimadzu Co.) which allow switchover from over-tube to under-tube or vice versa are used. Therefore, over-tube is used only when necessary and the frequency of usage is very low.

As to the device itself, there is a problem of I.I. (image intensifier) deterioration. The relative sensitivity (Gx) of I.I. was reduced by half in about 5–7 years in 9 DSA devices at 5 institutions investigated. In other words, the fluoroscopic images markedly deteriorate after 5 years or so. As a result, the X-ray dose has to be increased to make up for the deterioration. It is advisable to update the X-ray devices at the soonest practicable occasion.

As to the indication of irradiated dose, our DSA devices are equipped with a PEMNET system that always indicates the total dose of fluoroscopy and radiography so that the operator can find the real time dose. Such a system should be standardized as soon as possible.

Conclusion

The exposure of patients and operators is definitely on the increase in IVR cases. To reduce the exposure, the operator should have sufficient knowledge about protection and should always bear in mind the danger of exposure while conducting the procedure. Furthermore, it is important to use X-ray devices provided with the best protective measures.

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Chronic Disease and Pregnancy Care: Requisites for Permissible Pregnancy and Timing of Shift to Obstetric Management

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Abstract: Very-low-calorie therapy was performed in a patient with severe obesity, diabetes mellitus, and hypertension who was on antihypertensive therapy, oral antidiabetic therapy, and insulin therapy and who had been advised by her doctor to avoid becoming pregnant. Since the blood glucose level and blood pressure normalized without medication, the patient was given permission to conceive, and ovulation induction and artificial insemination with her husband's semen were performed because of sterility. As a result, the patient conceived and gave birth to a healthy baby. Requisites for permissible pregnancy should always be subject to reconsideration as perinatal medical care advances. Attempts to conceive have recently increased in patients with chronic diseases that used to preclude them from conceiving. However, when giving permission for pregnancy, it is necessary for doctors to provide patients with relevant medical information and to base decisions on the individual case, while respecting the patient's right to self-determination based on the information given on possible risk. To optimize obstetric management of a patient with chronic disease, the patient should be referred to an obstetrician prior to conception, so that an optimal environment for pregnancy can be prepared beforehand.

Key words: Diabetes mellitus; Hypertension; Prepregnancy management; Requisites for permissible pregnancy

Introduction

This article discusses chronic disease and pregnancy care, with particular attention to requisites for permissible pregnancy and timing of the shift to obstetric management. However, since it is impossible to discuss all chronic diseases, a patient with a typical lifestyle-related disease will be described as an example.

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Case Report

Patient: A 31-year-old woman.

Chief complaints: Obesity, diabetes mellitus, hypertension, desire to have a baby.

Present illness:

The patient has been on treatment for obesity, diabetes mellitus, and hypertension under her internist since 1992, when she was 27 years old. For the treatment of diabetes, dietary instructions, oral antidiabetic therapy, and insulin therapy (since 1996) have been employed. A Ca antagonist and a β-blocker have been used for the treatment of hypertension.

The patient married when she was 24 years old, and because of lack of pregnancy, she visited an obstetrics and gynecology clinic at the age of 26 years and another clinic at 28 years, with the desire to have a baby. At these clinics, she received ovulation induction therapy and artificial insemination with her husband's semen, which ended in failure. On November 6, 1996, she visited another obstetrics and gynecology clinic with the desire to have a baby, but was referred to the department of obstetrics and gynecology of our hospital on November 13 because of complications such as diabetes mellitus and hypertension. She had been told by her doctor to avoid conceiving because her blood pressure was high (190/110 mmHg), and thus discontinuation of antihypertensive drug therapy would be dangerous.

Family history: Diabetes mellitus (−). The patient's mother and brother were obese.

Menstrual history: Menstruation cycle, 28–30 days; duration, 6 days.

Physical examination: The patient was 167 cm tall and weighed 102 kg. Blood pressure was 132/62 mmHg on the first examination and 161/89 mmHg on the second examination. There were no other particular abnormalities on physical examination.

Major laboratory findings:

Blood biochemistry

Glu 194 mg/d*l* ↑, HbA_{1C} 9.0% ↑, GOT 33 IU/*l*, GPT 44 IU/*l*, and serum creatinine 0.6 mg/d*l*. No other abnormalities were noted.

Urinalysis

Urinary protein 7 mg/d*l*, urinary trace albumin 122.7 mg/day ↑.

Endocrinology

PRL 71.8 ng/m*l* ↑, LH 2.40 mIU/m*l*, FSH 2.10 mIU/m*l*, T 47.2 ng/d*l*

Funduscopy

Fukuda's classification AI.

Diagnoses: Obesity, diabetes mellitus, suspected diabetic nephropathy, diabetic retinopathy, hypertension, infertility, and hyperprolactinemia.

Concept of Permissible Pregnancy in the Present Case

1. Blood glucose control in the initial stage of pregnancy and permissible pregnancy

A variety of perinatal complications may occur in pregnant women with diabetes. Poor blood glucose control in the early stage of pregnancy elevates the incidence of congenital malformation. Because congenital malformation cannot be prevented if blood glucose control is initiated after the patient has conceived, it is important to pursue planned pregnancy after strict blood glucose control has been achieved.[1)]

There is a correlation between the glycosylated hemoglobin (HbA_{1C}) level in the early stage of pregnancy and the incidence of congenital malformation. Values not more than mean + 4SD denote low risk, whereas moderate risk is denoted by values corresponding to mean + 6SD to 10SD, and high risk by those exceeding mean + 10SD to 12SD (Table 1).[2)] The HbA_{1C} value was 9.0% (normal range 4.3–5.8%) in the present case. This value corresponds to mean + 10SD, with the mean value and SD set at 5.0% and 0.39, respectively. The risk level of this patient was, thus, moderate to high. This level of risk may be assessed by the patient herself as high or low depending on her interpretation of the incidence of congenital malformation of 2–4% in healthy pregnant

Table 1 Maternal Glycosylated Hemoglobin Level and the Incidence of Congenital Malformation (Major Deformity)

Author	Year	No. of cases	Glycosylated hemoglobin level (No. of SDs exceeding the normal mean value) No. of cases of major deformity (incidence rate)		
Milher *et al.*	1981	106	<7 2/48 (4.2%)	7~9.8 8/35 (22.9%)	≧10 5/23 (21.7%)
Ylinen *et al.*	1984	142	<6 2/63 (3.2%)	6~9.8 5/62 (8.1%)	≧10 4/17 (23.5%)
Reid *et al.*	1984	127	<6 2/58 (3.4%)	6~9.9 5/44 (11.4%)	≧10 6/25 (24.0%)
Key *et al.*	1987	61	<5.8 2/45 (4.4%)	5.8~9.4 4/13 (30.8%)	≧9.5 3/3 (100%)
Greene *et al.*	1989	250	<6 3/99 (3.0%)	6~12 6/123 (4.9%)	≧12 11/28 (39.3%)
Hanson *et al.*	1990	491	<6 3/429 (0.7%)	6~7.9 2/31 (6.5%)	≧8 5/31 (16.1%)
Rosenn *et al.*	1994	228	<4 4/95 (4.2%)	4.0~9.9 7/121 (5.8%)	≧10 3/12 (25.0%)
Total		1,405	18/837 (2.2%)	37/429 (8.6%)	37/139 (26.6%)

(Adapted from Reference 2)

women. This assessment should be left to the patient, not to the doctor. In this case, after an explanation of the relevant data had been given to the patient, the decision was made to attempt pregnancy after controlling her blood glucose level. The patient's consent for this course of action was obtained.

2. Presence of diabetic retinopathy and permissible pregnancy

Pregnancy is one of the factors that causes worsening of diabetic retinopathy. If there is preproliferative or proliferative retinopathy, the patient is permitted to conceive after the prepregnancy blood glucose level has been improved and after retinopathy has been relieved by ophthalmic treatment including photocoagulation therapy of the retina. If the patient conceives while proliferative retinopathy is present, she will be informed of the risk of losing her eyesight as well as the success rates of photocoagulation and vitreous surgery, and continuation or artificial termination of the pregnancy will be determined by a doctor designated under the Mother's Body Protection Law, on the basis of discussion with the patient herself and her husband and ophthalmologist. Because rapid normalization of the blood glucose level may aggravate retinopathy, it is desirable for the patient to conceive after the blood glucose level has been adequately controlled.

3. Diabetic nephropathy and permissible pregnancy

Currently, diabetic nephropathy accompanied with atherosclerotic cardiac disease is a contraindication of pregnancy. Patients with this condition should avoid conceiving because the vital prognosis of the mother is poor. Gestational toxicosis frequently occurs among pregnant women with diabetic nephropathy. Patients with decreased renal function (CCr 30 m*l*/min or less, serum creatinine 3–5 mg/d*l*

or more) often fail to maintain pregnancy to the terminal stage. Such patients should be advised to conceive after the initiation of dialysis or kidney transplantation. However, it should be noted that the probability of achieving a live birth on dialysis is low. For patients with kidney transplantation, it is preferable that pregnancy occur 2–5 years after kidney transplantation, the period in which the patient usually is most stable.

Whether pregnancy deteriorates the natural course of diabetic nephropathy is controversial. Some reports claim no effects, whereas others indicate the possibility that pregnancy reduces the length of time until the introduction of dialysis. The present case was in the early stage of diabetic nephropathy, which does not constitute a reason for inhibiting pregnancy.

4. Oral antidiabetic drugs and permissible pregnancy

As a general rule, oral antidiabetic drugs are replaced by insulin before the patient becomes pregnant. However, it has been reported that the use of oral antidiabetic drugs is a useful means particularly in developing countries because these drugs are not associated with an increase in congenital malformation and because drug-induced neonatal hypoglycemia can be prevented by changing them to insulin at the time of delivery.[3)] In the present patient, oral antidiabetic medication was discontinued and switched to insulin monotherapy, which is known to be safe for the fetus.

5. Hypertension and permissible pregnancy

Women with chronic hypertension have a high potential to bear a healthy baby if there is no complication; however, the result worsens if the patient develops toxemia of pregnancy. Toxemia of pregnancy is apt to develop when there is accompanying renal disease or severe hypertension (160/110 mmHg or higher).

Hydralazine and α-methyldopa are antihypertensive drugs that have long been used. Currently, β-blockers, α/β-blockers, and Ca antagonists are also in clinical use. ACE inhibitors, however, are contraindicated because of their possible adverse effects on the fetus. Not a few drugs, particularly new drugs, are described as contraindicated for pregnant women on package inserts merely because of the lack of experience with their use in pregnant women.

The present patient was on antihypertensive drug therapy without established safety, and was at high risk of developing gestational toxicosis, which would have made the pregnancy a challenge if it had occurred under the existing circumstances. The possibility existed that the patient's hypertension might improve with treatment of obesity, and the patient had four years until she would reach 35 years of age, when a decrease in the pregnancy rate becomes apparent. Taking all this into consideration, the strategy that pregnancy be attempted after treatment of obesity was adopted, as the patient agreed to it.

Course of Illness in This Patient

Outpatient treatment

The patient received treatment for diabetes and obesity at our outpatient clinic as well as continuing antihypertensive treatment at the office of her own doctor. Diet therapy (1,500 kcal/day) was initiated with the assistance of dietitians in our hospital. Intensive insulin therapy was begun, while oral antidiabetic therapy was discontinued.

In June 1997, although the HbA_{1C} value decreased to 6.6% and body weight to 96.5 kg, her blood pressure remained at 163/96 mmHg, an insufficient decrease on antihypertensive therapy. Her condition began to worsen around this period, and the values of $HbA_{1C,}$ body weight, and blood pressure increased to 7.0%, 102.5 kg, 172/99 mmHg, respectively, in March 1998. Since the patient claimed that she was reaching the limits of her effort, a very-low-calorie diet (VLCD) program was attempted.

Very-low-calorie diet (VLCD)

The patient underwent a VLCD program in the Third Department of Internal Medicine of our hospital from April 9 to June 27 1998, in which caloric intake was reduced to 420 kcal/day. Her body weight and HbA_{1C} value were 104.5 kg and 8.1%, respectively, on admission. After 20 days of hospitalization, her blood glucose level and blood pressure were normalized in the absence of insulin and antihypertensive drugs. Her body weight, blood pressure, and HbA_{1C} value were improved to 85.5 kg, 113/49–133/96 mmHg, and 5.6%, respectively, at the time of discharge.

Course of pregnancy and delivery

Since the blood glucose level and blood pressure were normalized without medication, the patient was permitted to conceive. She underwent four sessions of ovulation induction by hMG-hCG with administration of bromocriptine and artificial insemination with the husband's semen at our infertility clinic. As a result, the patient conceived in December 1998. The HbA_{1C} value increased to 7.0% during pregnancy, and therefore insulin therapy was resumed. During pregnancy, weight gain was 12 kg, and values of urinary protein, blood pressure, and HbA_{1C} varied within ranges of 12–33 mg/day, 136/80–156/95 mmHg, and 5.0–7.0%, respectively. On August 30, 1999 (39 weeks, 0 day), the patient underwent cesarean section because bradycardia was noted on a fetal nonstress test (fetal cardiotocography), and she gave birth to a healthy male baby weighing 3,074 g.

Discussion

1. Concept of the requisites for permissible pregnancy

The requisites for permissible pregnancy should always be subject to reconsideration as perinatal medical care advances. According to Davison *et al.*,[4] perinatal mortality due to pregnancy complicated by severe renal dysfunction as indicated by a serum creatinine level of 2.8 mg/d*l* or higher has improved dramatically over time: from 100% in the 1950s, to 91% in the 1960s, 56% in the 1970s, 53% in the 1980s, and 10% in the 1990s.

Thus, patients with chronic disease, in whom pregnancy would not have been permitted in the past, have a greater chance of conceiving. However, such pregnancies remain a challenge, and should be attempted only in a hospital fully equipped with a perinatal care center.

Medical ethics have also changed in Japan, with more respect given to the patient's own wishes as to treatment policy, even when this may threaten the patient's life, as exemplified by the lawsuit regarding blood transfusion to followers of Jehovah's Witnesses. In this sense, the term "permission to conceive" suggest paternalism on the part of the doctor and should be reconsidered.

In assessing whether patients with chronic diseases should conceive, the doctor must provide the patient with as much currently available information as possible, fully explain the risks to the patient under the current level of medical care, and make assessments on the basis of the individual case while respecting as much as possible the patient's right to self-determination.

2. Timing of shift to obstetric management: Need for prepregnant obstetric management

Patients with chronic disease should be referred to an obstetrician prior to pregnancy, so that they can conceive under optimal circumstances, as is clear from the present case. If the patient is referred to obstetric care after conception has occurred, a difficult decision as to the propriety of artificial termination of the pregnancy may be necessary. In extreme cases, the internist in charge of the patient may provide an explanation of artificial termination of the pregnancy before referring the patient to an obstetrician. Such explanations involve delicate legal issues and can only be given by doc-

tors designated to do so under the Mother's Body Protection Law.

The management of pregnant women with chronic disease represents an area of patient care that is difficult for both internists and obstetricians, and appropriate management is often not provided. Specialists who have sufficient knowledge and experience in this border zone are thought to be indispensable. For instance, at Mie University, almost all management of pregnant women with diabetes, including insulin therapy, is carried out from the prepregnant stage by a diabetic treatment team of obstetricians. Another possible option is medical management of the pregnant woman by a maternity physician in a hospital that has a department of maternity medicine. In any case, in the management of pregnant women with chronic disease, it is important to provide team care from prepregnancy to postpartum, based on close cooperation among the departments of obstetrics and internal medicine, related departments, and co-medical areas.

Conclusion

The concepts of prerequisites for permissible pregnancy, importance of prepregnancy management, and need for cooperation among relevant departments have been discussed with an illustrative example case of pregnancy in a woman with chronic disease.

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Acute Abdomen in Pregnancy

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Abstract: The diagnosis and important aspects in treating acute abdomen tend to be delayed due to the peculiar physiological features of pregnancy and the restrictions imposed on image diagnostic techniques such as x-ray and CT. Physicians should pay attention in this regard as any delay may seriously deteriorate the condition of both mother and fetus. Detailed questioning of the patient and abdominal findings, especially information obtained by palpation, are considered essential in making a diagnosis and determining proper treatment. Ultrasonography is noninvasive to both the mother and fetus and is useful for diagnosing illness during pregnancy, including acute abdomen, acute appendicitis, and ileus. In treating the pregnant patient, high priority should be placed on improving the patient's condition and determining the necessity of surgery. Rather than postpone the decision to opt for surgery, the physician in charge is advised to seek additional professional opinions and enlist the support of other surgeons in order to arrive at earlier diagnosis and treatment.

Key words: Acute abdomen; Pregnancy

Introduction

Acute abdomen is a general term for "acute abdominal diseases accompanied primarily by sudden abdominal pain for which a decision to perform emergency surgery must be made in a very short time".[1] Causes of acute abdomen in pregnancy include ectopic pregnancy, peduncular torsion of an ovarian cyst, ovarian bleeding, and pelvic inflammation.[2] However, it may also be caused by such illnesses as acute appendicitis, ileus, and cholecystitis.[3] The specific physiological features of the mother and possible influences on the fetus have to be taken into consideration in the treatment of acute abdomen in pregnancy. Because of the pregnancy, restrictions are imposed on image diagnostic techniques such as x-ray and CT. Due to these considerations and restrictions, delay in diagnosis and treatment could lead to a serious condition in both the mother and fetus. Thus, prompt and appropriate decision-making and subsequent treatment are needed.

This paper addresses approaches to accurate diagnosis and the important aspects in the treatment of acute abdomen in the field of surgery.

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Table 1 Acute Abdomen Complications in Pregnancy in the Past 19 Years (1973.1～1991.12)

Disease/Case	Number of cases (%)	Age (mean age)
Acute appendicitis	40 (70.1)	20～35 years old (25.2)
Ileus [hernia impaction]	12 (21.0) [8 (14.0)]	21～40 years old (29.4) [22～39 years old (29.4)]
Peduncular torsion of ovarian cyst	3 (5.3)	22～34 years old (28.5)
Acute cholecystitis, cholangitis	2 (3.6)	38, 39 years old (38.5)
Total	57 (100.0)	20～40 years old (26.7)

(Inoue, M. *et al.*, "Acute abdomen during pregnancy." Progress of abdominal emergency treatment, 1992; 12: 900)

Acute Abdomen in Pregnancy

Acute abdomen in pregnancy may be caused by various illnesses not related to pregnancy. According to Inoue *et al.*, appendicitis accounts for 70.1% (including 10% complicated with perforating peritonitis) of the diseases that cause acute abdomen, followed by ileus (21.0%), peduncular torsion of ovarian cyst (5.3%), and acute cholecystitis and cholangitis (3.6%) (Table 1).[3] Acute pancreatitis[4] and ureterolith,[5] which also cause acute abdomen, are conservative treatment cases.

Approaches to Diagnosis

1. Auscultation

The symptoms observed in acute abdomen are often similar to digestive symptoms associated with pregnancy. In this regard, detailed questioning of the patient is necessary. The major symptom of acute abdomen is abdominal pain. As a first step, the causative disease should be determined on the basis of the site and characteristics of the abdominal pain as well as what the patient has eaten. Sudden, violent pain is characteristic of such occurrences as digestive tract perforation, mesenteric artery embolism, and ureterolith. Acute appendicitis starts with the pain and discomfort in the upper abdomen, which localizes in the lower right abdomen (the site later moves upward, corresponding to the gestational cycle). Acute cholecystitis and acute pancreatitis frequently occur after eating rich food. Information on associated symptoms, and descriptions of stools, as well as the patient's medical history are also helpful for diagnosis. If there is a post-surgical history and severe vomiting, ileus can be suspected. Tarry stools suggest the perforation of a duodenal ulcer. Bloody stools may indicate ischemic colitis or mesenteric artery embolism. Similar symptoms may have occurred several times in the past, in the case of acute cholecystitis, due to gallstones.

2. Physical findings

Abdominal findings, particularly those obtained by palpation, are indispensable for both diagnosis of the causative disease and determining proper treatment. Decisions to conduct emergency surgery or opt for conservative treatment, by placing the patient under observation, should be made on the basis of symptoms such as peritoneal irritation. Even if the laboratory test findings indicate no abnormalities, celiotomy should often be conducted when the peritoneal symptoms are severe. The Blumberg sign and muscular defense are important findings based on which the causative disease, the severity and the extent (localized or diffuse) of peri-

tonitis can be determined with reference to the site of most severe pain.

Diagnosis is often made more difficult during pregnancy due to the deviation of organs caused by an enlarged uterus and relaxation of the abdominal wall. It is a well-known fact that the position of the appendix shifts upward and to the right with the progress of gestation.[6] This makes it difficult to differentiate appendicitis from acute cholecystitis and duodenal ulcer perforation. In addition to acute abdominal pain, the absence of bowel sounds during auscultation is an important finding indicating panperitonitis. Spread of inflammation into the pelvis can be suspected if rectal probing causes tenderness at the Douglas pouch.

3. Laboratory findings

(1) Blood test

An increase in the leukocyte count is to be expected in the case of acute abdomen associated with infection. However, the leukocyte count often exceeds 10,000/mm^3 during pregnancy.[7] Accordingly, increases in the neutrophil count and CRP also have to be taken into consideration. The leukocyte count increases along with the deterioration of the condition, further decreasing the count rather than increasing it so that it is not advisable to judge the degree of inflammation based on leukocyte count alone. In addition, deterioration in pathology may lead to sepsis and the complication of disseminated intravascular coagulation (DIC). Because of this, it is necessary to check the platelet count and the coagulation system. Biochemical tests are conducted to check for the presence of any hepatic, cholangial and pancreatic diseases and to check renal function.

(2) Abdominal ultrasonography

Ultrasonography is the first choice in making a diagnosis of acute abdomen in pregnancy because it is non-invasive to both the mother and fetus and because a large amount of information can be obtained by this simple procedure.

Appendicitis: Acute appendicitis is suspected if a swollen appendix (short axis diameter of 6 mm) is imaged at the point that corresponds with the tenderness. In this case, the inflammation is considered to have reached or exceeded the phlegmonosa. When the layer structure becomes obscure, gangrenous appendicitis is suspected. Imaging of stool stones is also helpful in the diagnosis. In the case of catarrhal appendicitis, however, the appendix is not detected and the finding is difficult to obtain. A low echo site in the periphery indicates the presence of abscess, and the findings including the retention of ascites, thickening of the peripheral intestinal wall, and the intestinal tract dilated by palsy of peristalsis indicate the spread of inflammation into the periphery (Fig. 1).[8]

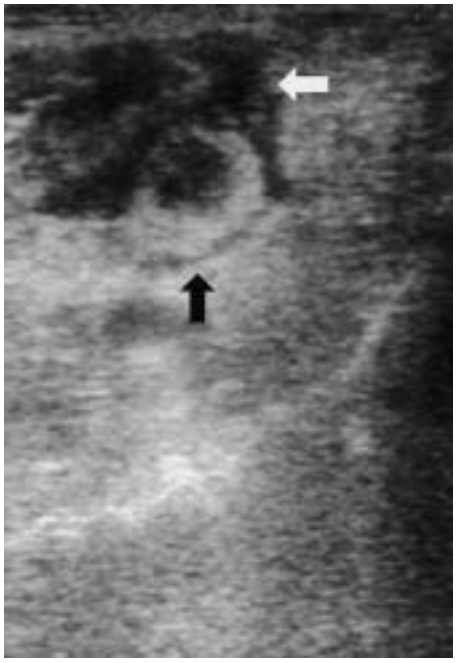

Fig. 1 Ultrasonography of acute appendicitis
Swollen appendix (⬆) and abscess (⇦) in the periphery

Ileus: Characteristic ultrasonography findings of simple ileus include dilated intestinal tract and full intestinal image as well as intestinal folds (the keyboard sign) (Fig. 2-a).[8] Ultrasonography is useful for the diagnosis of ileus in which the x-ray detects scarcely any gas. When ileus is clinically suspected, ultrasonography should definitely be conducted. By check-

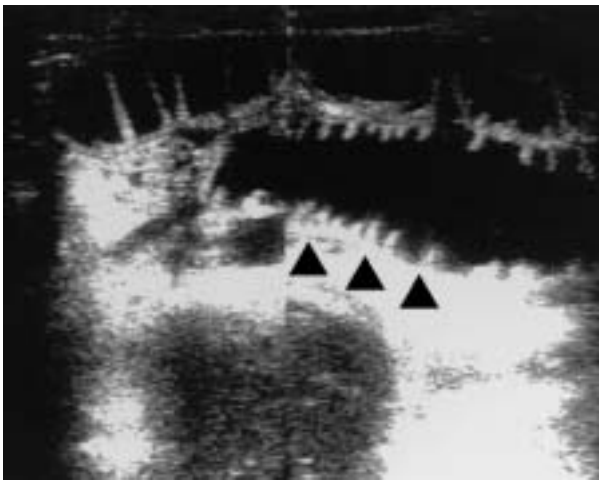

Fig. 2-a Ultrasonography of simple ileus
Dilated intestinal tract and intestinal folds (keyboard sign, ▲) are observed.

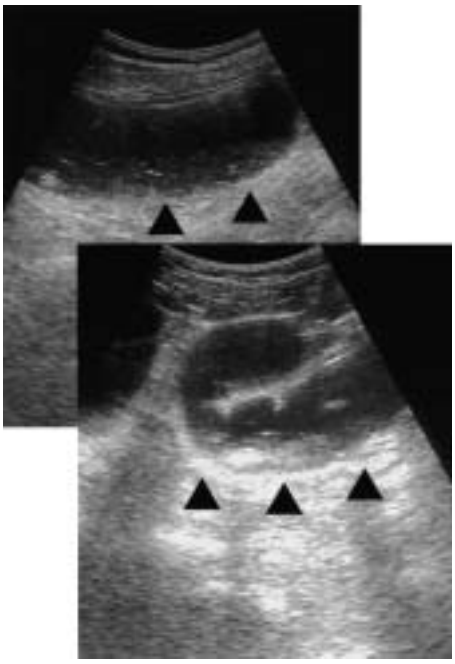

Fig. 2-b Ultrasonography of strangulated ileus
Intestinal folds (keyboard sign) become obscure (▲).

ing the to-and-fro movement of the intestinal contents, it is possible to detect the presence or absence of intestinal peristalsis. If peristalsis is present, it is mechanical ileus. If it is absent, it is paralytic ileus.

If the above symptoms are accompanied by an obscure keyboard sign, disappearance of to-and-fro movement and ascites retention, strangulated ileus is conceivable (Fig. 2-b).

Other cases: In the case of ureterolith, dilated renal pelvis and urinary tract are imaged. It is also useful in the differential diagnosis of acute cholecystitis as well as hepatic, cholangial and pancreatic diseases.

(3) **Abdominal x-ray**

To avoid any influence on the fetus, x-rays of the abdomen are taken only when necessary. However, if the condition of the mother and fetus requires emergency treatment or surgery, x-rays should be taken regardless of the pregnancy. If abdominal free air and niveau are revealed, the physician may diagnose the patient as having a digestive tract perforation or ileus. However, attention should be paid to cases of serious strangulated ileus showing less intestinal gas.

(4) **Abdominal centesis**

A description of ascites (bloody or purulent) is helpful to make a diagnosis and evaluation of severity. A safe site for centesis is sought by ultrasonography and the ascites are collected by centesis from the patient under local anesthesia. The scope of applications for ultrasonography is extensive.

Important Points in the Treatment

1. Improvement of the systemic condition

First, the systemic condition of the patient is investigated based on vital signs such as circulatory pattern, respiratory condition, and presence of fever, then measures are taken to facilitate improvement in the systemic condition. It should be remembered that prolonged hypotension, hypoxemia, and acidosis may result in the death of the fetus.

2. Cooperation with other departments

As pregnancy is a special condition, acute abdomen requires accurate diagnosis as well as prompt and appropriate treatment. In severe

cases, where the patient has gone into shock or the case is complicated with peritonitis, delay in treatment may result in a poor prognosis for the mother and fetus. Physicians are advised to place high priority on improving the patient's condition and determining the necessity of surgery. When diagnosis is difficult, it is best to enlist the cooperation of other surgeons to facilitate early diagnosis and treatment.

Conclusion

This paper has described the approaches to diagnosis and the most important points in the treatment of acute abdomen in pregnancy. The specific physiological features of pregnancy and any influence on the fetus have to be taken into consideration in the treatment of acute abdomen in pregnant patients. Furthermore, restrictions are imposed on making diagnoses. Due to these considerations and restrictions, delay in diagnosis and treatment could lead to a serious condition in both mother and fetus. Thus, it is necessary to be in close contact with a surgeon for multidisciplinary diagnoses and treatment.

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Environmental Factors and Fetal Abnormalities

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Abstract: Studies on fetal anomalies related to environmental factors were initiated in the 1950s after malformations were found to be caused by various chemicals and phocomelia was caused by thalidomide. Currently, the most controversial topic in this field is the issue of endocrine disruptors. The causes of reproductive and developmental anomalies can be classified as genetic or environmental. The anomaly is genetic in about 25% of cases, environmental in 10%, and multifactorial (both mechanisms combined) in 65%. Among the environmental factors, viruses cause 3%, maternal disorders cause 3–4%, and mechanical factors account for 1–2%. Anomalies caused by drugs and chemicals account for only about 1%. Teratogenic agents may induce congenital malformations when exposure occurs during organ development period (gestational weeks 2–14). Exposure before the period of organogenesis results in infertility or fetal/embryonic death, whereas exposure after this period gives rise to organ dysfunction. The levels of endocrine disruptors to which the general population are exposed are currently within the respective safety ranges and are several hundred-fold lower than the estimated maximum tolerable doses.

Key words: Reproductive toxicity; Developmental toxicity; Teratogenicity; Endocrine disruptors; Environmental factors; Fetal anomalies

Environmental Factors and Fetal Anomalies: History and Scientific Background

In pregnancy, both the mother and the unborn baby are very sensitive to various chemicals, so they need to be protected from numerous environmental factors. This is a long-established concept. Although it was long ago demonstrated by various animal experiments that some environmental factors were teratogenic, no human teratogenicity was documented until 1941 when the Australian ophthalmologist Gregg reported the congenital rubella syndrome.

In the 1950s, various agents, including hormones and anticancer drugs, were successively

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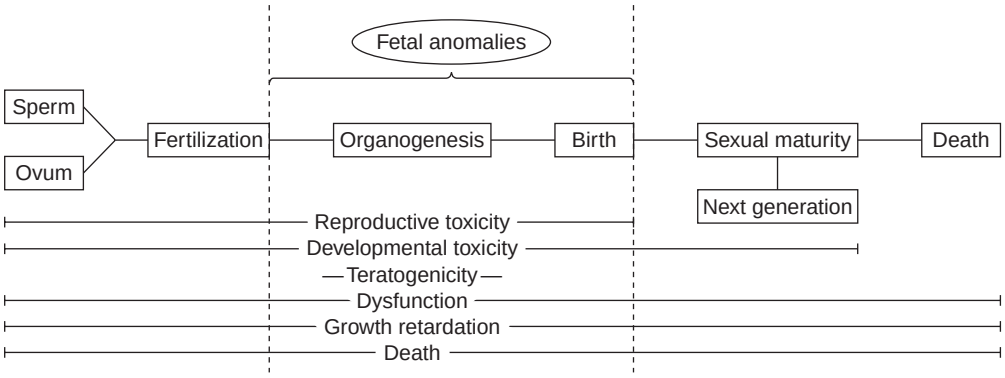

Fig. 1 Concept of reproductive and developmental toxicity and fetal anomalies
Fetal anomalies are included in the category of reproductive toxicity. When fertilized ova and undifferentiated embryos are exposed to toxic environmental factors, such exposure results in infertility or embryonic death (spontaneous abortion). Consequently, fetal anomalies mainly consist of malformations. Some types of dysfunction (including growth retardation) are also included.

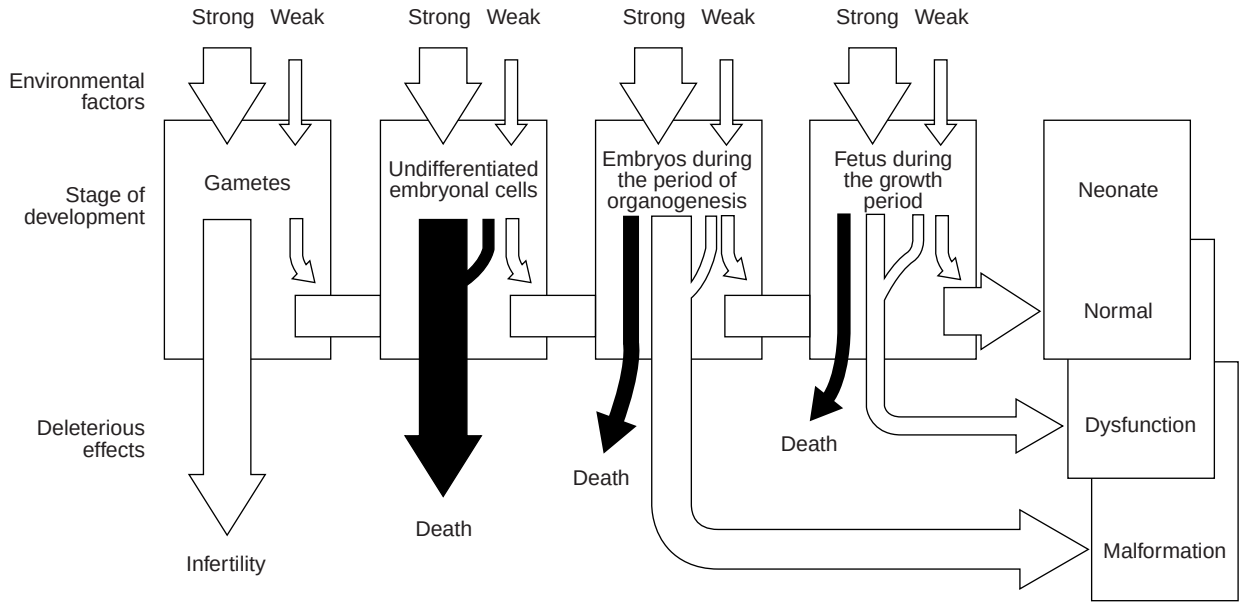

Fig. 2 Effects of environmental factors on the embryo and fetus
Exposure of gametes or embryos to environmental factors may cause sterility and death, respectively. Exposure during the period of organogenesis and later fetal life results in malformation or dysfunction, respectively.

reported to be teratogenic in humans. In 1961, it was found that the hypnotic thalidomide had caused phocomelia, with the worldwide number of victims totalling more than ten thousand. This triggered off full-scale investigation and research into the field of teratogenicity. Subsequent detection of fetal Minamata disease was followed by confirmation of the toxic effect of a synthetic estrogen (diethylstilbestrol (DES)) on fertility and the reproductive organs in the 1970s. From the 1980s onwards, concerns were raised by "Our stolen future" (a monograph on the reproductive disorders occurring in wildlife) and other reports, while a decrease of the

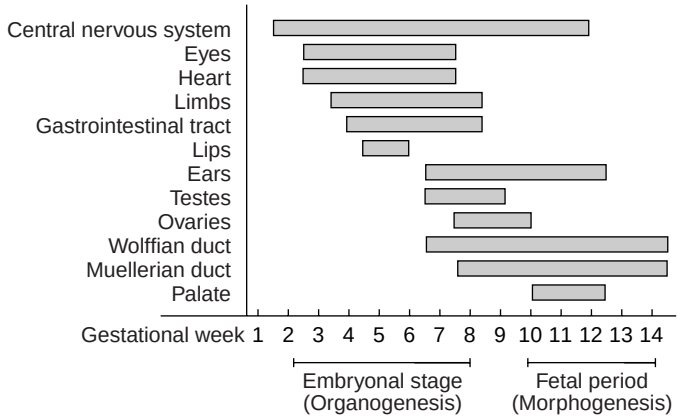

Fig. 3 Organogenesis and morphogenesis in humans[2)]
Exposure to environmental factors during these periods results in malformations.

sperm count in humans was reported in 1992 by Skakkebaek. As a result, people began to develop apprehension about endocrine disruptors.

Various terms have been used to describe fetal abnormalities, ranging from congenital anomalies and congenital malformations to fetal toxicity and the more comprehensive concept of reproductive and developmental toxicity, resulting in considerable confusion. These concepts can be defined as shown in Fig. 1. The term "fetal anomalies" has mainly been used in relation to teratogenicity.

The risk of embryonic or fetal anomalies being caused by environmental factors varies widely depending on the stage of fetal development. Each organ is only vulnerable to malformation when exposure occurs during its development (Fig. 2). Soon after implantation (up to 2 weeks in humans), an undifferentiated embryo consists of cells that are all equally sensitive. When exposed to a teratogen, such early embryos either die and are absorbed or continue to develop normally depending on the strength of the harmful effect. In contrast, exposure during the periods of organogenesis and morphogenesis results in malformations. During the subsequent fetal period, exposure may either result in death or in the induction of functional abnormalities. In humans, the organs are formed and develop as shown in Fig. 3.

Causes of Fetal Anomalies

Reproductive and developmental toxicities can be classified into three groups depending on the causative mechanism, which are genetic, environmental, and mixed. If all congenital anomalies are assessed irrespective of the causative mechanism, the contributions of genetic and environmental factors alone or in combination are estimated to be shown in Table 1a. Although congenital malformations caused by drugs and chemicals have attracted much attention, they account for only about 1% of the total. Multifactorial anomalies have no specific cause, with genetic and environmental factors apparently cooperating with each other in such cases.

The major environmental factors recognized to date and their reproductive and developmental toxicities are listed in Table 1b. This table shows that each of the environmental factors causes characteristic malformations when pregnant women are exposed during the periods of organogenesis and morphogenesis. The relationship between pregnancy and drugs is described in detail in a separate article of this series.

Table 1 Categorization of Birth Defects in Humans (a) and a List of Major Causative Factors (b)

a: Categorization of congenital anomalies (Brent, 1979)[3)]

Genetic	Genetic mutations	20%
	Chromosomal aberrations	5%
Environmental	Fetal infection (mainly viruses)	3%
	Maternal disease (endocrine and metabolic abnormalities, etc.)	3–4%
	Mechanical factors	1–2%
	Drugs and chemicals	1%
Multifactorial		65%

b: Major causative factors (cited from the literature)

I. Drugs	Major abnormalities
Thalidomide	Malformations of four limbs
Diethylstilbestrol	Vaginal cancer
Synthetic corpus luteum hormone	Masculinization
Warfarin (anticoagulant)	Nasal hypochondroplasia, abnormalities of the central nervous system
Hydantoin (anticonvulsant)	Facial anomalies, microcephaly, mental retardation
Trimethadione (anticonvulsant)	Growth retardation, cleft lip, cleft palate
Aminopterin (folate antagonist)	Spontaneous abortion, hydrocephalus
Streptomycin	Hearing loss
Tetracycline	Dental pigmentation, enamel hypoplasia
Valproic acid	Neural tube defects
Vitamin A acid	Cranial and facial anomalies, neural tube defects
Lithium	Cardiac malformations
Anti-thyroid drugs	Hypothyroidism, thyroid tumors
II. Infection	
Rubella	Hearing loss, cataract, cardiac malformations
Cytomegalovirus	Growth retardation, mental retardation, hearing loss
Toxoplasma	Hydrocephalus, visual disorders, mental retardation
Chickenpox	Muscular atrophy, mental retardation
Venezuelan equine encephalitis	Cerebral defects, cataract
Syphilis	Dental anomalies, skeletal anomalies, mental retardation
III. Industrial chemicals	
Lead	Infertility, spontaneous abortion, mental retardation
Mercury	Stillbirth
Methyl mercury	Cerebral palsy, microcephaly
PCB	Spontaneous abortion, stillbirth, pigmentation of skin and teeth
Organic solvents (e.g., toluene)	Low birth weight, birth defects
Ethylene glycol	Spontaneous abortion, infertility (decreased sperm count), birth defects
Cadmium	Infertility, delayed neurological development
Heat	Infertility, decreased sperm count
Radiation	Microcephaly, mental retardation
Other chemicals that may decrease the sperm count: dibromopropane, dibromochloropropane, etoxyethanol, methoxyethanol, boron, carbon disulfide, etc.	
IV. Others	
Alcoholic beverages	Growth retardation, microcephaly, mental retardation
Tobacco smoking	Spontaneous abortion, intrauterine growth retardation
Diabetes mellitus	Congenital heart disease, malformations of the lower trunk
Iodine deficiency	Thyroid tumors, mental retardation, growth retardation
Maternal phenylketonuria	Microcephaly, mental retardation

Table 2 Developmental and Reproductive Disorders Caused by Endocrine Disruptors in Humans

- Possible effects to which the general population is considered vulnerable. The causal relationship remains to be fully investigated and has not yet been adequately established.
  - Decreased sperm count
  - Cancer (hormone-dependent tumors, including those of the breast, cervix, ovaries, prostate, and testes)
  - Endometriosis and infertility
  - Immune disorders and allergic diseases
  - Congenital anomalies (anomalies of the reproductive organs, low birth weight, spina bifida, etc.)
  - Growth disturbance (abnormal psychological development, low IQ, delayed sexual maturation, etc.)
  - Neurological abnormalities (including behavioral disorders and Parkinson's disease)
- Disorders observed in individuals and workers after excessive exposure
  - Vaginal and testicular cancer (DES)
  - Decreased sperm count (bromopropane, ethylene glycol, etc.)*
  - Reproductive disorders (heavy metals, chlorophane etc.)*

*Direct reproductive toxicity rather than that mediated by hormones

Recent Topics

1. Effects of endocrine disruptors on the human fetus

Endocrine disruptors exert a toxic effect mainly by binding to the estrogen receptors on cells and thus suppressing or enhancing the actions of estrogens. Theoretically, these agents are considered to have reproductive toxicity. Endocrine disruptors which may have effects in humans are listed in Table 2. Because the effects caused by excessive exposure are considered to be attributable to direct toxicity, the toxic effects listed in this table are still a matter of conjecture, except for those caused by DES.

The results of toxicity studies on the major endocrine disruptors documented in the literature are summarized in Table 3. Only dioxins, which are endocrine disruptors in a broad sense, have been reported to cause toxicity in humans, while toxicity data for the other agents have only been obtained in animal experiments and no studies have been done in humans. Endocrine disruptors other than dioxins have a very weak estrogenic activity and the maximum tolerable doses for reproductive toxicity (estimated from the respective minimum doses causing reproductive toxicity) are extremely high among those verified so far. The maximum tolerable dose equals the maximum ineffective dose (minimum reproductive toxic dose estimated in animals $\times 1/10) \times 1/100$. The concentrations of such substances in river water collected in Japan were very low and only very small amounts were released from containers in leakage tests. Consequently, the safety ranges estimated from their maximum tolerable doses for reproductive toxicity and their daily tolerable intake are extremely broad in humans.

The reproductive toxicity data obtained in general toxicity studies performed by certain researchers has raised the greatest controversy.[5,6] Because the toxicities reported were not reproduced when the same experiments were repeated for validation, it remains unclear whether such chemicals can have reproductive toxicity or cause damage to the fetus at very low concentrations.

For dioxins, toxicity data obtained in humans are available. Even at blood levels that are 20 to 100 times higher than those observed in community-based populations, these agents have no apparent reproductive toxicity.

2. Human reproductive dysfunction caused by bromopropane

In a Korean factory where electronic parts are produced, workers in a section where 2-bromopropane was used as an alternative to chlorofluorocarbons for washing recently developed reproductive dysfunction (Table 4). Female victims had amenorrhea and male vic-

Table 3 Reproductive Toxicity of Endocrine Disruptors

	Activity relative to female E_2	Estimated maximum tolerable dose for human reproductive toxicity ($\mu g/kg/day$)[a]	Tolerable daily intake in humans ($\mu g/kg/day$)[b]	River water			Leakage test		
				Highest measured concentration ($\mu g/l$)×2l (day)= Maximum daily intake[c]	Safety range		Maximum concentration determined by leakage test ($\mu g/l$)×2l (day)= Maximum daily intake[d]	Safety range	
					Ratio to maximum tolerable dose for reproductive toxicity	Ratio to TDI		Ratio to maximum tolerable dose for reproductive toxicity	Ratio to TDI
Estradiol (E_2)	1	0.16	—	0.001	160	—	—	—	—
DES	50	0.008	—	—	—	—	—	—	—
Nonyl phenol	0.0018	20.8 (30)[e]	—	0.076	274	—	—	—	—
Octyl phenol	0.001	400	—	0.02	20,000	—	—	—	—
Bisphenol	0.00025	437 (2–20)[e]	50	0.06	7,300	833	0.2	2,185	250
Phthalic acid (BBF)	0.000004	555	1,000	0.052	10,700	19,230	2.6	1,923	385

Dioxins (TCDDs)	Blood level (pg/g fat)	Effects in humans
General population	1–5	—
Persons exposed for 1 year or less	114	No increase in the frequency of spontaneous abortion
Persons exposed for 15 years or longer	148	Luteinizing hormone ↑, testosterone ↓
Victims of the Seveso accident:		
Mothers	>126	Birth of only girls
Fathers	>104	
Victims of the Seveso accident	15–443	No increase in the incidence of malformations during the 6-year period after exposure
Vietnam veterans	>130	No abnormalities of testosterone and test
Vietnam veterans (Fathers)	79–1,425	A few spontaneous abortions, no growth retardation

a) The maximum tolerable dose for reproductive toxicity in humans is defined as follows: Maximum no-effect dose (i.e., minimum reproductive toxic dose ×1/10)×1/100.

b) Official values calculated based on characteristic general toxicity data.

c) The value estimated based on the highest measured concentration determined by the Ministry of Construction (1998) with the assumption that people drink 2 liters of water a day.

d) The value estimated based on the highest concentration determined by leakage tests with the assumption that people drink 2 liters of water a day.

e) Cited from studies conducted by von Saal[5] and Sharpe.[6] The minimum toxic dose for maternal animals giving birth to offspring having testes of abnormal size. Neither these nor other researchers have verified the results.

(This table contains data compiled from many sources.)

Table 4 Decreased Reproductive Function (Female Ovarian Function and Male Spermatogenesis) in Korean Factory Workers from the Tactile Switch Assembly Section Who Were Exposed to 2-Bromopropane

Type of work		Number of workers	Not affected	Victims			
				Reproductive hypofunction alone	Myelo-suppression alone	Both effects	Total (Incidence)
Tactile switch assembly	Men	8	2	5	—	1	6 (75.0%)
	Women	25	8	11	—	6	17 (68.0%)
Other switch sections	Men	12	2	—	—	—	—
	Women	65	65	—	—	—	—

Takeuchi (1997)[7]

tims showed a decrease of the sperm count. In rats exposed to 2-bromopropane at concentrations of 300 ppm or more for 8 hours a day for 9 weeks, similar disorders were detected. Of 17 female victims, only 2 resumed a normal menstrual cycle and one of them gave birth to a normal baby. However, toxicity persists in other women.

In this article, the history and current state of knowledge about fetal anomalies related to environmental factors, particularly chemicals, were summarized. Reproductive and developmental toxicity will remain one of the most important subjects for toxicological research in the future. It is hoped that such studies will be accomplished so that the results can be utilized clinically.

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Antiphospholipid Antibody Syndrome and Pregnancy

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Abstract: It is well known that positive serologic tests for syphilis do not necessarily indicate the presence of syphilis, but may be biological false positive (BFP) cases. The antigen used in serologic tests for syphilis is cardiolipin extracted from the bovine heart, and it has become apparent that the presence of anticardiolipin antibody in the blood is related to a series of disease states. BFP results have attracted particular attention in relation to SLE, and the relation between abortion in SLE patients and antiphospholipid antibodies has been examined. In addition to abortion, thrombocytopenia and arterial or venous thrombosis may occur. Recent studies of antiphospholipid antibodies have led to the establishment of antiphospholipid antibody syndrome (APS). The relation between APS and habitual abortion (intrauterine fetal death) is clinically significant. Prophylactic treatment is necessary for patients with APS who have a past history of abortion. Further investigations are awaited that will clarify the mechanism of thrombosis and its relation with abortion and premature delivery in APS.

Key words: Antiphospholipid antibody syndrome; Anticardiolipin antibody; Lupus anticoagulants; Habitual abortion

Introduction

Pathological conditions associated with autoantibodies against phospholipids are frequently complicated by arterial or venous thrombosis, habitual abortion, and thrombocytopenia.

It is a common knowledge that serologic test results for syphilis include false-positive cases in addition to true syphilis cases. Such cases are called biological false-positive (BFP) cases. BFP cases are also seen in malaria, tuberculosis, and viral hepatitis as well as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). In SLE in particular, BFP cases account for about 25% among them, and the revised 1982 American Rheumatism Association (ARA) criteria for systemic lupus erythematosus (SLE) include a description of these BFP cases. The antigen used for the syphilis test is cardiolipin extracted from the bovine heart.

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Positive tests denote the presence of anticardiolipin antibody in blood.

It was well known that patients with SLE who become pregnant are apt to suffer from abortion or stillbirth, and then an attention to the relation between SLE and antiphospholipid antibodies has been drawn. Antiphospholipid antibodies have also attracted attention in the field of obstetrics and gynecology, because of the fact that many women who have a past history of habitual abortion or intrauterine fetal death are positive for antiphospholipid antibodies.

Antiphospholipid antibodies initially were considered to be antibodies against phospholipids themselves, including cardiolipin. In recent years, however, studies have revealed that many of them are not antibodies to phospholipids themselves but to serum proteins bound to phospholipids. Blood coagulation disorder caused by autoantibodies related to phospholipids and various resultant types of thrombosis are clinically important and have become known as antiphospholipid syndrome (APS).

This paper discusses APS in relation to pregnancy.

What is Antiphospholipid Antibody Syndrome (APS)?

Antiphospholipid antibody syndrome is a syndrome characterized by clinical findings of arterial or venous thrombosis, neurological symptoms, habitual abortion, and thrombocytopenia in persons positive for antiphospholipid antibodies such as anticardiolipin antibody and lupus anticoagulants (LA).

Although SLE frequently underlies APS, APS may also occur in collagen diseases such as progressive systemic sclerosis (PSS), mixed connective tissue disease (MCTD), and overlap syndromes. These conditions are known as secondary APS. Among the antiphospholipid antibodies, anticardiolipin IgG antibody is detected in as many as 40% of patients with SLE. Hence, the clinical significance of antiphospholipid antibodies has been discussed with attention centered on SLE. In fact, these features have led to further revision of the criteria for the classification of SLE. In the revised criteria of SLE, reaction to LE cells was deleted because, by itself, this reaction is of little diagnostic value. False-positive syphilis test was also eliminated, and positive antiphospholipid antibodies (anticardiolipin antibody and LA) were added instead.[1] This means that the complication of APS should be taken into consideration when diagnosing SLE.

In contrast, APS occurring without a definite diagnosis of underlying disease is called primary APS. It has been reported that the prevalence of autoantibodies other than antiphospholipid antibodies is low in primary APS patients and that the titer of antinuclear antibody, if present, is low, with the absence of any specific antinuclear antibody.[2] When these seemingly healthy antiphospholipid antibody-positive women without any underlying disease (primary APS patients) conceive, abortion and intrauterine fetal death become significant issues.

In addition, another type of APS is attracting particular attention, namely, catastrophic APS, which is characterized by abrupt onset and poor prognosis.[3] In catastrophic APS, multiple arterial or venous thromboses occur in various organs, including the kidney, possibly accompanied by cerebrovascular disorder and consciousness disturbance in the central nervous system, acute respiratory distress syndrome (ARDS) in the respiratory system, and infarctions in the liver, digestive tract, and adrenal glands. Catastrophic APS reportedly often manifests with pregnancy or surgery serving as a trigger in patients in whom APS has been present.

Although APS presents a diverse clinical picture, it is based on thrombosis, with thrombus formation occurring in various arterial and venous systems. Table 1 shows the major clinical symptoms of APS. Thrombosis in APS is

Table 1 Major Clinical Symptoms of APS

Central nervous system	cerebral infarction (multiple, recurrent), TIA, dementia, migraine, spasm, etc.
Circulatory system	myocardial infarction, left heart valvular disease
Respiratory system	pulmonary infarction, pulmonary hypertension
Kidney	renal arterial thrombosis, renal venous thrombosis, renal hypertension
Digestive system	mesenteric arterial thrombosis, Budd-Chiari syndrome, hepatic venous thrombosis
Skin/peripheral vascular system	livedo reticularis, deep venous thrombosis (DVT), thrombophlebitis of lower limbs, gangrene of extremities
Eyes	retinal arterial and venous thrombosis, amaurosis fugax
Perinatal disorders	habitual abortion, intrauterine fetal death
Blood	thrombocytopenia, hemolytic anemia, DIC
Others	Addison's disease, nasal septum perforation, aseptic bone necrosis

characterized by recurrent thrombi at multiple sites. It is reported that recurrence is found on the same side as the initially affected side in about 91% of patients within 12 months after onset.[4)]

The responsiveness of antiphospholipid antibodies to antigens is also diverse. This diversity of antiphospholipid antibodies is thought to be the reason why APS is difficult to understand.

Initially, the concept of anticardiolipin syndrome was proposed by Hughes and Harris *et al.* (1986) on the basis of the results of clinical research on bovine cardiolipin used in BFP serologic syphilis tests. Since then, the diversity of antiphospholipid antibodies has become apparent. The most notable feature is that antiphospholipid antibodies do not recognize phospholipids themselves and are detected in the presence of a cofactor, β_2-glycoprotein I (β_2-GPI). Therefore, they are called β_2-GPI-dependent anticardiolipin antibodies, or anticardiolipin-β_2-GPI complex antibodies. In addition, it was found that they are not antibodies to cardiolipin, but are antibodies to β_2-GPI bound to cardiolipin.[5)] In other words, the antibodies previously thought to be antiphospholipid antibodies are in actuality anti-β_2-GPI antibodies, and β_2-GPI seems to cause abnormality in the response of the coagulation-fibrinolytic system through binding to antibody. The abnormality of this response is generally oriented to hypercoagulability, leading to thrombus formation. On the other hand, phenomena of inhibited coagulation, such as prolongation of activated partial thromboplastin time (APTT), are seen *in vitro*. These conflicting findings add complexity to the study of APS.

β_2-GPI is a plasma protein known as apoprotein H, a basic glycoprotein with a molecular weight of 50–kDa and pI of 6.5–7.0 that is composed of 326 amino acid residues. It is synthesized in the liver, and its normal concentration in plasma is about 200 μg/m*l*. β_2-GPI is composed of five repeated domains; the cardiolipin binding site is considered to be in the fifth domain, and the antigen determinant is located in the fourth domain.[6)]

LA are autoantibodies that prolong phospholipid-dependent coagulation time, while not inhibiting the activity of each coagulation

Table 2 Revised APS Classification Criteria

Clinical criteria

1. Thrombosis
2. Gestational complications
   (a) Intrauterine fetal depth of unknown etiology at or after the 10th week of gestation, or premature delivery of the fetus before the 34th week of gestation due to severe preeclampsia, eclampsia, or poor growth of the placenta.
   (b) Three or more consecutive miscarriages before the 10th week of gestation.

Laboratory criteria

1. Anticardiolipin IgG or IgM antibody is detected as β_2-GPI-dependent anticardiolipin antibody on 2 or more occasions at intervals of 6 weeks or more.
2. LA are detected by the standard method on 2 or more occasions at intervals of 6 weeks or more.

When at least one clinical criterion is met and at least one laboratory criterion is also met, the case is classified as APS.
There are no exclusion criteria

factor. Since the presence of such anticoagulants in SLE has been known for some time, they were named lupus anticoagulants. In fact, it has been reported that about 25–65% of patients with SLE are positive for LA.

Although APTT is a suitable index for the LA screening test, it lacks specificity because normal APTT does not necessarily deny LA positivity and because APTT may also be prolonged in other diseases. Therefore, when LA positivity is a possibility, as in suspected collagen disease or thrombosis, a mixing test of kaolin clotting time (KCT) and determination of dilute Russell's viper venom time (dRVVT) are required. If one of these two is positive, the case is judged to be positive for LA.

Prothrombin and β_2-GPI have been reported to be the antigens responsive to LA. However, there are a variety of the corresponding antigens, and it is also possible that different antigens are recognized in different measurement systems. In addition, the measurement systems have yet to be standardized.[7)]

Antiphospholipid antibodies thus show considerable diversity. Proteins reported as homologous antigens to antiphospholipid antibodies include annexin V, protein C, protein S, kininogen, and factor X. In view of this, some researchers advocate the use of the name "antiphospholipid-protein antibodies" rather than "antiphospholipid antibodies."[8)]

A diagnosis of APS is made on the basis of laboratory findings and clinical findings of various types of thrombosis and other pathological conditions. The diagnostic criteria proposed by Harries *et al.* (1996) had been used until the revised classification criteria that underlie the serologic test were proposed in 1998 (Table 2).[9)]

Relationship with Habitual Abortion (Intrauterine Fetal Death)

After a report documenting that abnormal coagulability and placental infarction were found in patients with habitual abortion,[10)] it became apparent that habitual abortion is common in women who are positive for LA or anticardiolipin antibody. This finding contributed much to the APS disease concept. Currently, positive antiphospholipid antibodies are regarded as a risk factor for spontaneous abortion in the first trimester of gestation and for intrauterine fetal death in the second and third trimesters. Pregnant women positive for these antibodies may experience fetal loss by the mid-gestational period, regardless of the type of underlying disease. If anticardiolipin-positive patients are left untreated, intrauterine

fetal death occurs in about 70% of them.[11] Therefore, measurement of antiphospholipid antibodies is necessary for pregnant women who have a past history of abortion in order to identify and treat those with APS.

However, since some women with positive anticardiolipin antibody do not experience habitual abortion, the mechanism of action of this antibody on pregnancy is not a simple one. The diversity of the antibody and problems involved in antibody measurement systems should also be considered here.

Although about 70% of SLE patients with habitual abortion are positive for anticardiolipin antibody,[12] the prevalence in those with habitual abortion who have no underlying disease is only 13%.[13] This suggests that anticardiolipin antibody is deeply involved in the occurrence of habitual abortion in SLE.

The mechanisms by which antiphospholipid antibodies cause intrauterine fetal death have yet to be clarified. The dominant theory ascribes such deaths to placental infarction, namely, thrombosis. Although decreased growth of the placenta and increased fetal mortality have been observed in animal experiments using monoclonal anticardiolipin antibody, much remains for further investigation.

The involvement of antiphospholipid antibodies has been suggested in the manifestation of gestational toxicosis, for which the cause remains unclear.[14] In this connection, the question arises as to whether or not measurement of antiphospholipid antibodies, particularly β_2-GPI-dependent anticardiolipin antibody, is useful for screening the general population of pregnant women for the purpose of predicting the course of gestation. Although this issue remains controversial, some consider that screening should be implemented to predict gestational prognosis at an early stage of pregnancy in the general population of pregnant women and early in pregnancy or, if possible, in prepregnancy in the high-risk population.[15] At present, it seems reasonable to determine antiphospholipid antibodies in obstetrically selected patients.[16] The American College of Obstetricians and Gynecologists (ACOG) recommends that patients with abnormal pregnancy be screened for APS and autoimmune disease through examination for antiphospholipid antibodies and antinuclear antibodies in the puerperal period.[17]

Treatment

To prevent thrombosis and intrauterine fetal death in patients with APS, anticoagulant or antiplatelet drug therapy is effective. In general, pregnant women who have positive antiphospholipid antibodies but no history of abortion are not candidates for treatment. If a woman has experienced even a single abortion, prophylactic treatment is indicated.[18]

Up to now, combination therapy with prednisolone (40–60 mg/day) and low-dose aspirin (75 mg/day) as proposed by Lubbe *et al.* has been employed,[19] with the efficacy rate reported to be 60–75%. However, it has been reported that aspirin monotherapy (50–100 mg/day), subcutaneous heparin injection (10,000–40,000 U, mean 25,000 U/day), or a combination of aspirin and heparin, without prednisolone therapy, is equally effective. In view of possible adverse reactions, combination therapy with aspirin and heparin is thought to be superior to the combination of prednisolone and aspirin. However, favorable results have also been obtained with decreased doses of prednisolone as compared with the original dose of Lubbe *et al.* and with prednisolone therapy initiated in prepregnancy and continued during pregnancy at decreased doses. In Japan, subcutaneous heparin injection is not preferred, and it appears that combined therapy with a steroid and aspirin is commonly used for patients with primary APS.[18]

However, many of the patients in whom treatment is effective have primary APS not complicated by SLE. Fetal death may not be prevented in patients who have APS complicated by SLE.

It is necessary to carefully observe the growth of the fetus by ultrasonography or other means while monitoring variations in the antiphospholipid antibody titer in pregnant women with APS.

Conclusion

The pathological condition known as APS was designated on the basis of two clinical findings; (1) the presence of BFP cases among those with SLE and (2) the high incidence of abortion among SLE patients. In addition, the abnormal coagulability (LA) that is well known in SLE patients corroborated the clinical picture of APS. It then became apparent that antiphospholipid antibodies, which had attracted the attention of researchers in the fields of collagen disease and the blood coagulation system, are involved in important clinical events, such as habitual abortion and infertility, thereby drawing researchers in obstetrics into this field of study.

It has been little more than ten years since the disease concept of APS was formed. Elucidation of the diversity of antiphospholipid antibodies, the search for homologous antigens, and the standardization of measurement systems await further investigations. In addition, future developments in research on the relation between the mechanisms of thrombus formation and the cause of abortion and premature delivery are expected, in light of the issue of prophylactic treatment.

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