Exposure to Radioactive Iodine-131 for Scintigraphy or Therapy Does Not Preclude Pregnancy in Thyroid Cancer Patients

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Radiation is known to be mutagenic. The aim of the present study was to ascertain whether exposure to ^{131}I induces genetic damage, as assessed by pregnancy outcomes and the health status of offspring of women previously exposed to ^{131}I during thyroid carcinoma treatment. **Methods:** Data on 2113 pregnancies were obtained by interviewing female patients treated for thyroid carcinoma who had not received any significant external radiation to the ovaries. **Results:** The incidence of miscarriages was 11% before any treatment for thyroid cancer; this number increased slightly after surgery for thyroid cancer, both before (20%) and after (20%) ^{131}I, but did not vary with the cumulative ^{131}I dose. Miscarriages were more frequent (40%) in the ten women who were treated with ^{131}I [mean dose: 3.8 GBq (108 mCi)] during the year preceding conception. Incidences of stillbirth, preterm birth, low birth weight, congenital malformation and death during the first year of life were not significantly different before or after ^{131}I therapy. The incidence of thyroid disease and nonthyroidal malignancy was similar in children born either before or after their mothers were exposed to ^{131}I. **Conclusion:** With the exception of miscarriages, there is no evidence that exposure to radioiodine affects the outcome of subsequent pregnancies and offspring. The question of whether an increased incidence of miscarriages within 1 yr of ^{131}I administration relates to gonadal irradiation or to insufficient control of hormonal thyroid status remains to be established.

Key Words: iodine-131; pregnancy outcome

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Iodine-131 is used widely in the diagnosis and treatment of thyroid diseases (*1,2*). The notion that radiation is mutagenic and may affect germ cells (thereby resulting in genetic damage to offspring) has raised concern regarding the use of radioiodine in the management of thyroid disorders in patients during their childbearing years.

The radiation dose delivered to the ovary is approximately 0.14 cGy after administration of 37 MBq (1 mCi) ^{131}I in normal subjects (*3*). After surgical removal of the thyroid, thyroid cancer patients may receive diagnostic doses of ^{131}I ranging from 37 to 185 MBq (1 to 5 mCi) and therapeutic doses ranging from 1.1 to 5.5 GBq (30 to 150 mCi) or more. Under these circumstances the radiation exposure for any given dose of ^{131}I may be higher, since functioning metastases may be in close proximity to the ovary, and patients may exhibit hypothyroidism at the time of radioiodine administration. This condition decreases renal iodine clearance, resulting in prolonged gonadal exposure (*4*).

The relevance of the mutagenic effects of radiation on germ cells as assessed by untoward pregnancy outcomes, such as miscarriages, congenital abnormalities and malignancies in offspring, remains to be clarified in humans. In an extensive study of Japanese atomic bomb survivors, no statistically significant effects were found (*5–7*). Moreover, no evidence of any significant genetic effect was found in two large studies of pregnancy outcomes and offspring of cancer patients who had been submitted to abdominal irradiation during childhood or adolescence (*8–10*). At variance with these data, an association between paternal preconception radiation exposure and increased risk of leukemia in offspring has recently been reported (*11*).

A high proportion of young patients with thyroid carcinoma are cured after surgery and appropriate treatment with radioiodine (*2,12–15*). Control of metastatic disease may require several courses of ^{131}I treatment, resulting in a cumulative dose of hundreds of mCi (*16,17*). These patients may provide an appropriate model for the study of the genetic effects of radioiodine.

Data on the genetic effects of ^{131}I therapy in thyroid disorders are scant. Studies on pregnancy outcomes and offspring among patients treated with ^{131}I for thyrotoxicosis (*18–20*) or thyroid carcinoma (*21–27*) failed to reveal any significant ^{131}I related effects. The value of this observation, however, is limited, given the small size of the series under study and the lack of internal controls.

In the present study, the question of whether, and to what extent, radioiodine administration has any significant genetic effect in humans was evaluated in a large series of women with thyroid cancer, who were previously submitted to diagnostic and/or therapeutic doses of ^{131}I, by assessing the outcomes of pregnancy and the health status of their children. Pregnancies occurring before differentiated thyroid carcinoma treatment were used as internal controls.

PATIENTS AND METHODS

Data Collection

Unselected female patients with a history of differentiated thyroid carcinoma were interviewed by trained data managers between February 1990 and December 1993. Interviews of male patients are currently in progress. Of the 2573 female patients treated at the participating centers, 376 (15%) died, 318 (12%) were lost to follow-up, two (.07%) refused to be interviewed and 1877 (73%) were interviewed. Interviews were conducted at the time of annual evaluation among 996 female patients at the Institut Gustave-Roussy (IGR), Villejuif, France; 235 patients at the Institute of Endocrinology of the University of Pisa, Italy; 583 patients at the Institut Jean Godinot, Reims, France and 63 patients at the Institut François Baclesse, Caen, France. This inclusion method was reliable, given that patients with differentiated thyroid carcinoma are evaluated at yearly intervals. No selection criteria

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TABLE 1
Pregnancies and Induced Abortions as a Function of Radioiodine Exposure

Factor	No. of pregnancies	Induced abortions (%)	Age at conception (yr) (mean ± s.d.)	Low socioeconomic status (%)	Alcohol intake (%)	Smoking habit (%)
Before any treatment	1770	174 (10)	27 (±6)	276 (16)	156 (9)	212 (12)
After surgery for thyroid cancer	343	71 (21)	30 (±6)	42 (12)	72 (21)	43 (13)
Cumulative activity of ^{131}I (MBq) before conception (mean ± s.d.)						
0	85	19 (22)	29 (±5)	14 (16)	14 (16)	8 (9)
<370 (85 ± 67)	122	25 (20)	30 (±6)	13 (11)	32 (26)	23 (19)
370–3700 (2035 ± 925)	40	10 (25)	30 (±5)	3 (8)	2 (5)	3 (8)
>3700 (8103 ± 5772)	96	17 (18)	30 (±5)	12 (13)	24 (25)	9 (9)
Activity of ^{131}I during year before conception (MBq) (mean ± s.d.)						
0	247	45 (18)	30 (±6)	28 (11)	49 (20)	33 (13)
<370 (78 ± 56)	76	16 (21)	29 (±6)	12 (16)	18 (24)	9 (12)
≥370 (3493 ± 962)	20	10 (50)	29 (±6)	2 (10)	5 (25)	1 (5)

including age, were used; the interviews lasted 20–60 min and included questions on each pregnancy, possible complications and outcome, as well as questions on marital and socioeconomic status, medical history, smoking habits, alcohol intake and use of medications during pregnancies.

Information on all types of radiation exposure, including radioiodine (activity and day of administration), radiographs and external radiotherapy, was obtained from medical records.

Patients

Patients were treated for differentiated thyroid carcinoma according to standard protocols (*12,28*). After surgery, 1.2–3.7 GBq (30–100 mCi) of radioiodine were administered to all patients in Pisa (*27*) and to patients with residual neoplastic tissue or with poor prognostic indicators in Villejuif (*12*), Reims and Caen. Whole-body ^{131}I scanning, using 37–185 MBq (1–5 mCi) was performed each year for the first 2 yr and every 5 yr thereafter. Chest radiographs were obtained routinely at the time of the whole-body ^{131}I scan, and bone radiographs were obtained only in patients with clinical or scintigraphic suspicion of bone involvement. In patients with distant metastases or local recurrence, the ^{131}I treatment dose was 3.7–5.5 GBq (100–150 mCi). This was repeated every 4 to 12 mo, until any signs of significant uptake disappeared. Although patients were advised not to become pregnant for 1 yr after ^{131}I administration, more than one-third of the conceptions occurring after radioiodine administration were recorded during this period of time. Most of these conceptions occurred after a diagnostic ^{131}I whole-body scan, at a time when patients were informed that there was no detectable residual disease (Table 1).

All patients were given L-Thyroxine (LT4) treatment at a mean daily dose of 2.4 μg/kg. Since the availability of TSH measurements in 1972, the serum TSH level was measured 4 mo after the initiation of LT4 treatment and yearly thereafter. Moreover, the daily dose of LT4 was adjusted to suppress TSH secretion. A hormonal evaluation, including serum TSH level, was performed during the third month of pregnancy and, when necessary, the LT4 daily dose was increased until the end of pregnancy to ensure suppression of TSH secretion.

Parameters Studied

The following features were recorded for each pregnancy: induced abortion, miscarriage, stillbirth, prematurity (defined as a gestational age below 37 wk), birth weight below the 10th percentile for the gestational age (*29*), congenital abnormality and death during the first year of life. Congenital abnormalities were defined on the basis of the International Classification of Diseases 9 (ICD-9) rubrics (*30*). Later deaths, thyroid diseases and tumors at other sites were recorded for liveborn children.

Data analysis took into account both the whole series of pregnancies and the subgroup of the first series of pregnancies, since the outcomes of multiple pregnancies in a given mother are often interdependent.

Data Validation

A pilot study was performed on 116 pregnancies in various obstetric hospitals. The response rate was 90%; the information provided on events related to pregnancies by interviews proved to be virtually correct all the time. It is noteworthy that only reported data could be taken into account and that early abortions not recognized as such were not included in the present analysis.

Fifty-six of the 61 major birth defects identified from maternal interviews were confirmed by medical reports obtained from obstetric hospitals; thyroid diseases and malignancies at other sites in children were also confirmed by clinical examination of the children and/or histological review of the diagnosis.

Data Analysis

To study the association between the radioiodine dose and the occurrence of adverse events, a Poisson distribution was assumed for the observed number of events and data were analyzed with the AMFIT computer program (*31,32*). Results were verified using logistic regression analysis (*33*). The significance of the relationships was established using the score test (*33*). Pregnancies occurring before any administration of radioiodine were used for the unexposed group for these calculations.

The expected numbers of thyroid and other cancers among liveborn children were estimated using PYRS software (*34*), which resulted in standardized incidence ratios (SIRs). SIRs express the ratio between observed and expected numbers of cancers. Calculations were stratified based on sex, age and calendar period. Data from French cancer registries were used as a reference (*35*), given that the incidence of cancer below age 40 is similar among most countries.

We were unable to compare the observed number of deaths during the first year of life to the expected number from external statistics because the definition of a stillbirth varied among countries during the study period and because it was not possible to match information obtained from the interviews with legal definitions. The expected number of deaths among children after the first year of life was computed using French national data and yielded standardized mortality ratios (SMRs), which express the ratio between the observed and expected numbers of deaths. During the

TABLE 2
Untoward Outcomes of 2113 Pregnancies as a Function of Risk Factors Other than Radiation History at the Time of Pregnancy

Factor	No. of Pregnancies	Induced abortions (%)	Miscarriages (%)*	Stillbirths (%)*	Livebirths†			
					Term <37 wk (%)	Low birth weight‡ (%)	Death <1 yr (%)	Malformation (%)
Age at conception								
>35 yr	261	24††	23††	3	8	10	3	3
<35 yr	1852	10	11	2	5	10	1	4
Smoking habit								
Yes	255	27††	12	2	7	14	2	1
No	1840	9	12	2	5	10	1	4
Alcohol intake								
Yes	228	22††	13	1	7	14	2	1
No	1869	10	12	2	5	10	1	4
Socioeconomic status								
Low	318	10	12	3	6	16§	2	4
Not low	1634	12	13	2	6	9	1	4

* Percentage of pregnancies, excluding those ending by induced abortion.
† Percentage of livebirths.
‡ Birth weight below the 10th percentile for the gestational age (*29*).
§ $p < 0.05$; †† $p < 10^{-3}$.

study period, this death rate in the general population was similar in France and in Italy.

RESULTS

Of the 1877 women interviewed, 1565 (83%) became pregnant at least once and 4766 pregnancies in total were recorded. Among the 312 women who did not become pregnant, only 118 had a partner, 42 of whom tried unsuccessfully to get pregnant. The reasons for infertility were not investigated. No chemotherapy was administered before any pregnancy. The 2528 pregnancies which occurred before 1970 were excluded from the analysis since adequate validation of the reported information was not obtainable in the majority of these patients. Of the 2238 remaining pregnancies, 125 were excluded because of previous radiation exposure to sources other than ^{131}I: 32 after therapeutic external irradiation to the neck for thyroid carcinoma and 93 after abdominal or pelvic radiographs unrelated to thyroid carcinoma. These pregnancies were excluded because the dose delivered to the ovaries during external radiotherapy to the neck was estimated to range from 10–20 cGy (*36*) and from 0.08–0.8 cGy per radiographic examination (*37*), which is of the same order of magnitude as the dose delivered to the ovaries after ^{131}I administration for diagnostic purposes.

The remaining 2113 pregnancies, registered in 923 women, were included in the study; 1770 pregnancies occurred before any treatment for thyroid carcinoma, 85 occurred in patients who had undergone surgery for thyroid carcinoma and had not received radioiodine and 258 in patients who had received radioiodine. Among patients who were treated with 3.7 GBq (100 mCi) radioiodine, 51 received one treatment, 32 received two, 9 received three, 5 received four, 1 received five and 2 received six treatments, respectively. The mean time interval between last treatment and conception was 26 mo (range 0–222 mo). No progression of thyroid carcinoma as assessed by follow-up data obtained during pregnancy (clinical examination and Tg determination on LT4 treatment), was observed in these women during pregnancies and in the subsequent period (^{131}I-TBS and Tg determination off LT4 treatment).

Factors other than radiation history that may have influenced the outcome of the pregnancy were taken into account. Age, smoking habits, alcohol intake and use of medications during pregnancy (such as anti-depressive drugs and beta-blockers) and socioeconomic status were considered. Low socioeconomic status was defined on the basis of the International Classification of Professions (*38*). Classifications 520–599, 610–640, 710–839, 870–874, 890–910, 930–939 and 950–958 were included. In the absence of a defined profession of the patient, that of the husband was taken into account.

As reported in Table 2, induced abortions were more frequent in women over 35 yr and in those who did not avoid alcohol intake or smoked during their pregnancies ($p < 0.001$). Miscarriages occurred more frequently in the older age group ($p < 0.001$) and low birth weights occurred more frequently in the low socioeconomic group ($p < 0.05$). None of the medications studied had a significant influence on the pregnancy outcomes (data not shown).

Induced Abortion

A total of 245 induced abortions was reported (Table 1). Of these, 174 occurred before any treatment, 19 after thyroid surgery and 52 after both thyroid surgery and exposure to ^{131}I. Induced abortions were more frequent after surgical treatment, both without or after ^{131}I administration, but there was no correlation with the cumulative dose of ^{131}I. A higher frequence of induced abortions, however, was observed among the 20 pregnancies which occurred in the patients who had received therapeutic doses of ^{131}I [more than 370 MBq (10 mCi)] during the year which preceded the conception ($p < 0.001$). Among these 20 pregnancies, eight occurred 6 mo or less after radioiodine administration, resulting in six induced abortions and two miscarriages. Twelve pregnancies occurred more than 6 mo after the radioiodine administration and resulted in four induced abortions and two miscarriages. Seven of these ten induced abortions were performed to prevent a feared negative outcome; reasons for the other three abortions were not specified.

The following parameters were studied after exclusion of pregnancies which ended by induced abortion.

Miscarriages and Stillbirths. One hundred and seventy-nine miscarriages (11%) were observed in the 1596 pregnancies which occurred before any treatment. Miscarriages were more frequent (19%) in the pregnancies which occurred after treatment for thyroid cancer. As indicated in Table 3, however, such

TABLE 3
Outcome of Pregnancies as a Function of Radioiodine Exposure, Excluding Those Ending by Induced Abortion

Factor	No. of pregnancies	Miscarriages		Stillbirths	
		No.	%	No.	%
Before any treatment	1596	179	11	27	2
After surgery for thyroid cancer	272	53	19	4	1
Cumulative activity of ^{131}I (MBq) before conception					
0	66	13	20	2	4
<370	97	19	20	2	3
370–3700	30	3	10	0	0
>3700	79	18	23	0	0
Activity of ^{131}I during the year before conception (MBq)					
0	202	36	18	4	2
<370	60	13	22	0	0
≥370	10	4	40	0	0

an increase was unrelated to the cumulative activity of ^{131}I administered before conception. In fact, the frequency of miscarriages was 20% in the 66 pregnancies which occurred after surgery, but without any previous exposure to radioactive iodine.

When exposure during the year which preceded conception was taken into account, the frequency of miscarriages increased from 18% in women who did not receive any ^{131}I during that year to 40% in the ten women who were submitted to a ^{131}I administration during the same year of the conception. Despite the small number of observations in the latter group, the difference was significant (95% CI: 10%–70%). This relationship remained significant after stratification based on the mother's age at conception and after adjustment on the cumulative dose of radioactive iodine administered during the previous years.

Table 3 also reports the stillbirths in treated and untreated groups. No difference was found between the two groups.

Livebirths. Table 4 reports the following characteristics of the 1599 livebirths: sex, prematurity, low birth weight, death during the first year of life, later death, malformation, thyroid disease and nonthyroidal malignancy. None of these parameters appeared to be changed by previous surgery or radioiodine exposure. These data were confirmed by the study on the first 923 pregnancies.

Twelve children born of unexposed mothers died after the first year of age, leading to a cumulative death rate of 0.94%, from 1 to 20 yr. This was not different from that observed in the general population (SMR = 1.3, 95% CI: 0.7%–2.1%).

Sixty-one liveborn children presented with malformation. Of these, four were born of an exposed mother: two children had pyloric stenoses, one had esophageal atresia and one had a hip luxation. Their mothers were exposed before conception to a cumulative dose of 7.9, 4.8, 1.8 GBq and 222 MBq of radioiodine, respectively. Table 5 shows the distribution of these observed malformations. Some specific diagnosis, such as an undescended testicle, skin tags and birthmarks, were excluded. Mean follow-up of the offspring was 12.7 yr (range 0–23 yr).

Thyroid diseases were observed in 16 children. Their distribution is illustrated in Table 6. Two children had autoimmune hypothyroidism, one had Graves' disease, four nontoxic goiter, eight benign adenoma and one differentiated thyroid carcinoma at an age of 16 yr. Twelve children with thyroid disease were born of an unexposed mother and four of an exposed mother. There was no significant increase in thyroid diseases, and in particular in cancer, among children born subsequent to a mother's exposure to radiation.

Six children (1%) developed malignant diseases at sites other than the thyroid gland at a mean age of 115 mo (range: 5–230 mo). These malignancies were: lymphoma in two and leukemia in four. Only one child born of an exposed mother developed leukemia. The cumulative incidence of cancers at the age of 20 mo, including the thyroid carcinoma, was 0.7% (95% CI:

TABLE 4
Outcome of 1599 Livebirths as a Function of Radioiodine Exposure

Factor	Livebirths	No. of girls (%)	Term <37 wk (%)	Low birth weight (%)*	Death <1 yr (%)	Death ≥1 yr (%)	Malformation (%)	Thyroid disease (%)	Cancer at another site (%)
Before any treatment	1384	680 (49)	76 (5)	150 (11)	21 (2)	1	57 (4)	12 (1)	6 (1)
After surgery for thyroid cancer	215	97 (45)	15 (7)	16 (7)	2 (1)	0	6 (3)	4 (2)	1 (1)
Cumulative activity of ^{131}I (MBq) before conception									
0	51	29 (49)	3 (6)	3 (6)	0	0	2 (4)	0	0
<370	76	41 (54)	6 (8)	9 (12)	2 (3)	0	1 (1)	3 (4)	1 (1)
370–3700	27	12 (44)	1 (4)	0 (0)	0	0	1 (4)	1 (4)	0
>3700	61	19 (31)	5 (8)	4 (7)	0	0	2 (3)	0	0
Activity of ^{131}I during the year before conception (MBq)									
0	162	79 (49)	12 (7)	10 (6)	2 (1)	0	6 (4)	3 (2)	1 (1)
<370	47	16 (34)	2 (4)	5 (11)	0	0	0	1 (2)	0
≥370	6	2 (33)	1 (17)	1 (17)	0	0	0	0	0

*Birth weight below the 10th percentile for the gestational age (29).

TABLE 5
Classification of 61 Congenital Malformations Observed Among 1599 Liveborn Children*

Congenital malformations (ICD-9 code)	No. of malformations	Previous exposure to radioiodine (MBq)
Neural tube defects (742)		
Hydrocephalus	1	0
Anencephaly	1	0
Hemiparesia	1	0
Anomalies of eye (743)		
Cataract	1	0
Glaucoma	2	0
Other	1	0
Anomalies of ear, face and neck (744)		
Deafness	1	0
Heart defects (745–746)		
Tetralogy of Fallot	1	0
Cardiac septal defect	4	0
Other	1	0
Anomalies of respiratory system (748)		
Collapsed lung	1	0
Cleft palate (n = 1) and cleft lip (n = 1) (749)	2	0
Anomalies of the digestive system (750–751)		
Oesophageal atresia	1	222
Gastroschisis	2	0
Pyloric stenosis	6	0 (4), 4810, 7881
Anomalies of genital organs (752)		
Hypospadias	3	0
Anomalies of urinary system (753)		
Bladder dysfunction	5	0
Ureter obstruction	2	0
Other	1	0
Musculoskeletal abnormality (754–755)		
Polydactyly, syndactyly	5	0
Hip dysplasia	10	0 (9), 1776
Talipes equinovarus	2	0
Leg atrophy	1	0
Patella anomaly	1	0
Thoracic anomaly	1	0
Others	2	0
Down's syndrome (758-0)	1	0
Marfan's syndrome (759-8)	1	0

* Numbers in parentheses are ICD-9 code. Four malformations occurred after exposure to radioiodine.

0.1%–1.3%). The relative risk was 2.1 (95% CI: 0.8%–4.3%) when compared to the expected number of cancers from French cancer registries. No association was observed between the occurrence of a malignancy and that of a congenital abnormality.

DISCUSSION

Radiation is a known mutagen. Current information on the mutagenic effects of radiation on germ cells is based mainly on experimental evidence in animals since only scant data are available in humans (*39*). Some studies have suggested an association between occupational exposure to ionizing radiation received by fathers and an increased risk of congenital abnormalities (*40*) and leukemia (*11*) among their offspring. Extensive studies on the survivors of the atomic bombs in Japan (*5–7*) and of childhood or adolescent cancer survivors who had received radiation to the abdomen or pelvis (*8–10*), however, have failed, so far, to provide any clear evidence of increased germ cell mutation subsequent to exposure.

In the present study, radioiodine was the only identified medical source of gonadal irradiation after the diagnosis of thyroid carcinoma, since pregnancies after external irradiation or radiographs of the abdomen or pelvis were excluded. Chest radiographs were the only radiographs routinely performed during the follow-up of these patients, but the estimated dose of radiation to the ovaries per chest radiograph is as low as 0.006 cGy (*37*). Furthermore, factors other than radiation history that may influence the outcome of pregnancy were taken into account for the analysis of ^{131}I-related effects.

With the exception of miscarriages, our data do not indicate any increase in the untoward outcome of pregnancy associated with radioiodine exposure, even after administration of large cumulative activities. This observation is consistent with previous studies on smaller series (*18–27*).

The incidence of miscarriages increased when radioiodine was administered during the year which preceded conception and increased further with higher radioiodine activities received during that year. The eight pregnancies that occurred within 6 mo after the last administration of a therapeutic dose of radioiodine resulted in six induced abortions and two miscarriages. This relationship was not linked to the cumulative dose of ^{131}I administered previously and remained significant after adjustment of factors such as the mother's age (over 35). The contribution of other factors cannot be excluded, as suggested by the increase in miscarriages observed in patients who had undergone surgery for thyroid carcinoma and became pregnant before any exposure to ^{131}I. A possible explanation for this finding is an inadequate control of the thyroid hormonal status

TABLE 6
Thyroid Diseases Among 1599 Livebirths as a Function of Radioiodine Exposure

Factor	Livebirths	Total no. of thyroid diseases	Hypothyroidism	Graves' disease	Euthyroid goiter	Benign nodule	Differentiated thyroid carcinoma
Before any treatment	1384	12	2	0	4	6	0
After surgery for thyroid cancer	215	4	0	1	0	2	1
Cumulative activity of ^{131}I (MBq) before conception							
0	51	0	0	0	0	0	0
<370	76	3	0	0	0	2	1
370–3700	27	1	0	1	0	0	0
>3700	61	0	0	0	0	0	0
Activity of ^{131}I (MBq) during the year before conception							
0	162	3	0	0	0	2	1
<370	47	1	0	1	0	0	0
≥370	6	0	0	0	0	0	0

following thyroidectomy. LT4 treatment was instituted at suppressive doses in all patients, and the administration of excessive doses of LT4 at some stages of the pregnancy cannot be ruled out. Particularly relevant for the higher incidence of miscarriages during the first year following ^{131}I administration is the possible failure to control the hypothyroid status rapidly, since this was the condition for ^{131}I administration.

After radioiodine administration, the primary sources of radiation to the ovaries are the blood, bladder, gut and ^{131}I uptake in metastases close to the ovaries. Mathematical models which take into account the individual morphology of the patient lead to ovary dosage estimations that are roughly threefold higher than the MIRD estimation of 0.14 cGy/37 MBq (1 mCi) (*3,4*). Furthermore, patients were hypothyroid at the time of radioiodine administration and this condition can decrease iodine renal clearance and result in a more prolonged gonadal exposure. Women treated with more than 3.7 GBq (100 mCi) of radioiodine generally had lung metastases and received a mean cumulative activity of 8.8 GBq (237 mCi) before conception. In these women, the dose delivered to the ovaries can be estimated to be 0.4 cGy/37 MBq, assuming lung uptake of 10% at 24 hr, leading to a mean total dose to the ovaries of about 1 Gy.

Fifty-seven malformations were recorded among the 1384 children born to unexposed mothers. Assuming a doubling dose of 1 Gy (*39*), a theoretical number of 5.02 malformations would be expected for the 61 children born of mothers exposed to more than 3.7 GBq (100 mCi). Based on this theoretical value, the probability of observing among these 61 children two or less malformations is 13% (*33*). In fact, only two malformations were observed. This excludes, with a probability of 87%, that a radiation dose of 1 Gy to the ovaries results in an increase in the risk of malformation by a factor of two or more. This may be related to uncertainty regarding the doubling dose in humans which may be much higher than 1 Gy in women (*5,39*), and to the low dose rate of ^{131}I. Induced abortions are unlikely to have masked an increased incidence of malformations, since the incidence of induced abortions was not related to the cumulative activity of radioiodine administered before pregnancy.

The incidence of thyroid diseases was 1% in liveborn children, with no difference between exposed and unexposed groups.

A total of seven malignancies was observed among children, five born to unexposed mothers and two to exposed mothers. When compared to the number of expected cancers from French cancer registries, the relative risk was 2.1 (95% CI: 0.8%–4.3%), which is not increased significantly. This is in agreement with studies of offspring of the survivors of the atomic bombs in Japan (*7*) and of childhood cancer survivors who had received abdominal irradiation (*8,9*). At variance with these data, however, an association between paternal preconception exposure to radiation and the risk of leukemia among offspring has been reported in children of workers at the Sellafield nuclear plant (*11*).

CONCLUSION

With the exception of miscarriages, there is no evidence that exposure to radioiodine affects the outcome of subsequent pregnancies and offspring, even in women receiving cumulative doses to the ovaries as high as 1 Gy. Although the number of children born of mothers exposed to radioiodine is relatively small, the present data indicate that there is no reason for patients exposed to radioiodine to avoid pregnancy. The only adverse effect observed in our series is an increased incidence of miscarriages in women exposed to therapeutic radioiodine during the year which preceded conception. The question of whether and to what extent this should be attributed to radioiodine exposure remains to be established. In fact, it might well be related to an abnormal thyroid hormonal status. On the basis of the present study, we would recommend postponing conception for 1 yr after therapeutic administrations of radioiodine until control of the thyroid hormonal status has been achieved.

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EDITORIAL

Genetic Risk Assessment after Iodine-131 Exposure: An Opportunity and Obligation for Nuclear Medicine

All diagnostic and therapeutic modalities should be assessed carefully for the relative benefits and hazards so patients and physicians can make rational decisions. Although this basic principle would seem to be self-evident, the objective, practical evaluation of the pros and cons of ^{131}I therapy is a particularly complex task.

The diagnostic and therapeutic use of ^{131}I for the evaluation of thyroid remnants and regional and distant metastases of differentiated thyroid carcinoma (DTC), the ablation of remnants and the ^{131}I therapy of avid metastases have been routine for decades. It has been half a century since ^{131}I was introduced into medical practice, and a large body of information has been gathered on the diagnostic and therapeutical effectiveness of this modality (*1–4*). Nevertheless, definitive results have yet to be acquired, and the indications for the diagnostic and therapeutic use of ^{131}I are still the subject of dispute (*5,6*). Much of the difficulty arises from the low prevalence of DTC and the unusually long, natural history of the disease which necessitates the assembly of large series which are meticulously followed for decades. While the exact utility of diagnostic and therapeutic ^{131}I remains controversial, the evaluation of the hazards of these applications remains even more controversial and difficult to define. Despite the fact that virtually every paper dealing with ^{131}I treatment of DTC mentions the chance of untoward effects, particularly those proposing more restrictive protocols, the available data on this issue are scant and inconclusive.

Every nuclear physician should have a clear impression from clinical practice that ^{131}I therapy is safe and that the level of risk is smaller than that of other therapeutic modalities routinely used in oncology (e.g., external beam radiotherapy and chemotherapy), but the time has come to support this impression with indisputable data. While the risks are obviously small, fear of the unknown is the worst enemy of the medical use of radionuclides. The accurate and objective evaluation of the risk is thus an important primary task of the nuclear medicine community.

COMPLICATIONS FROM IODINE-131 THERAPY

The most common acute complications of ^{131}I therapy, radiation thyroiditis, sialadenitis, gastrointestinal discomfort and nausea, xerostomia and altered taste sensation are usually mild and self-limiting (*7,8*); in fact, specific treatment is only occasionally required. In the case of commonly used doses of ^{131}I, impairment of gonadal function appears to be a temporary reversible effect (*9,10*). Edema and hemorrhage into the tumor may rarely cause serious problems when metastases are located in the brain or near the airways. Among the late effects, permanent myelosuppression and pulmonary radiation fibrosis are dose dependent, and thus, only the minority of patients treated with very high cumulative doses are at risk. In contrast to these risks, the potential hazards from ^{131}I therapy, which have the greatest impact on the decision to utilize this modality, are the induction of second tumors (*11,12*) and genetic damage (*13–23*). These are considered to be stochastic effects with no threshold; virtually every patient treated with any dose of ^{131}I is exposed to some potential risk. Chromosomal abnormalities and genetic mutations which express themselves in the offspring of exposed subjects are only relevant to fertile individuals of reproductive age.

Nuclear physicians dealing with radionuclide therapy are asked almost daily by patients and referring physicians to define the extent of the risk. Thus, the rare contributions to the literature on this subject, such as that from Schlumberger et al. in this issue of the *Journal* (*24*), are especially valuable and useful in every day clinical practice.

The paucity of available data in the literature on this topic stems from a number of factors. Remarkable methodological difficulties arise when assessing effects that are both infrequent and which have long latent intervals before becoming manifest (years for carcinogenesis and at least a generation for diseases formed from genetic mutations). Tumors and mutations induced by exposure to ionizing radiation for medical purposes are generally indistinguishable from those arising from other causes (e.g., chemicals, viruses and background radiation). Therefore, determining the cause of carcinogenesis and of genetic mutations from ^{131}I exposure is impossible in individual cases (even if these are grouped together), but depends on the

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