Therapeutic Administration of ^{131}I for Differentiated Thyroid Cancer: Radiation Dose to Ovaries and Outcome of Pregnancies

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Radiation is known to be mutagenic. The present study updates a 10-y-old study regarding pregnancy outcome and the health of offspring of women previously exposed to radioiodine (^{131}I) during thyroid carcinoma treatment, by doubling the number of pregnancies that occurred after exposure. **Methods:** Data on 2,673 pregnancies were obtained by interviewing female patients who were treated for thyroid carcinoma but had not received significant external radiation to the ovaries. **Results:** The incidence of miscarriages was 10% before any treatment for thyroid cancer; this percentage increased after surgery for thyroid cancer, both before (20%) and after (19%) ^{131}I treatment, with no variation according to the cumulative dose. In contrast to previously reported data, miscarriages were not significantly more frequent in women treated with radioiodine during the year before conception, not even in women who had received more than 370 MBq during that year. The incidences of stillbirths, preterm births, low birth weight, congenital malformations, and death during the first year of life were not significantly different before and after ^{131}I therapy. The incidences of thyroid and nonthyroid cancers were similar in children born either before or after the mother's exposure to radioiodine. **Conclusion:** There is no evidence that exposure to radioiodine affects the outcomes of subsequent pregnancies and offspring. The question as to whether the incidences of malformations and thyroid and nonthyroid cancers are related to gonadal irradiation remains to be established. The doubling dose is still being heatedly debated, and the value of 1 Gy as the doubling dose in humans should be reevaluated.

Key Words: differentiated thyroid carcinoma; radioiodine therapy; pregnancy outcome; radiation dose; ovaries

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Radioiodine (^{131}I) is widely used in the treatment of thyroid cancer (*1,2*), and the high ^{131}I activities administered may deliver significant radiation doses to the ovaries. Treatment with radioiodine usually consists of administering 3,700 MBq (100 mCi), and the radiation dose to the ovaries has been estimated to be 140 mGy for 3,700 MBq (*3*). However, very few studies have reported on outcomes, such as miscarriages, congenital abnormalities, and malignancies, in the offspring of young women treated for this cancer (*4,5*).

In 1996, we reported the largest study on pregnancies (n = 2,113) occurring after 1970, 258 of which occurred after exposure to radioiodine (*6*). The only adverse effect observed was an increased incidence of miscarriages in women exposed to therapeutic radioiodine during the year preceding conception. On the basis of that study, we recommended postponing conception for 1 y after the therapeutic administration of radioiodine and until the thyroid hormone status was verified. However, in that same study, only 96 pregnancies occurred after exposure to activities exceeding 3,700 MBq. We present here an update of that study, by doubling the number of pregnancies that occurred after ^{131}I therapy.

MATERIALS AND METHODS

Patients

All women seeking care for a differentiated thyroid carcinoma between February 1990 and December 1993 at the Institut Gustave Roussy, Villejuif, France; the Institut Jean Godinot, Reims, France; the Institut François Baclesse, Caen, France; and the Institute of Endocrinology of the University of Pisa, Pisa, Italy, were interviewed by a trained data manager. A total of 1,869 women were thus interviewed. The details of treatments that these women received have been described elsewhere (*6*). From 1994 to 2004, we routinely interviewed the entire population of women with thyroid cancer who sought care at the Institut Gustave Roussy.

The following features were recorded for each pregnancy: induced abortion, miscarriage, stillbirth, prematurity (defined as a gestational age of <37 wk), birth weight below the 10th percentile for the gestational age, congenital abnormality, and death during the first year of life. Congenital abnormalities were defined according to International Classification of Diseases, 9th Revision (ICD-9), rubrics. Later deaths, thyroid diseases, and tumors at other sites were recorded for live-born children. Only pregnancies occurring after 1970 were considered. A validation

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study performed on 116 pregnancies confirmed high-quality interviews (*6*).

Radiation Doses to Ovaries

After radioiodine therapy, the primary sources of radiation doses to the ovaries are the blood, bladder, gut, and ^{131}I uptake in metastases close to the ovaries. Mathematic models of individual patient morphology have estimated doses to the ovaries to be approximately 3-fold higher than the MIRD estimation of 1.4 mGy/37 MBq (1 mCi) (*3*). Furthermore, hypothyroidism at the time of radioiodine administration can decrease renal iodine clearance and result in more prolonged gonadal exposure.

Women treated with more than 3.7 GBq (100 mCi) of radioiodine generally had lung metastases and had received a mean cumulative activity of 8,800 MBq (237 mCi) before conception. For these women, the dose delivered to the ovaries was estimated to be 4 mGy/37 MBq, assuming 10% lung uptake at 24 h, leading to a mean total dose to the ovaries of approximately 1 Gy.

Statistical Methods

To take into account possible multiple pregnancies and the correlation between the outcomes of pregnancies in the same women, we analyzed pregnancy outcomes by using a generalized estimating equation (*7*) for repeated measurements. We chose an exchangeable working correlation matrix. This assumption implies that the correlation between distinct pregnancies in the same woman is the same regardless of the rank of the pregnancy. The correlation structure can thus be described with a single correlation parameter, $0 < \rho < 1$. For studying the association between radioiodine activity and the occurrence of adverse events, a binomial distribution was assumed for the observed events. Results were verified by basic logistic regression analysis. Parameters were tested with Wald and likelihood ratio tests. For these calculations in the unexposed women, we used only the pregnancies that occurred before any radioiodine administration.

We investigated the risk factors exclusively for induced abortions and miscarriages and not for thyroid diseases and other cancers in children because satisfying analyses were not possible with the small number of cases.

Because factors other than radiation history may have influenced the outcome of a pregnancy, analyses were adjusted for these variables. Age, smoking, alcohol intake, use of medication (such as antidepressants and β-blockers) during pregnancy, and socioeconomic status were considered. A low socioeconomic status was defined according to International Classification of Professions criteria (*8*). The following classifications were included: 520–599, 610–640, 710–839, 870–874, 890–910, 930–939, and 950–958. If the definition of a patient's profession was missing, then that of the spouse or partner was considered. All of these analyses were performed with SAS computer software (SAS Institute Inc.).

The observed number of thyroid and other cancers in live-born children was compared with the expected number from incidence data in the French general population. Because no national cancer registry exists in France, we used estimations published by the French Network of Local Cancer Incidence Registries (Francim). These rates were used for all children, including Italian children, because the incidences of cancer below the age of 40, the approximate maximum age of offspring potentially included in the present study, are similar among most countries (*9*). The standardized incidence ratio was defined as the ratio of the observed number of cancers to the expected number of cancers, and its confidence interval (CI) was estimated by assuming a Poisson distribution for the observed number of cancers and using maximum-likelihood methods (*10*). 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 definitions of stillbirth differed in France and Italy during the study period and because it was impossible 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 from French national data and yielded standardized mortality ratios, which express the ratio of observed number of deaths to expected number of deaths. During the study period, these death rates in the general population were similar in France and Italy. These analyses were performed with AMFIT software (Hirosoft Int. Corp.).

RESULTS

Of the 1,869 interviewed patients, 1,534 (82.1%) became pregnant at least once, and a total of 5,723 pregnancies were recorded. The 2,852 pregnancies that occurred before 1970 were excluded from the analysis because the information reported for most of these patients was not adequately validated. Of the 2,871 remaining pregnancies, 198 were excluded because of previous exposure to therapeutic radiation other than radioiodine.

The remaining 2,673 pregnancies, registered in 1,126 patients, were included in the present study: 2,078 pregnancies had occurred before thyroid carcinoma treatment, 112 had occurred in patients who had undergone surgery alone for thyroid cancer, and 483 had occurred in patients who had been exposed to radioiodine. Among these last patients, 212 of whom had been treated with 3,700 MBq or more of ^{131}I, 95 (45%) had received 1 treatment, 58 (27%) had received 2 treatments, 33 (16%) had received 3 treatments, and 26 (12%) had received 4–11 treatments. The mean interval between the last ^{131}I treatment and conception was 35 mo (range, 0–243 mo). No progression of thyroid carcinoma, as assessed by follow-up data obtained during pregnancy (clinical examination and thyroglobulin determination on levothroxine treatment), was observed in any of these women during pregnancy.

Induced Abortions (Therapeutic and Elective)

A total of 341 induced abortions (therapeutic and elective) were reported (Table 1), 221 before any treatment, 26 after thyroid surgery alone, and 94 after both surgery and exposure to ^{131}I. Induced abortions were more frequent after surgical treatment both without and with ^{131}I administration than before any treatment (OR = 2.14, 95% CI = 1.67–2.75). After adjustment for age at pregnancy, exposure to higher ^{131}I activity before pregnancy was not associated with a greater probability of an induced abortion (OR [for 3,700 MBq] = 0.83, 95% CI = 0.68–1.00). Nevertheless, both the cumulative radioiodine activity received during the year preceding pregnancy ($P < 10^{-4}$ for trend) and smoking during pregnancy (OR = 2.15, 95% CI = 1.15–4.0) were found to play significant roles in the probability of an induced abortion. Induced abortions

TABLE 1
Pregnancies and Induced Abortions (Therapeutic and Elective) as Function of Radioiodine Exposure

Factor (overall population)	No. of pregnancies	No. (%) of induced abortions	Age (y) at conception (mean ± SD)	No. (%) with: Alcohol intake	Smoking habit
Before any treatment	2,078	221 (11)	27 ± 6	158 (8)	238 (11)
After surgery for differentiated thyroid carcinoma	595	120 (20)		95 (16)	71 (13)
Cumulative radioiodine activity (MBq) before conception (mean ± SD)					
0	112	26 (23)	30 ± 5	12 (11)	14 (13)
<370 (185 ± 77)	197	45 (23)	31 ± 6	41 (22)	29 (15)
370–3,700 (2,257 ± 1,147)	74	15 (20)	30 ± 5	7 (10)	8 (11)
>3,700 (8,066 ± 5,735)	212	34 (16)	31 ± 6	35 (17)	20 (9)
Radioiodine activity during year before conception (MBq)					
0	437	71 (16)	32 ± 6	62 (15)	58 (13)
<370	124	31 (25)	30 ± 6	26 (22)	12 (10)
≥370	34	18 (50)*	29 ± 6	7 (21)	1 (3)

*$P < 0.05$, as determined by χ^2 test for heterogeneity.

(Table 2) were more frequent in women over 35 y and in those who had not avoided alcohol or tobacco during pregnancies ($P < 10^{-4}$, OR = 3.3, 95% CI = 2.5–4.3).

A total of 18 induced abortions were observed among the 34 pregnancies that occurred in women who had received ^{131}I activities equal to or higher than 370 MBq (10 mCi) during the year preceding conception, and this proportion was higher than those during the other pregnancies ($P < 10^{-4}$). The proportion of induced abortions did not vary according to the interval between ^{131}I administration and pregnancy: 22 pregnancies occurred 6 mo or less after radioiodine therapy and resulted in 2 miscarriages and 12 induced abortions, and 12 pregnancies occurred between 6 and 12 mo after the last ^{131}I administration and resulted in 6 induced abortions and 1 miscarriage.

The following parameters were studied after the exclusion of pregnancies that ended in induced abortions.

TABLE 2
Untoward Outcomes of 2,673 Pregnancies as Function of Other Risk Factors at Time of Pregnancy

Factor (overall population)	No. of pregnancies	Induced abortions (%)	Miscarriages (%)	Stillbirths (%)	% of live births (n = 2,009) with: Term of <37 wk	Low birth weight	Death at <1 y	Malformation
Age (y) at conception								
<35	2,320	11	9	1.6	6.8	8	0.9	3.4
>35	353	27.5*	19*	2.1	5.4	6	1.4	1.7
Smoking habit								
No	2,319	10.1	10.5	1.6	6.6	7.8	1	3.5
Yes	309	25.6*	11	1.5	5.5	8.1	0.7	1.3*
Missing	45							
Alcohol intake								
No	2,372	10.8	10.5	1.7	6.8	7.8	0.9	3.5
Yes	253	21.7*	12.3	1.2	4	8.3	1.2	0.8*
Missing	48							
Socioeconomic status								
Not low	1,750	12.6	11.1	1.7	5.5	7	1	3.4
Low	354	9.9	10.9	2	4.7	10.9*	1.3	3.9
Missing	569							

*$P < 0.05$, as determined by χ^2 test for heterogeneity.
Induced abortions include both therapeutic and elective.

Miscarriages and Stillbirths

A total of 193 miscarriages (10.4%) were observed among the 1,857 pregnancies that occurred before any treatment. They were more frequent (20.7%) in pregnancies occurring after surgery for differentiated thyroid cancer, but the frequency of miscarriages was 19.0% in the 86 pregnancies that occurred after surgery alone and after no previous exposure to ^{131}I. The only significant factors in the occurrence of miscarriages were the occurrence of a pregnancy after thyroid cancer (with or without radioiodine treatment) (OR = 1.59, 95% CI = 1.19–2.13), the mother's age at pregnancy exceeding 35 y (for both treated and untreated women) (OR = 2.12, 95% CI = 1.54–2.91), and a low birth weight, which was more common in the low-socioeconomic-status group ($P < 0.05$). After adjustment for age at pregnancy, no correlation was evidenced between cumulative ^{131}I activity and the occurrence of a miscarriage. These results were confirmed when only exposure was considered during the year before conception.

Table 3 shows stillbirths in both treated and untreated women, and Table 4 gives the odds ratios for risk factors regarding abortions and miscarriages for all the women after thyroid surgery ($n = 595$). During the pregnancies of women who took medications ($n = 791$), miscarriages were slightly more frequent (9.9% vs. 12.4%, $P = 0.06$, OR = 1.04, NS) and prematurity was significantly more frequent (10.4% vs. 5.5%, $P = 2.10–4$, OR = 1.85, 95% CI = 1.34–2.56).

Live Births

Table 5 shows the following characteristics for the 2,009 live births: sex, prematurity, low birth weight, death during the first year, thyroid disease, and nonthyroid cancers. None of these characteristics appeared to be modified by previous surgery or radioiodine exposure.

Twenty-two of the 1,633 children born to unexposed mothers died before their first birthday, and 3 of 309 died after exposure (OR = 0.41, 95% CI = 0.12–1.37), leading to a cumulative death rate of 1.35% from 1 to 20 y. This rate was not different from that observed in the general population (standardized mortality ratio, 1.3; 95% CI = 0.8–1.9).

Seventy-nine live-born children had a malformation. Among them, 9 were born to a previously exposed mother: 3 had a cardiac malformation (222, 8,140, and 740 MBq), 1 had esophageal atresia (222 MBq) and died, 1 had coloboma iridis (11,396 MBq), 1 had Down syndrome (1,702 MBq), 2 had a hip luxation (4,810 and 1,776 MBq), and 1 had a digestive malformation (4,810 MBq) (Table 6). The risk of a malformation was not associated with cumulative ^{131}I activity previously administered for thyroid carcinoma (OR [for 3,700 MBq] = 0.88, 95% CI = 0.55–1.40).

Assuming an average radiation dose of 140 mGy/3.7 GBq, the average dose received by the ovaries before conception was 161 mGy in the 309 pregnancies that occurred after exposure to radioiodine. Four malformations were observed in the 139 children born to mothers who had received more than 3.7 GBq (mean activity = 8.1 GBq, mean dose to ovaries = 305 mGy). Assuming a doubling dose of 1 Gy, a theoretic number of 7.6 malformations would be expected in these patients, a value that can be excluded with a probability of 88%.

Thyroid diseases were observed in 42 children (Table 7), 8 of whom were born to exposed mothers. Six children developed autoimmune hypothyroidism, 1 had Graves' disease, 8 had nontoxic goiter, 4 had benign nodules, 14 had a nonoperated nodule, and 3 had thyroid cancer (at the ages of 17, 17, and 21 y). Neither cumulative ^{131}I activity nor the activity administered during the year before conception was associated with an increased risk of thyroid diseases in children, and no thyroid cancer occurred in children born to exposed mothers. Our study was adequately powered (12%) to evidence an increase in risk by a factor of 1.3 (assuming a doubling dose of 1 Gy, applied to an estimated dose of 305 mGy) in the 139 pregnancies that occurred after ^{131}I therapy. The theoretic number of thyroid

TABLE 3
Outcomes of 2,332 Pregnancies as Function of ^{131}I Exposure, Excluding Those Ending in Induced Abortions

Factor (overall population)	No. of pregnancies	Miscarriages		Stillbirths	
		No.	%	No.	%
Before any treatment	1,857	193	10.4	28	1.5
After surgery for thyroid cancer	475	92	20.7	6	1.6
Cumulative radioiodine activity before conception (MBq)					
0	86	17	19.8	2	2.3
<370	152	28	18.4	3	2.0
370–3,700	59	9	15.3	0	0
>3,700	178	38	21.4*	1	0.6
Radioiodine activity during year before conception (MBq)					
0	366	69	18.9	6	1.6
<370	93	20	21.5	0	0
≥370	16	3	18.8	0	0

*$P < 0.05$, as determined by χ^2 test for heterogeneity.

TABLE 4
Risk Factors for Induced Abortion (Therapeutic and Elective) and Miscarriage Among 595 Women After Thyroid Surgery, Adjusted for Age at Pregnancy

Risk factor	Induced abortions OR	Induced abortions 95% CI	Miscarriages OR	Miscarriages 95% CI
Cumulative ^{131}I* activity (for 37 MBq)	0.998	0.996–1	1.0004	0.999–1.002
Alcohol intake vs. no alcohol intake†	2.43	1.73–3.40	1.27	0.68–2.37
Smoking habit vs. no smoking habit†	3.21	2.37–4.34	1.04	0.68–1.61
Low socioeconomic status vs. high socioeconomic status†	0.71	0.90–1.99	1.58	0.84–2.98
Medications vs. no medications†	0.67	0.429–1.05	0.75	0.32–1.75
Dose during last year before pregnancy (MBq)				
3.7–370 vs. <3.7	1.75	1.08–2.82	1.10	0.63–1.91
More than 370 < 3.7	5.74	2.79–11.8	0.53	0.15–1.91

*Kept as confounder in multivariate analysis.
†During pregnancy after occurrence of thyroid cancer.

diseases would be 2.6, a value that can be excluded with a probability of 88%.

Four children (0.4%) developed malignant disease at sites other than the thyroid gland at the mean age of 20 y (range, 8–29 y): non-Hodgkin's lymphoma at the age of 11 y, Hodgkin's disease at the age of 27 y, malignant melanoma at the age of 27 y, and a brain tumor at the age of 29 y. None of these 4 children was born to a mother who had been exposed to therapy with radioiodine. The cumulative incidence of cancer was 0.4%, and the relative risk was 2.0 (95% CI = 0.8–4.0), compared with the expected number of cancers from Francim estimations.

DISCUSSION

We report here the largest cohort of pregnancies in women treated for thyroid cancer, including 2,673 pregnancies, 483 of which occurred after ^{131}I therapy. No increases were evidenced in miscarriages, malformations, thyroid diseases, and cancer in offspring conceived after ^{131}I administration. Our study was sufficiently powered to provide additional information on the assessment of the teratogenic risks of ^{131}I.

We excluded 2,852 pregnancies that occurred before 1970 because the information reported for most of these patients could not be adequately validated. Also, most of these pregnancies occurred before radioiodine administration and would therefore not have been relevant for investigating the risk of ^{131}I exposure in offspring.

In the present study, radioiodine was the only identified source of radiation therapy before pregnancy; all women who reported other types of radiation therapy were excluded.

In contrast, we did not exclude pregnancies in women who had undergone radiographs of the pelvis or abdomen.

TABLE 5
Outcomes of 2,009 Live Births as Function of Radioiodine Exposure

Factor (overall population)	Radiation dose, in mGy, to ovaries (range)	No. of live births	% of girls	% (no.) with: Term of <37 wk	Low birth weight	Death at <1 y	Malformation	Thyroid disease	Cancer
Before any treatment		1,633	49.3	7.0 (114)	10.3 (168)	1.4 (22)	4.2 (68)	2.1 (34)	0.4 (6)
After surgery for thyroid cancer		376	45.3	12.8 (44)	8.6 (33)	0.8 (3)	2.9 (11)	2.1 (8)	0.5 (2)
Cumulative radioiodine activity before conception (MBq)									
0	0	67	40.6	6.0	7.5	0.0	3.0	0.0	0.0
<370	7 (0–13)	121	50	11.6	13.2	1.6	1.7	4.0	2.4
370–3,700	85 (14–140)	49	40.8	4.1	2.0	0.0	6.1	2.0	0.0
>3,700	305 (141–1,443)	139	45	17.3	6.5	0.7	2.9	1.4	0.0
Radioiodine activity during year before conception (MBq)									
0	0	290	46.6	12.8	8.0	1.0	3.4	1.7	1.0
<370	3.92	73	39.7	12.3	8.2	0.0	2.7	4.1	0.0
≥370	144.2	13	46.2	15.4	7.7	0.0	0.0	0.0	0.0

TABLE 6
Classification of 79 Congenital Malformations Observed in 2,009 Live-Born Children

Congenital malformation (ICD-9 code)	*n*
Neural tube defects (742)	
Hydrocephalus	1
Anencephaly	1
Hemiparesis	1
Anomalies of eyes (743)	
Cataract	3
Glaucoma	2
Other	2
Anomalies of ear, face, and neck (744)	
Deafness	2
Heart defects (745–746)	
Tetralogy of Fallot	1
Cardiac septal defect	5
Other	3
Anomalies of respiratory system (748–749)	
Collapsed lung	2
Cleft palate	1
Cleft lip	1
Anomalies of digestive system (750–751)	
Esophageal atresia	1
Gastroschisis	2
Pyloric stenosis	6
Diaphragmatic hernia	1
Other	1
Anomalies of genital organs (752)	
Hypospadias	3
Cryptorchidism	2
Anomalies of urinary system (753)	
Bladder and ureter dysfunction	10
Musculosketetal abnormalities (754–755)	
Polydactyly and syndactyly	7
Hip dysplasia	9
Talipes equinovarus	3
Leg atrophy	2
Patella anomaly	1
Thoracic anomaly	1
Other	2
Down syndrome (758.0)	2
Marfan syndrome (759.8)	1

This decision was made because only information on radiographs during the follow-up of thyroid cancer was available, and this information was probably only part of a lifetime radiologic history. It is highly unlikely that our choice introduced a bias leading to an underestimation of the risk attributable to ^{131}I exposure in the present study. Indeed, in the present study, women who had the most radiographs had also received the largest amounts of ^{131}I: The mean total ^{131}I activity before pregnancy was 518 MBq in women who did not report any radiograph of the pelvis or the abdomen during the follow-up of thyroid cancer, whereas the activities were 4,995 MBq in those who reported 1 radiograph, 5,143 MBq in those who reported 2 radiographs, and 10,175 MBq in those who reported 3–6 radiographs.

This update confirms all of the results of our previous publication (*6*), except for the notable increased risk of miscarriage with increasing activity administered the year before conception, a finding that was not confirmed in the present study. In fact, since this last publication (*6*), 6 additional pregnancies have been registered in the highest category of activity (>370 MBq), and none has ended in a miscarriage. In addition, 1 of the 4 miscarriages previously reported in this category occurred after external radiotherapy and was therefore excluded from the present analysis. We use the term "induced abortion" because we were not able to classify these abortions as therapeutic or elective. Indeed, we were able to document the abortion for only 45 pregnancies, all of them for therapeutic purposes (dreaded exposure, ongoing treatment, and malformation suspicion).

In the absence of consensus for another value, we assumed a doubling dose (the dose required to produce genetic damage equal to the spontaneous mutation rate) of 1 Gy for some of our analyses. The 1993 report of UNSCEAR, which mentioned this value, also showed that it is probably conservative and that atomic bomb survivor results led to values 3 times higher and that strong uncertainties remain about this value in humans, in whom it may be much higher (*11–14*) (UNSCEAR), because humans could be genetically less radiosensitive than mice (*15,16*).

In general, few women had received a dose to the ovaries approximating 1 Gy in the present study: Only 139 women had received more than 140 mGy (mean dose: 305 mGy). Whatever the particular event studied, the present study was not sufficiently powered to detect an increase in risk.

We did not find any increase in untoward pregnancy outcomes, such as stillbirths or malformations. Our results concerning stillbirths are consistent with the last publication on stillbirths in the offspring of female Japanese atomic bomb survivors, which included 55,303 births after a mean dose approximating 140 mGy; 894 of those pregnancies ended in a stillbirth (*17*). Our results are also consistent with those of the Childhood Cancer Survivor Study, which included 4,029 pregnancies; 37 of those pregnancies ended in a stillbirth (*18*). Up to now, studies regarding the consequences of the Chernobyl accident have been less informative because they are only temporal trend studies without individual dose estimations: An increased risk of stillbirths was found in some Eastern European countries during a period starting 1 mo after the Chernobyl accident and ending 2 y thereafter, but the results were considered by the authors to be inconsistent with the low level of effective radiation doses received by these populations (0.1–0.2 mSv/y) (*19*). Similar results for similar dose levels were found in Bavaria and throughout Germany during the year after the accident, but total infant mortality gradually decreased during the same period (*19–21*). In contrast to but consistent with the Japanese atomic bomb survivor results, the stillbirth rate appeared to be unaffected by the Chernobyl accident in Finland, despite a well-documented monthly dose estimation (*22*), in Sweden (*23*), and in Norway (*24*).

TABLE 7
Thyroid Diseases in Live-Born Children as Function of Radioiodine Exposure

Factor (overall population)	No. of live births	Total no. of thyroid diseases	No. with: Hypothyroidism	Graves' disease/ hyperthyroidism	Euthyroid goiter	Benign nodule	Differentiated thyroid cancer	Nonresectable nodule
Before any treatment	1,633	34	5	3	8	2	3	13
After surgery for thyroid cancer	376	8	1	3	1	2	0	1
Cumulative radioiodine activity before conception (MBq)								
0	67	0	0	0	0	0	0	0
<370	121	5	0	1	1	2	0	1
370–3,700	49	1	0	1	0	0	0	0
>3,700	139	2	1	1	0	0	0	0
Radioiodine activity during year before conception (MBq)								
0	290	5	1	0	0	2	0	0
<370	73	3	0	2	1	0	0	0
≥370	13	0	0	0	0	0	0	0

We failed to find increases in all-cause mortality and cancer mortality among live-born children. These results are consistent with those observed for the offspring of female Japanese atomic bomb survivors: 1,281 deaths, 278 of which were from cancer (*25*). Similar results were observed for cancer incidence in the offspring of female Japanese atomic bomb survivors in a study including 709 cancers (*26*).

In the present study, only 9 malformations were observed in 309 live births to exposed women (2.9%), compared with the 12.9 malformations expected from the rate observed in offspring conceived before thyroid cancer or iodine therapy, in the absence of the effect of exposure, and compared with the 16.9 malformations expected with the assumption of a doubling dose of 1 Gy. Despite these low values, we can exclude the value of 16.9 with a probability of 88%. Our findings are consistent with the fact that preconception irradiation is not related to malformations in live births, as highlighted in a previous, larger study (*17*). Similarly, our cohort included only 8 thyroid diseases in 309 live births to exposed women (2.5%). Among the 2009 live births in our cohort, only 3 developed differentiated thyroid carcinoma, of whom none were born to the 309 previously exposed mothers. Therefore, we were not able to demonstrate that radiation exposure of the mother detectably increased the thyroid cancer incidence.

Differentiated thyroid cancer is one of the nonfamilial cancers that generates the highest heritability: The proportion of such cancer attributable to genetic susceptibility was estimated to be 53% in an analysis based on the national Swedish Family Cancer Database, a value higher than that for any other cancer (*27*). Because our study included only 2009 live births, we were not able to join the debate about differentiated thyroid cancer heritability, by comparing the incidence of thyroid cancer among the offspring in our cohort with that expected in the general population.

We did not analyze the neuropsychological development of the offspring, which cannot be investigated by a face-to-face interview with the mother. Nevertheless, published data consistently document a relationship between perturbation of maternal thyroid hormone status and developmental outcomes in offspring (*28*). These results could have major implications in thyroid cancer offspring, and therefore further studies should investigate this issue.

CONCLUSION

There is no evidence that exposure to radioiodine affects the outcome of subsequent pregnancies and offspring, even in women receiving cumulative radiation doses to the ovaries as high as 1 Gy. Although the number of children born to mothers exposed to radioiodine is relatively small, the data that we report here indicate that there is no reason for patients exposed to radioiodine to avoid pregnancy after ^{131}I treatment for differentiated thyroid carcinoma. The question as to whether and to what extent adverse events should be attributed to radioiodine exposure continues to fuel debate. An abnormal thyroid hormone status may be a factor. On the basis of the present study, we recommend postponing conception until the thyroid hormone status has been verified.

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REFERENCES

1. Beierwaltes WH, Nishiyama RH, Thompson NW, Copp JE, Kubo A. Survival time and "cure" in papillary and follicular thyroid carcinoma with distant metastases: statistics following University of Michigan therapy. *J Nucl Med.* 1982;23:561–568.
2. Dunn JT. Choice of therapy in young adults with hyperthyroidism of Graves' disease: a brief, case-directed poll of fifty-four thyroidologists. *Ann Intern Med.* 1984;100:891–893.
3. Loevinger R, Budinger TF, Watson EE. *MIRD Primer.* Reston, VA: Society of Nuclear Medicine; 1999.
4. Bal C, Kumar A, Tripathi M, et al. High-dose radioiodine treatment for differentiated thyroid carcinoma is not associated with change in female fertility or any genetic risk to the offspring. *Int J Radiat Oncol Biol Phys.* 2005;63:449–455.
5. Ehrenheim C, Hauswirth C, Fitschen J, Martin E, Oetting G, Hundeshagen H. Genetic risk after high dose radioiodine therapy with regard to gonadal dose [in German]. *Nuklearmedizin.* 1997;36:157–166.
6. Schlumberger M, De Vathaire F, Ceccarelli C, et al. Exposure to radioactive iodine-131 for scintigraphy or therapy does not preclude pregnancy in thyroid cancer patients. *J Nucl Med.* 1996;37:606–612.
7. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics.* 1988;44:1049–1060.
8. *Classification Internationale Type des Professions*. Bureau International du Travail; 1985.
9. Muir C, Waterhouse J, Mack T, Powell J. *Cancer Incidence in Five Continents*. Lyon, France: IARC; 1987. IARC Scientific Publication No. 88.
10. Breslow NE, Day NE. *Statistical Methods in Cancer Research.* Vol II. The Design and Analysis of Cohort Studies. Lyon, France: IARC; 1987. IARC Scientific Publication No. 82.
11. Sankaranarayana K, Chakraborty R. Ionizing radiation and genetic risks. XI. The doubling dose estimates from the mid-1950s to the present and the conceptual change to the use of human data on spontaneous mutation rates and mouse data on induced mutation rates for doubling dose calculations. *Mutat Res.* 2000; 453:107–127.
12. Schull WJ, Otake M, Neel JV. Genetic effects of the atomic bombs: a reappraisal. *Science.* 1981;213:1220–1227.
13. Lyon MF. James Neel and the doubling dose concept. *Mutat Res.* 2003;543: 115–120.
14. Nomura T. Transgenerational carcinogenesis: induction and transmission of genetic alterations and mechanisms of carcinogenesis. *Mutat Res.* 2003;544:425–432.
15. Neel JV, Schull WJ, Awa AA, et al. The children of parents exposed to atomic bombs: estimates of the genetic doubling dose of radiation for humans. *Am J Hum Genet.* 1990;46:1053–1072.
16. Neel JV, Lewis SE. The comparative radiation genetics of humans and mice. *Annu Rev Genet.* 1990;24:327–362.
17. Otake M, Schull WJ, Neel JV. Congenital malformations, stillbirths, and early mortality among the children of atomic bomb survivors: a reanalysis. *Radiat Res.* 1990;122:1–11.
18. Green DM, Whitton JA, Stovall M, et al. Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Am J Obstet Gynecol.* 2002;187:1070–1080.
19. Grosche B, Irl C, Schoetzau A, van Santen E. Perinatal mortality in Bavaria, Germany, after the Chernobyl reactor accident. *Radiat Environ Biophys.* 1997; 36:129–136.
20. Scherb H, Weigelt E, Bruske-Hohlfeld I. European stillbirth proportions before and after the Chernobyl accident. *Int J Epidemiol.* 1999;28:932–940.
21. Scherb H, Weigelt E, Bruske-Hohlfeld I. Regression analysis of time trends in perinatal mortality in Germany 1980-1993. *Environ Health Perspect.* 2000;108: 159–165.
22. Auvinen A, Vahteristo M, Arvela H, et al. Chernobyl fallout and outcome of pregnancy in Finland. *Environ Health Perspect.* 2001;109:179–185.
23. Ericson A, Kallen B. Pregnancy outcome in Sweden after the Chernobyl accident. *Environ Res.* 1994;67:149–159.
24. Irgens LM, Lie RT, Ulstein M, et al. Pregnancy outcome in Norway after Chernobyl. *Biomed Pharmacother.* 1991;45:233–241.
25. Izumi S, Suyama A, Koyama K. Radiation-related mortality among offspring of atomic bomb survivors: a half-century of follow-up. *Int J Cancer.* 2003;107:292–297.
26. Izumi S, Koyama K, Soda M, Suyama A. Cancer incidence in children and young adults did not increase relative to parental exposure to atomic bombs. *Br J Cancer.* 2003;89:1709–1713.
27. Czene K, Lichtenstein P, Hemminki K. Environmental and heritable causes of cancer among 9.6 million individuals in the Swedish Family-Cancer Database. *Int J Cancer.* 2002;99:260–266.
28. LaFranchi SH, Haddow JE, Hollowell JG. Is thyroid inadequacy during gestation a risk factor for adverse pregnancy and developmental outcomes? *Thyroid.* 2005;15:60–71.