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Effects of Environmental Factors on Perinatal Outcome: Neurological Development in Cases of Intrauterine Growth Retardation and School Performance of Children Perinatally Exposed to Ionizing Radiation

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We performed two studies to investigate environmental factors in relation to neurological development in infants. The first, a field study, examined the elementary school performance of 929 children who were born from mothers exposed to the atomic bombing of Hiroshima, Japan, August 6, 1945. The most severe mental retardation was observed in the group exposed between 8 and 15 weeks following fertilization, and the second most severely damaged group was exposed between 16 and 25 weeks. The second, a clinical investigation, examined infants in the perinatal center who survived intrauterine growth retardation (IUGR). Those who survived with abnormal neurological development had a mean growth arrest corresponding to a uterine height of 27 weeks of gestation. This was at an earlier stage than those who survived with normal neurological development and had a mean growth arrest corresponding to 29–30 weeks of gestation. A smaller head circumference at birth was closely correlated with abnormal neurological sequelae. These results indicate that the brain development of the fetuses may have been affected by neurotoxic events similar to ionizing radiation. We emphasize the importance of avoiding neurotoxic stress to pregnant women when the fetus is in the critical period of neuronal development, before 27 weeks of gestational age.

Introduction

During pregnancy, environmental factors acting on the fetus play an important part in allowing adequate fetal growth *in utero*. There have been several reports indicating that environmental factors including nutrition (*1*), socioeconomic status (*2*), and drugs such as heroin, methadone, alcohol, aminopterin, coumadin, dilantin, and trimethadione (*3*) have an effect on fetal growth. Infants born in a growth-retarded condition are susceptible to a variety of different agents that frequently cause adverse effects in the neonatal period and are detrimental to the subsequent outcome. Neurological handicap in particular has become an important problem in the management of intrauterine growth-retarded fetuses and newborns.

A critical period exists in neuronal development of the fetus, and if there is an interference with brain development during this period, normal neurological development cannot follow. In this paper we present data to support this concept collected from a field and a clinical study. The aim of the field study was to assess the effects of exposure to ionizing radiation on the developing embryonic and fetal brain. This was performed by examining the school performance of children who survived prenatal exposure to radiation following the atomic bombing of Hiroshima, Japan in 1945. The second study was the clinical study in which we surveyed 475 growth-retarded infants who were born in our institute to determine the perinatal details and the clinical characteristics.

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Materials and Methods

Study 1

The subjects of this study were 929 children who were born between August 6, 1945, and May 31, 1946, from mothers exposed to the atomic bombing on August 6, 1945 (*5*). The duration of gestation at the time of the bombing was based on the inferred first day of the last menstrual period and was calculated from the formula below:

Days of pregnancy at the time of bombing =
280 − (number of days between August 6, 1945 and date of delivery)

assuming that the mean duration of pregnancy was 280 days.

The duration of pregnancy from the presumed time of fertilization to the date of irradiation was subdivided into 4 categories, *viz.*: 0–7 weeks, 8–15 weeks, 16–25 weeks, and more than 26 weeks. The estimated radioactive dose was calculated from the so-called DS86 dosimetry (*6*). The DS86 uterine doses are the estimates computed individually, taking into account orientation and posture of survivors within 1600 m of Hiroshima.

The school performance of the children under investigation were measured for seven subjects that are studied in Japanese elementary schools: language, social studies, mathematics, science, music, drawing and handicrafts, and gymnastics. The performance was assessed by teachers and scored from 1.0 to 5.0. Any alteration in school performance associated with radioactive dose was correlated with the duration of pregnancy at the time of exposure, and the subgroups were compared with each other.

Study 2

In the second study, 475 infants with intrauterine growth retardation were recruited from 14,418 newborn children who were born between January 1979 and December 1987 in Kagoshima Municipal Hospital. The diagnostic criteria for intrauterine growth retardation were based on the standard curve of fetal growth calculated from the examination of normal Japanese newborn children (*7*). Neurological examination was performed on the children who survived by the pediatric neurologist at another institute in our area. The outcome, especially neurological development, was correlated with clinical features such as the incidence of fetal asphyxia, the head circumference of newborns, uterine height at the end of pregnancy, and maternal complications during pregnancy.

Results

Study 1

Table 1 gives details of the 929 children who were exposed *in utero* to radiation from the Hiroshima atomic bombing and who had school records. The number of children is subdivided by dose level and by gestational age at exposure. The dose level is the fetal absorbed dose based on DS86 dosimetry, and the numbers in parenthesis refer to the 14 children who were judged clinically to be mentally retarded. It can be seen that 64% (9/14) of the mentally retarded children were discovered in the group exposed to radiation 8–15 weeks after fertilization, and a further 29% (4/14) were in the group exposed at 16–25 weeks. The highest incidence of neonatal retardation was found among those exposed to the highest dose levels (≥ 1 Gy). At this level of irradiation, four of the four children in the 8–15-week group, and two of the five children in the 16–25-week group were mentally retarded.

Figure 1 shows school performance correlated with gestational age at exposure, and dose level. This group indicates a striking decline in school achievement among those exposed to radiation at 8–15 weeks and 16–25 weeks of gestation but not among those exposed at 0–7 weeks or more than 26 weeks.

Study 2

Among the 475 fetuses showing intrauterine growth retardation, 429 were liveborn and the other 46 suffered intrauterine death. Of the liveborn infants, a further 46 died in the neonatal period and 383 survived to be discharged from the neonatal center (Fig. 2). Fetal and/or chromosomal anomalies were found in 31 cases of whom 5 were stillborn and 26 died in the neonatal period. The gestational age at birth of these 31 cases ranged from 30 to 42 weeks, and 15 of these 31 infants underwent chromosomal studies, 11 showing abnormal results.

The survival rate of the infants diagnosed as having intrauterine growth retardation on the basis of gestational age was analyzed. There were no survivors among those born at less than 27 weeks of gestation, and there was a marked improvement in the survival rate once gestation extended beyond 32 weeks. The maternal complications, in order of incidence, associated with intrauterine growth retardation of the fetus were toxemia of pregnancy alone,

Table 1. Children whose mothers were exposed during pregnancy to irradiation from the atomic bomb of Hiroshima and who have school records available.[a]

Dose category, Gy	Mean dose, Gy	Gestational age at exposure, weeks after fertilization				
		All	0–7	8–15	16–25	26+
Control	0	634 (2)	77	142	182(1)	233(1)
0.01–0.09	0.04	153 (1)	17	36	44(1)	56
0.10–0.49	0.22	101 (2)	12	33(2)	26	30
0.50–0.99	0.64	27 (3)	2	10(3)	12	3
1.00–1.99	1.16	13 (6)	0	5(4)	5(2)	3
2.00+	2.41	1	1	0	0	0
Total	–	929(14)	109	226(9)	269(4)	325(1)

[a]Doses are intrauterine doses absorbed according to DS86 dosimetry. Numbers of severely retarded cases are shown in parentheses.

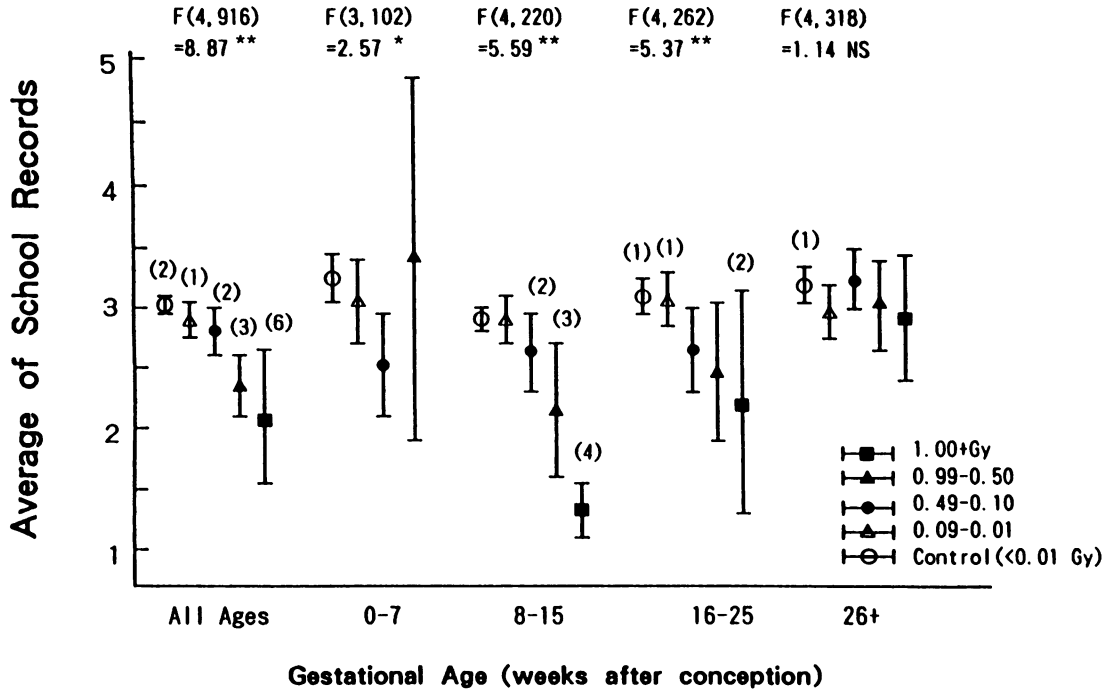

FIGURE 1. School performance scores of pupils who were exposed prenatally to ionizing radiation as a result of the atomic bombing of Hiroshima. The bars depict the average school subject score in the first grade with 95% confidence limits. The pupils are grouped according to the gestational age at which they were exposed, and the different bars correspond to the different tissue-absorbed doses as indicated. Numbers in parentheses are severe mentally retarded cases. Significance levels are (NS) $p > 0.10$; (*) $p < 0.10$; (**) $p < 0.01$.

toxemia of pregnancy together with other obstetric abnormalities, multiple pregnancy, and other medical complications. The perinatal mortality of the infants with intrauterine growth retardation did not differ significantly among the different types of maternal complications. The outcome was very poor in the group of infants born before 32 weeks of gestation, and the major factors contributing to stillbirth were toxemia developing early in the second trimester and umbilical cord problems.

Excluding the 31 fatal cases associated with chromosomal abnormalities, 444 infants with intrauterine growth retardation were managed in our perinatal medical center, and 383 survived the neonatal period, among whom 17 infants were found to have an abnormal neurological exam-

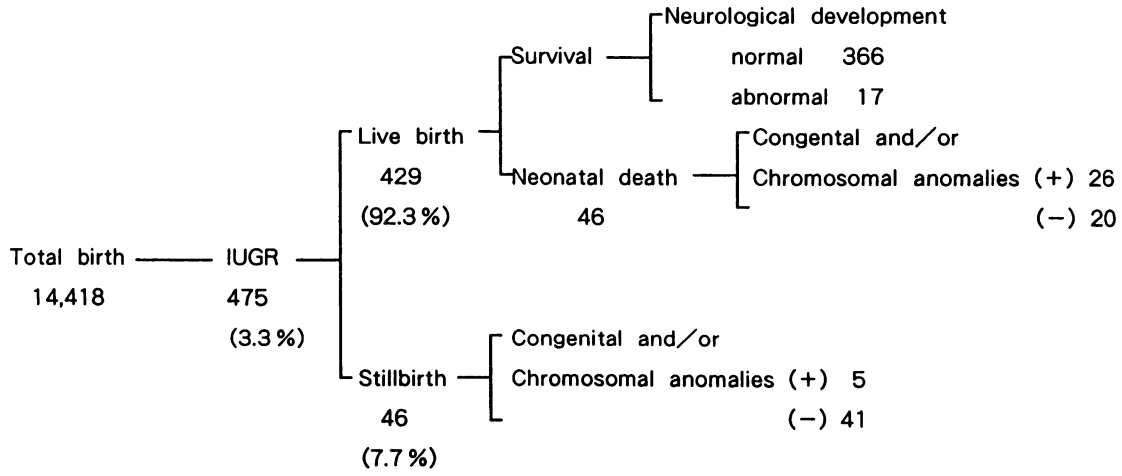

FIGURE 2. The subjects of study showing the outcome of intrauterine growth retardation (IUGR). (+) Congenital and/or chromosomal anomalies present, (−) congenital and/or chromosomal anomalies absent.

Table 2. Neonatal outcome of intrauterine growth-retarded infants according to whether there was fetal asphyxia caused by antenatal fetal distress.

	Fetal asphyxia	
	+	−
Death*	12	4
Survival*	131	206
Normal neurological development (NS)	10	6
Abnormal neurological development (NS)	121	200

NS, not significant.
*$p < 0.01$ for death and survival.

Table 3. Neonatal outcome of intrauterine growth-retarded infants according to head circumference at birth.

	Small head circumference	Normal head circumference
Death (NS)	4	12
Survival (NS)	87	258
Normal neurological development*	9	8
Abnormal neurological development*	78	250

NS, not significant
*$p < 0.05$ for normal and abnormal neurological development.

ination. There were 61 deaths without associated chromosomal abnormalities, 41 of these being stillbirths and the other 20 died in the neonatal period. The incidence of neurological abnormality among the surviving infants was much higher when they were born at less than 32 weeks of gestation. After 32 weeks, the incidence of neurological abnormality was very low, and those cases that were detected were evenly distributed among each week of gestation above 32 weeks right up until full-term delivery. The neurological abnormalities in the surviving infants were analyzed according to their birth weight and gestational age. A more normal neurological status was found with greater birth weight and with more advanced gestational age at birth. The placental wet weight was found to be higher in the group of neurologically abnormal infants.

The neonatal death rate was significantly higher when fetal distress was present in the antenatal period than when there was no fetal distress. The neurological development of the infant was not significantly affected by fetal distress (Table 2).

Infants whose head circumference at birth was below normal by at least 1.5 standard deviations showed a significantly higher incidence of abnormal neurological development. On the other hand, the degree of the lessening of the head circumference at birth was not correlated with the neonatal death rate (Table 3).

Figure 3 shows the mean gestational age at which the growth of the uterine height was arrested for three different groups of infants categorized according to the neonatal outcome. The mean uterine height of the infants who died in the neonatal period showed growth arrested at 26 weeks of gestation. Those who survived with abnormal neurological development were arrested at a mean uterine height of 27 weeks of gestation. The group who survived and had normal neurological development arrested at a uterine height corresponding to 29–30 weeks gestation.

Discussion

In our first study, the field study, we showed that the developing fetus is most vulnerable to irradiation at 8–15 weeks after conception (10–17 weeks of gestation). Prenatal exposure to ionizing radiation at this stage increases the frequency of mental retardation from a background level of 0.8% to a frequency of about 46% among those ex-

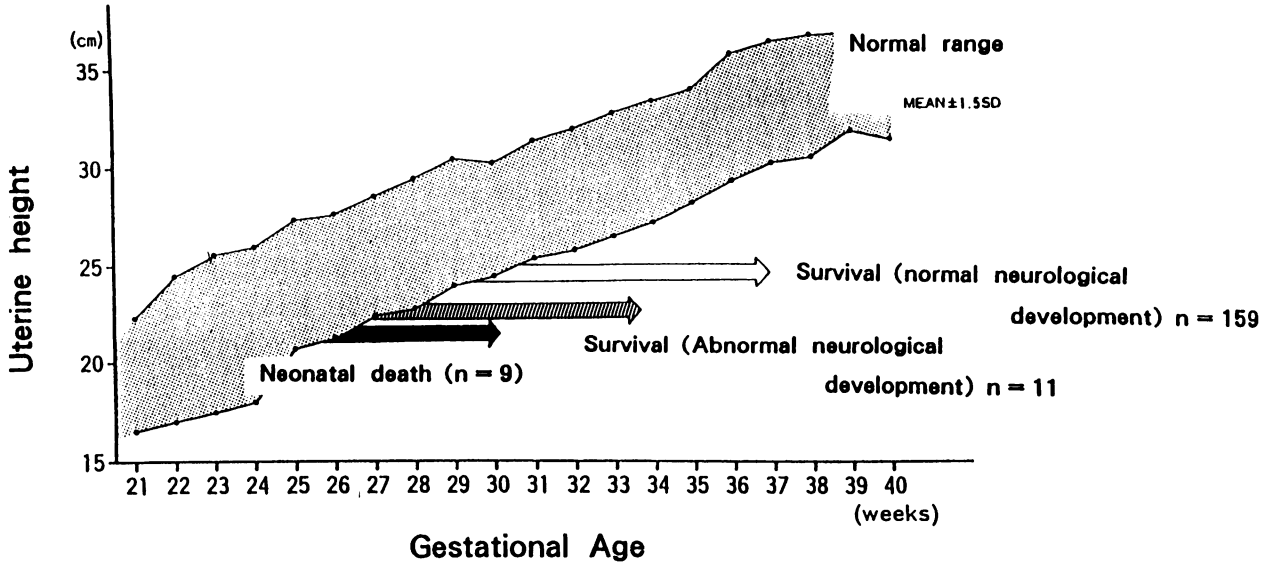

FIGURE 3. The outcome of arrest of growth of uterine height. The arrows indicate the severity of the growth retardation and the effect on the fetus or neonate.

posed to 1 Gy or more. We found that prenatal exposure to 1 Gy produced a mean decrease in school performance score of about 1.6, which is tantamount to a shift for an average individual from a score of 3.0 to about 1.4. The second most vulnerable period was 18–27 weeks of gestation.

We subdivided the period of pregnancy into four groups; 0–7 weeks, 8–15 weeks, 16–25 weeks, and 26 weeks or more after fertilization. In the first period, the precursors of the neurons and neural cells, which are the two principal types of cells giving rise to the cerebrum, have already emerged and are mitotically active (*8*). In the second period there is a rapid increase in the number of neurons, and they migrate to their final developmental sites, soon losing their capacity to divide and thereby becoming permanent cells. In the third period, there is an acceleration of *in situ* differentiation, and an increase in the formation of synaptic connections which began about the eighth week: the definitive cytoarchitecture of the brain unfolds. The fourth period is largely one of continued architectural and cellular differentiation and further development of synapses (*4*).

The stages of neuronal development and maturation accord with the finding that arrest of the growth of uterine height at a level that corresponds to less than 28 weeks of gestational age results in abnormal neurological development that can be detected in neonates who survive the perinatal period. It is assumed that the fetus itself had been affected by unknown factors at a much earlier stage of pregnancy than the final uterine height equivalent. Furthermore, the fact that smaller head circumference at birth was closely related to abnormal neurological sequelae indicates that the brain development of the fetus might have been affected by neurotoxic agents with similar effects to ionizing radiation. We emphasize the importance of pregnant women avoiding neurotoxic stress when the fetus is in the critical period of neuronal development, which is before 27 weeks of gestational age.

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