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ORIGINAL CONTRIBUTIONS

LONG TERM EFFECTS OF RADIOACTIVE IRON ADMINISTERED DURING HUMAN PREGNANCY[1]

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Hagstrom, R. M. (Vanderbilt Univ. School of Medicine, Nashville, Tenn. 37203), S. R. Glasser, A. B. Brill and R. M. Heyssel. Long-term effects of radioactive iron administered during human pregnancy. Amer. J. Epid., 1969, 90, 1–10.—The effects of maternal and prenatal exposure to the radioactive isotope ^{59}Fe have been analyzed 18–20 years after exposure. Of 751 pregnant women attending the Vanderbilt University Hospital Prenatal Clinic who received the orally administered isotope as part of a study of iron metabolism in pregnancy, 679 (90%) were located and their experience compared with 705 (91%) of 771 women chosen randomly from the same clinic population who did not receive radioiron. Frequency and type of malignancy occurring in the followup period did not differ for the two pregnant female groups. Effect of prenatal exposure to radioactive iron was analyzed in children born to these mothers. For 634 exposed children, one case of leukemia and two cases of sarcoma were discovered. No malignancies occurred in the 655 children in the comparison group. This represents a small, but statistically significant increase ($p = .03$), and is consistent with previous radiobiologic experience. No difference in the frequency or the type of congenital defect was noted for exposed compared to non-exposed children when analyzed by trimester of radioiron administration. For children born to exposed mothers following the study pregnancy, no differences in the frequency or the type of congenital defect were noted when compared with subsequent children of non-exposed mothers.

fetus; leukemia; neoplasms; prenatal influences; radiation effects; radioisotopes

INTRODUCTION

Postnatal exposure to irradiation results in an increased incidence of leukemia and malignancies in both children and adults (1–7). In the majority of studies concerning effects of in utero diagnostic x-ray exposure, an increased incidence of leukemia and other malignancies has been noted (8–11). There are reports of only two medically unselected populations irradiated in utero. One involves pregnant women exposed to the atomic bomb explo-

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sions in Japan (12). A second is an unselected group of women given diagnostic pelvimetry early in pregnancy in an attempt to assess the value of the procedure in improving obstetrical management (13). No significant relationship between cancer mortality and exposure has been observed in either study.

During the years 1945–1949, a group of medically unselected pregnant women received tracer doses of radioactive Iron-59 to assess iron absorption during pregnancy. These women were part of a larger survey of nutrition in pregnancy conducted at Vanderbilt University Hospital. In view of later reports, cited above, suggesting a relation between fetal exposure to low level irradiation and development of malignancies, a study was initiated to determine morbidity and mortality experiences in the children and mothers fed radioactive iron. Similar data were obtained from children and mothers not receiving the isotope who attended the clinic during the same years. The present report deals with the occurrence of malignancies in the mothers, and malignancies and congenital malformation in the study children and their siblings.

MATERIALS AND METHODS

Study population

The study population consisted of pregnant women attending the Vanderbilt University Hospital Prenatal Clinic during the years 1945 through 1949, and the children resulting from this and subsequent pregnancies. In order to investigate iron absorption in pregnancy (14, 15), an unselected group of women admitted to the clinic were fed single doses of iron tagged with the radioactive isotope, ^{59}Fe, on their second prenatal clinic visit.

The original radioiron-fed group consisted of 829 pregnant females. Of this group, hospital records could be found for 751 mothers (table 1). For comparative purposes, 831 control pregnancies were selected at random from non-radioiron-fed pregnancies identified in records of the Vanderbilt Cooperative Study. Of these control pregnancies, we were able to identify hospital records for 771 mothers, an attrition comparable to the radioiron-fed group. The total population of infants identified for followup was 719 born to mothers fed radioiron and 734 infants in the control group. The difference between total populations of mothers and their infants results from the loss of infants through neonatal deaths, still births and abortions.

Six hundred seventy-nine of the radioiron-fed mothers (90.4 per cent) and 705 of the control mothers (91.4 per cent) subsequently responded to questionnaires. Comparable figures for offspring were 88.2 and 89.2 per cent. The characteristics of study and control groups in terms of mother's age at delivery, years of followup of mothers and children, and median calendar year of entry into the study are given in table 2. There are no essential differences except in terms of year of entry into the study and this is reflected in years of followup. The difference derives from the protocol of the original Vanderbilt Cooperative Study in which the percentage of pregnant women fed radioiron was highest in the early phases of the study. Characteristics for mothers lost to follow-up are

TABLE 1
Study population

	Index group	Control group
Mothers		
Total population	751	771
No. located	679	705
% followup	90.4	91.4
Children		
No. of pregnancies	751	771
Fetal and neonatal loss	32	37
Total live children for followup*	710	734
No. located	634	655
% followup	88.2	89.2

* Twins, triplets, etc. were deleted as a group.

TABLE 2

Characteristics of ^{59}Fe fed and control population

	Completed followup	
	Iron Fed	Control
No. of children	684	655
No. of mothers	679	705
Mothers' age at delivery		
Mean	24.57	24.19
SD	6.29	6.50
Years followup		
Children		
Mean	18.44	17.20
SD	2.80	2.53
Mothers		
Mean	19.13	17.82
SD	2.40	3.04
Median calendar year at entry	1946	1946

	Lost to followup	
	Iron fed	Control
No. of mothers	72	66
Age at delivery		
Mean	24.00	23.50
SD	6.27	5.9
Pregnancy outcome		
Stillbirths	0	0
Neonatal deaths	2	3
Unknown outcome	12	11
Median calendar year at entry	1946	1947

similar to those found regarding calendar year at entry, mean age at delivery, and per cent fed radioactive iron (table 2).

Followup procedure

Radioiron-fed mothers and control mothers were traced through a mailed questionnaire or by interview if the questionnaire was not returned. Significant medical information was verified by subsequent review of physician and hospital records. Attempts were made to obtain a completed questionnaire for each mother and child in the study. At no point until final analysis of data was a study individual identified as belonging to iron-fed or control group.

The information recorded for mothers was cause of death, benign or malignant tumors, and morbidity resulting from a variety of diseases. For the index child and subsequent sibling, the same information plus the presence of congenital malformations, behavior or learning disorders and number of school grades completed was recorded. Reported occurrences of deaths or tumors were confirmed by study of death certificates, physician and hospital records and review of pathology material where possible. Followup was instituted in 1964 and terminated in 1967.

Estimate of radiation dose to mother and fetus

Hahn (1963 personal communication) estimated the radiation dose to the fetus as 5 to 15 rads. In the original publication, "Iron Metabolism in Human Pregnancy Studied with the Radioisotope ^{59}Fe" (16), no estimates of fetal absorbed dose were given, although estimates of 0.2 roentgens to blood and 0.02 roentgen to total body tissues were given for the maternal organism. These calculations are based on measurements suggesting a body burden of ^{59}Fe of 2 to 4 uc. There is, unfortunately, great uncertainty in these original estimates of Hahn's and in any refinement we can make at this time. Assuming that the efficiency of counting of ^{59}Fe is 25 per cent as described by Hahn, it is possible from his original data to reconstruct the actual number of microcuries fed each mother. Because of the method used for determining "iron absorption," it is not possible to determine the microcuries absorbed by the mother nor to make other than an estimate of how much of the absorbed dose passed from the mother to the fetus. The method used was to feed a single isotope of iron (^{59}Fe), wait two to four weeks, secure an aliquot of maternal blood and determine the counts per minute of ^{59}Fe in the blood sample. The maternal blood volume was estimated and the total amount of ^{59}Fe in blood calculated. This value was then divided by the counts fed to give per cent absorption. The method assumes that all, or at the very least, a reasonably constant and large proportion of absorbed radioiron is incorporated into maternal hemoglobin. In normal subjects, this assumption can be shown to be true, and at least relative absorption (for instance, the effect on absorption of different dosage levels of elemental iron) can be determined using a single isotope of iron and blood samples (17).

In pregnancy, however, plasma iron is directed not only to the maternal bone marrow for new heme synthesis, but also traverses the placenta to the fetus. Effectively then, the values for absorption of iron given by Hahn and coworkers underestimate the amount absorbed since he measured only the proportion of iron which reappeared in maternal hemoglobin. Iron which went directly to the fetus would not be measured as "absorbed." In the first trimester, less than 1 per cent of a ^{59}Fe tracer dose injected intravenously into well nourished mothers is picked up by the human fetus (18). On a weight basis, however, this is approximately a 100-fold greater uptake by the fetus than expected on the basis of the maternal accumulation. In the rat, by the third trimester of pregnancy, fully 50 per cent of plasma radioiron is destined for the multiple fetuses (19).

Hahn and his colleagues recognized and commented on the methodologic problems in determining iron absorption in pregnancy (16). Nevertheless, in the light of present day knowledge the number of microcuries actually absorbed by the mother and the proportion which was directed to the fetus remain uncertain. Thus, of necessity, comparisons in our study have been made for high and low dose feedings by trimester based on counts per minute fed. At present we are unable to obtain valid estimates of absorbed radiation dose, for analysis of dose-response relationships.

Results

No differences were found for per cent live births between the radioiron and control pregnancies, nor were any significant differences found for the two groups in frequency of abortions, stillbirths, or neonatal deaths (table 1). In the 679 iron fed pregnancies on which there was complete followup, there were 12 neonatal deaths, nine stillbirths and 11 abortions; and for 705 non-fed pregnancies, 14 neonatal deaths, nine stillbirths and 14 abortions. Previous findings in the original Vanderbilt Cooperative Study are similar, with frequency for stillbirth and neonatal death of 1.5 and 2.0 per 100 total births.

Non-accidental deaths among the children occurring after the neonatal period through age 15 years totalled 17 for the iron-59 group compared to 12 for controls. Death rate based on person years of observation through age 15 years for the irradiated and non-irradiated group is 1.62 and 1.25 per 1,000 person years, respectively. Twenty-one non-accidental deaths occurred among radioiron fed and 14 among control mothers, yielding death rates of 1.7 and 1.1 per 1,000 person years, respectively.

Four malignancies occurred among the children receiving prenatal radiation exposure, and none were found among the non-exposed children. One of the malignancies was a primary carcinoma of the liver in a male age 11 years at death. This tumor is probably unrelated to radiation since fatal primary liver carcinoma also occurred in two of his older male siblings. This familial occurrence has been reported elsewhere (20).

Acute lymphatic leukemia occurred in one female whose mother received ^{59}Fe in the 23rd week gestation. The child died at age five years and 11 months, having developed symptoms attributed initially to rheumatoid arthritis four months before death.

A third study child, a female, died at

TABLE 3

Congenital defects in ⁵⁹Fe fed and control children

⁵⁹Fe fed		Control	
Type defect	Frequency	Type defect	Frequency
First trimester		Congenital heart disease	2
Congenital heart disease	1	Congenital heart disease with congenital absence of radii	1
Hydrocephalus	1	Aberrant blood vessel	1
Mongolism	1	Hydrocephalus	2
Ectopic kidney	1	Spina bifida occulta spine	1
Cleft palate	1	Cretinism	1
Pilonidal cyst	1	Mongolism	1
Second trimester		Absence of falx cerebri and microgyria	1
Congenital heart disease	2	Redundant ureter	1
Congenital hydrocephalus, talipes varus, syndactylism	1	Congenital urinary tract disorder	1
Hypospadias	3	Exstrophy of bladder and epispadias	1
Polycystic kidney, pulmonary atelectasis	1	Dislocated hip	1
Talipes varus, valgus	3	Talipes	5
Hemangioma	8	Tibial torsion	1
Supernumerary toe	1	Hemangioma	7
Pilonidal cyst or sinus	2	Cleft palate	2
Strabismus, esophoria	2	Spade hand, supernumerary thumb	2
Accessory azygus lobe	1	Bifid uvula	1
Atelectasis	1	Pilonidal cyst or sinus	3
Thyroglossal duct cyst	1	Strabismus	3
Defects of cranial bones	1	Bronchial cleft cyst	1
Third trimester		Muscular dystrophy	1
Congenital heart disease	1	Amaurotic familial idiocy	1
Congenital hydrocephalus	2	Vitamin D resistant rickets	1
Microcephaly	1	Familial periodic paralysis	1
Generalized cortical atrophy	1	Multiple (Cleft palate, hypospadias, pilonidal sinus, talipes varus)	1
Urethral obstruction	1	Total defects	47
Talipes varus, valgus	4	Total pregnancies	705
Hemangioma	3	Defects per 100 pregnancies	6.7
Hand deformity	1		
Pilonidal cyst or sinus	1		
Strabismus	1		
Biliary atresia	1		
Total defects	44		
Total pregnancies	679		
Defects per 100 pregnancies	6.5		

age 11 years of synovial sarcoma of the right thigh metastatic to the lungs. Symptoms from the tumor had been noted from age ten and one-half years. The ⁵⁹Fe was fed in the thirteenth week of gestation.

The fourth child, a male, died at age 11 years of lymphosarcoma of the cecum metastatic to the omentum, after an illness of two months. The mother had received radioiron in the 20th week of gestation.

There were 23 malignancies in mothers who received radioiron and 24 in the control group. Relative frequency of the various types was roughly comparable in the two groups, and no particular type of tumor seemed related to the higher doses as measured by counts per minute fed.

Congenital defects are tabulated in table 3. In this study congenital defect refers to both gross structural defects present at birth and microscopic malformations or physiological disturbances present though not necessarily recognised at birth. Defects which have been excluded from analysis are hydrocele, hernia, and pes planus. There were 6.5 defects per 100 pregnancies for mothers receiving radiation and 6.9 per 100 for controls. Fetal sensitivity to induction of congenital malformation is highest in the first trimester. For this reason congenital defects were grouped by trimester of iron administration. Iron was administered in the first trimester for 106 pregnancies, in the second for 344, and in the third trimester for 219. For ten pregnancies trimester of feeding was unknown. No differences were noted in frequency of total malformations or structural aberrations of the CNS when analyzed by trimester of iron administration.

To evaluate possible genetic effects in mothers fed radioactive iron, congenital defects for siblings born after the study pregnancy were assessed. The frequency for congenital defects in siblings per 100 live births following the study pregnancy is similar for study and control groups (table 4).

Other defects resulting from genetic damage may have occurred in offspring of study children but no data were collected on these. There have been 171 offspring born to iron-fed and 74 to non-iron-fed children. (Iron-fed children at end of followup were slightly older than the comparison group.)

TABLE 4

Congenital defects in younger siblings of ^{59}Fe fed and control children

^{59}Fe fed		Control	
Type defect	Frequency	Type defect	Frequency
Tetralogy of fallot	2	Congenital heart disease	4
Patent ductus	1	Congenital heart disease with pyloric stenosis	1
Right aortic arch	1		
Hydrocephalus	1	Mongolism	1
Craniostenosis	2	Hydrocephalus with talipes varus and spina bifida	1
Mental retardation	1		
Mongolism—lymphatic leukemia	1	Hydrocephalus	1
Congenital hydronephrosis	1	Bilateral hydronephrosis	1
Polycystic kidney	1	Congenital neuromuscular disorder urinary tract	1
Meatal atresia	1		
Pilonidal sinus	1	Talipes varus	2
Talipes varus, valgus	1	Cleft palate	1
Congenital angulation tibia	1	Club food and congenital web	1
Congenital dislocated hip	1	Branchial cleft cyst	1
Hemivertebra	1	Thyroglossal duct cyst*	2
Hemangioma	3	Congenital atelectasis	1
Supernumerary finger	2	Mucoviscidosis	1
Pyloric stenosis and strabismus	1	Muscular dystrophy	1
Strabismus	1	Pseudohypertrophic muscular dystrophy*	1
Total defects	24		
Total live births following study pregnancy	709	Amaurotic familial idiocy*	1
Defects per 100 live births	3.1	Congenital papillomata (skin face) and displaced auricle	1
		Total defects	23
		Total live births following study pregnancy	855
		Defects per 100 live births	2.7

* Study child had same defect.

There were only five malignancies in children born following the study pregnancy, two in offspring of control women and three in offspring of women receiving radioiron. These tumors were a rhabdomyosarcoma of the neck and a Wilm's tumor in subsequent children of the non-radioiron-fed mothers. For the children of radioiron-fed mothers, a Wilm's tumor, a glioma of the optic chiasma, and acute lymphatic leukemia in a mongoloid child were recorded. The mother of the child with a glioma died of clear cell carcinoma of the kidney.

Discussion

Evidence is abundant relating the occurrence of leukemia to both prenatal and postnatal radiation exposure. Postnatal radiation induced leukemia has been observed in therapeutically administered radiation in children and adults (1–3), and following P-32 administered for polycythemia (4). The above observations are paralleled on well individuals exposed to radiation, an increased incidence of leukemia having been noted in Japanese exposed to the atomic bomb blast and in radiologists (5, 21).

In Japanese exposed in childhood, acute lymphatic and chronic granulocytic leukemia are most markedly increased with maximal incidence rates occurring during 1950–1954. Measurements of leukemia incidence continue to be made in survivors of the atomic bomb (6). The appearance time for acute leukemia, in the heavily exposed group, appears to be related to age at exposure and to dose, with latent periods of 8.6, 9.4, and 13.0 years for those between the ages of 0–14, 15–29, and 30, respectively, at time of exposure. From 1940 to 1964 the heavily exposed group continued to experience an increased incidence of leukemia compared to those individuals exposed at a greater distance from the center of bomb (7).

Several studies have revealed an increased incidence of leukemia in childhood following exposure to diagnostic x-ray exposure in utero (8–10). Court-Brown et al. found no increase in risk following such exposure (11). McMahon reported a relative risk for children exposed to radiation in utero of 1.4. More recently Graham et al. have found x-ray to all sites associated with a relative risk of leukemia of 1.59 and x-ray to abdomen alone with a risk of 1.40 (22).

No exact dose calculations are available for the progeny in the several studies of in utero exposure to diagnostic radiation but this has been estimated at approximately 5 rads.

Speculation has arisen as to whether some factor which dictates the need for diagnostic radiation in the pregnant mother predisposes in some unknown fashion to the occurrence of the disease itself in progeny irradiated while in utero (23). As noted previously, in reports on two unselected fetal populations exposed in utero, excess mortality from leukemia has not been observed (12, 13).

Other types of malignancies are known to occur following exposure to radiation. Beach and Dolphin have summarized three separate studies of children irradiated in infancy or childhood for thymus enlargement or other miscellaneous conditions who subsequently developed thyroid malignancies (24). A recent report has appeared of increased incidence of cancers of a variety of types in spondylitis patients receiving x-ray therapy (25), and an increased incidence of thyroid cancers, especially in females, has been observed in the atomic bomb exposed group (26, 27). Patients irradiated for tenia capita presented a larger number of cancers of a variety of types than non-irradiated patients with the same disease (28). A higher mortality from cancer, cardiovascular renal disease, and all other causes combined has been noted in members of the Radiological Society as compared with members of the American College of Physicians (21). The failure to find an increased incidence of neoplasms in mothers receiving radioiron compared to non-radioiron-fed controls may well be due to the small size of the study group and also to the small maternal absorbed dose.

The discovery of three cases of malignancy (excluding the case of familial liver cancer), in the present study in the radiation exposed group as opposed to none in the non-exposed group suggests a cause and effect relationship. However, based on 1950 and 1960 death rates for malignancies in the white population of Tennessee for all ages through 14 years, approximately 0.65 cases would be expected in the study population for the 8,660 person-years of observation through 14 years. The probability of observing three or more cases when less than one case is expected is .03.

Conflicting reports exist about the influence of gestation time of exposure on the effects of radiation. Stewart (8) found a higher case-to-control ratio for mothers x-rayed in the first half of pregnancy than for those x-rayed in the latter half for cases of leukemia and malignancy. Graham et al. have found that differences by trimester were small, but the estimated risk for leukemia in the latter trimester was somewhat larger than in the first (22). Too few cases are available in the present study to provide meaningful information on this point.

For the case and control groups in the present study no significant differences were noted in the frequency of congenital defects. The extensive literature related to congenital defects has been reviewed recently by Brill et al. (29) and a time table for human prenatal radiation effects has been presented by Dekabon (30).

Many congenital malformations, although obviously present at birth, are not discovered until several years later. In a fetal life study of 5,964 pregnancies, only 43.2 per cent of the malformation reported presented signs or symptoms observable at birth (31). In the Vanderbilt iron-fed and non-fed study group, 11 and eight infants, respectively, were found to have congenital defects in the neonatal period, and by the end of followup, 44 and 49 were recorded for the two groups. This frequency of 6.7 per cent, (93 defects for 1,384 pregnancies) is similar to the figure of 7.5 per cent for products of conception weighing over 500 gms reported by McIntosh (31).

The many studies of the Hiroshima and Nagasaki population which have attempted to measure the genetic effects of radiation have failed to demonstrate any increase in congenital malformations in children conceived following radiation exposure of their parents (32). Neal has summarized the various indicators of genetic damage employed in the Japanese studies; only one, the sex ratio, appears to be of possible significance (33). No evidence was found in the present study suggesting that radiation caused an increase in the frequency of congenital defects in exposed fetuses or in offspring of mothers born subsequent to the exposure and fed ^{59}Fe.

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