Radioiodine Therapy and Subsequent Pregnancy

artigo original

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Recebido em 17/08/06
Revisado em 26/12/06
Aceito em 07/01/07

ABSTRACT

Objectives: To evaluate abortion and fetal congenital anomaly rates in women previously submitted to radioiodine therapy for differentiated thyroid carcinoma. **Study design:** A case-control study of 108 pregnant women, 48 cases whose pregnancies were evaluated after they had undergone radioiodine therapy for differentiated thyroid carcinoma, and the control group consisted of 60 healthy pregnant women. **Results:** Of a total of 66 pregnancies, 14 conceived within the first year, 51 one or more years after the last administration of ^{131}I, the medical record of one patient was not available. The interval between the last radioiodine therapy administration and conception ranged from 1 month to 10 years. There were a total of 4 miscarriages, 2 of them for unknown reasons. There was one case of congenital anomaly and two preterms birth. Nine women presented the following pregnancy events: placental insufficiency, hypertensive crisis, placental detachment, risk of miscarriage, preterm labour and four miscarriages. No statistical difference was observed between the studied and control groups. **Conclusion:** Radioiodine was followed by no significant increase in untoward effects in neither the pregnancy nor the offspring. **(Arq Bras Endocrinol Metab 2007;51/4:534-540)**

Keywords: Radioiodine; Pregnancy; Abortion; Congenital anomaly

RESUMO

Gravidez Após Radioiodoterapia.
Objetivo: Avaliar a taxa de aborto e anomalia congênita em mulheres que engravidaram após radioiodoterapia para carcinoma diferenciado de tireóide. **Pacientes e método:** Estudo de caso controle com 108 mulheres, 48 submetidas à radioiodoterapia para carcinoma diferenciado de tireóide e 60 mulheres saudáveis (grupo controle). **Resultados:** De 66 gestações (grupo de pacientes que receberam radioiodo), 14 ocorreram no primeiro ano e 51 mais de um ano após a administração do ^{131}I. Não foi possível coletar dados de uma paciente. O intervalo entre a última dose de ^{131}I e a concepção variou de 1 mês a 10 anos. Ocorreram 4 abortos, 2 de causas desconhecidas. Houve 1 caso de anomalia congênita e 2 pretermos. Nove pacientes que receberam ^{131}I apresentaram intercorrências durante a gravidez: insuficiência placentária, crise hipertensiva, descolamento de placenta, ameaça de aborto, trabalho de parto prematuro e 4 abortos. Não houve diferença estatística entre o grupo estudado e o controle. **Conclusão:** O uso da radioiodoterapia para carcinoma diferenciado de tireóide em mulheres não foi relacionado com aumento de efeitos adversos nas mães e suas proles. **(Arq Bras Endocrinol Metab 2007;51/4:534-540)**

Descritores: Radioiodo; Gravidez; Aborto; Anomalia congênita

RADIOIODINE THERAPY HAS been used for more than 50 years in differentiated thyroid carcinoma (1-4). A high proportion of patients with thyroid cancer are cured after surgery and ^{131}I therapy (5). The need to control the metastatic disease may require more doses of ^{131}I, resulting in a cumulative dose of hundreds of mCi.

Young females compose the majority of patients with well-differentiated thyroid carcinoma (4,6-8) and pregnancy after undergoing thyroid carcinoma treatment is not uncommon.

The idea that radiation is mutagenic and may affect germ cells resulting in genetic damage to offspring, such as miscarriages, congenital anomalies and malignancies, has raised concern regarding radioiodine therapy in the management of thyroid diseases in women during their child-bearing years. Data on the genetic effects of ^{131}I therapy in thyroid disorders are scant. Studies on pregnancy and offspring outcomes in patients treated with ^{131}I for thyrotoxicosis (9-11) or thyroid cancer have not revealed any significant effects (12-14).

Several studies (4,6,15,16) have demonstrated that previous use of high doses of ^{131}I does not require the avoidance of pregnancy; however, it is important to recommend to those women of child-bearing age who have received therapy with ^{131}I thyroid cancer that pregnancy should be avoided, at least during the first year post-therapy. However, there is little information about that.

The purpose of this study is to investigate a group of women with differentiated thyroid carcinoma submitted to surgery and therapeutic doses of ^{131}I before conception, analyzing the pregnancy outcome and the health status of their offspring.

PATIENTS AND METHODS

In this case-control study, we evaluated the medical records of 240 female patients with differentiated thyroid carcinoma (199 cases of papillary and 41 of follicular carcinoma). At conception, patients aged from 13 to 42 years. They had previously undergone thyroidectomy, subsequent radioiodine therapy and were currently being treated with suppressive and replacement doses of thyroxine, being followed at the Departments of Nuclear Medicine at Hospital Universitário Clementino Fraga Filho, Instituto Nacional do Câncer (INCa) and Hospital Servidores do Estado do Rio de Janeiro (HSE), from 1980 to 2005.

Among the 240 recruited patients, 48 women had 66 single-fetus pregnancies with 6 abortions (2 patients had two induced abortions and became pregnant again, 2 were spontaneous abortions and 2 were for unknown reasons), 37 were above 44 years of age and presented no pregnancy history, 14 were submitted to hysterectomy and tubal ligation before radioiodine therapy, 21 did not become pregnant because they did not want to, 3 died (one died of AIDS, one died of thyroid cancer and the medical record of the third one did not state the cause of death), 1 lost her child in a car accident, 1 had an induced abortion and did not want to become pregnant again, 22 had already had children, 83 had no follow-up and 10 were lost to follow-up. The disease (thyroid carcinoma) was controlled in all of the patients. The serum levels of TSH (thyroid-stimulating hormone) were normal and suppressive.

The selected patients were invited either by letter or telephone to participate in an interview in order to collect the following data: age at diagnosis, age at conception, doses of ^{131}I, interval between the last administration of ^{131}I and conception, pregnancy events, birth weight, birth length, gender, congenital anomalies and health status of the child at the time of the interview; for the children who died in the first year, the age in months in which death occurred was recorded.

The control group consisted of 60 healthy single-fetus consecutive pregnant women with no thyroid disease, followed since the first trimester of pregnancy in the Obstetrics and Gynecological Department of Hospital Geral de Nova Iguaçu (Nova Iguaçu, RJ), between March 2000 and June 2002. The age of the women at conception varied from 15 to 39 years (mean of 24 years). The serum levels of TSH (thyroid-stimulating hormone) were normal and thyroid peroxidase antibodies (TPOAb) tested negative.

Standard descriptive statistical analyses were performed, including distribution rates for categorical data and calculation of means and standard deviations for continuous variables. Odds ratios and 95% CI were calculated in bivariate analyses to estimate the strength of the association between the iodine-131 dose and pregnancy events. The chi-square test (17) was used for differences of proportions and the Student's t-test for differences between the means. The software tool Statistical Package for Social Sciences was used for the calculations. The adopted level of significance was $\alpha = 0.05$ ($p = 0.05$).

The Ethics Committee from the University of Rio de Janeiro School of Medicine approved the protocol for the study. Written and informed consent was obtained from all participants according to Brazilian legal guidelines.

RESULTS

Sixty-six single-fetus pregnancies from 48 patients with differentiated thyroid carcinoma who had undergone surgery and subsequent radioiodine therapy before conception were evaluated (tables 1 and 2). Patients' age at the time of conception varied from 13 to 42 years (mean of 26,5 ± 6,2 years, figure 1). The control group consisted of 60 healthy single-fetus consecutive pregnant women (table 3). The Student's t-

test showed no statistical difference between the studied and control groups (p= 0.05).

Among the 66 pregnancies, 14 (21.2%) occurred within one year of the last administration of ^{131}I and 51 (77.2%) after one year. The medical record of one patient was not available. Tables 1 and 2 detail the medical record of each patient.

The total ^{131}I dose varied from 30 to 550 mCi and the interval between the last administration and conception ranged from 1 month to 10 years.

The women in the studied group delivered a total of 62 children (30 females – 48.4% and 32 males – 51.6%).

From the 66 pregnancies, 9 patients (14.1%) had pregnancy events. The 2 cases of non-spontaneous abortions were excluded from this total (cases nr. 14 and 26). There were 7 (11.6%) abortions in the control group and four (6.3%) in the studied group. The chi-squared test showed no statistical difference between the two groups (p= 0.289, figure 2). In the studied group, 2 (50%) abortions were spontaneous (patient nr. 4 abort-

Table 1. Clinical presentation of 48 patients with pregnancy after differentiated thyroid cancer treatment.

Case nr.	Age at conception (years)	Dose mCi	Interval (months) ^{131}I / pregnancy	Pregnancy events
1	23, 24	100	36, 48	No
2	28, 30	200	84, 108	No
3	34, 36	70	36, 60	No
4	39	150	36	Yes *
5	39	50	84	No
6		50		Yes*
7	42	200	3	No
8	14	46	48	No
9	36	100	72	Yes*
10	30	100	8	No
11	21	100	7	No
12	30, 32	30	72, 96	Yes* PI
13	25, 27	100	36, 60	No
14	26, 34	100	1, 96	Yes*
15	21, 23	100/150	6, 48	No
16	24	100/100	2	No
17	22, 24	150/150	48, 84	No
18	24	150/100/150	4	No
19	13	150	9	No
20	24, 29	93/100	15, 72	No
21	31, 33	50	24, 36	No
22	22	100	48	No
23	22	100	24	No
24	34	150	48	No
25	29, 32	100	84, 132	No
26	22, 25, 26	100/100	10, 48, 72	Yes*
27	25, 28	100	24, 60	No
28	21, 23	50/100	1, 36	No
29	25, 26	100	24, 36	Yes*
30	24, 29	150	48, 96	Yes* HC
31	25	100	96	Yes*
32	16	100	48	No
33	27	150	3	Yes* PD
34	24	100	7	No
35	19	150/100/150	24	No
36	25	100	72	No
37	33	100	60	No
38	21, 25	100	8, 60	No
39	22	100	15	No
40	27, 29	150	3, 24	No
41	33	100	36	No
42	26, 29	150	3, 36	No
43	30	150/150	11	No
44	30	100	48	No
45	33	100	22	No
46	29	150	44	No
47	31	100/150	24	No
48	24	300/100/150	19	Yes* PL

* pregnancy events: miscarriage (6), risk of miscarriage (1), placental insufficiency PI (1), hypertensive crisis HC (1), placental detachment PD (1), preterm labour PL (1).

Table 2. Birth history and present state of health of offspring.

Case nr.	Miscarriage	Birth health	Sex	Weight gr.	Length cm.	Death in 1st year	Age (years) / present health	
1	0	2 term	F	2,950	42	No	4 y	N
			F	2,720	41		3 y	N
2	0	2 term	F	3,295	50	No	6 y	N
			M	3,200	49		3 y	N
3	0	2 term	F	3,300	51	No	12 y	N
			F	3,050	50		10 y	N
4	1 A	—	—	—	—	—	—	
5	0	1 term	M	3,320	48	No	8 y	N
6	1 X							
7	0	1 term	F	3,350	50	No	13 y	N
8	0	1 term	M	2,960	50	No	13 y	N
9	1 X	—	—	—	—	—	—	
10	0	1 term	F	2,820	48	No	11 y	N
11	0	1 term	M	3,150	47	No	2 y	N
12	0	1 term	F	3,050	47		6 y	N
		1 preterm	F	1,900	45	No	4 y	*
13	0	2 term	M	3,400	51		8 y	N
			M	4,200	51	No	7 y	N
14	1 I	1 term	F	3,600	50	No	10 y	N
15	0	2 term	M	3,150	49		8 y	N
			F	2,650	41	No	5 y	N
16	0	1 term	M	4,060	53	No	2 y	N
17	0	2 term	M	2,950	50	No	2 y	N
			M	3,520	50		2 mo	N
18	0	1 term	F	3,450	50	No	2 y	N
19	0	1 term	M	3,500	51	No	12 y	N
	0	2 term	F	3,500	51	No	13 y	N
20						No		
			M	4,000	51		7 y	**
	0	2 term	F	4,360	49		4 y	N
21						No		
			M	3,840	47		2 y	N
22	0	1 term	M	2,900	47	No	13 y	N
23	0	1 term	F	3,200	49	No	10 y	N
24	0	1 term	M	3,100	50	No	2 y	N
	0	2 term	M	3,000	50		24 y	N
25						No		
26			F	3,000	50		20 y	N
	1 I	2 term	M	3,400	50		12 y	N
			M	3,070	49		10 y	N
	0	2 term	M	4,070	53		3 y	N
27						No		
			M	3,420	52		4 mo	N
	0	2 term	F	3,350	51		12 y	N
28						No		
			F	3,250	50		10 y	N
29	1 A	1 term	F	3,800	49	No	13 y	N
	0	2 term	M	3,500	51		14 y	N
30						No		
			F	3,800	51		9 y	N
31	0	1 term	F	2,800	50	No	1 y	N
32	0	1 term	M	3,000	49	No	4 y	N
33	0	1 term	F	3,070	48	No	1 y	N
34	0	1 term	F	2,980	50	No	2 mo	N
35	0	1 term	F	3,060	49	No	10 mo	N
36	0	1 term	M	3,500	48	No	5 mo	N
37	0	1 term	M	3,480	51	No	4 mo	N
	0	2 term	M	3,150	47		4 y	N
38			M	3,328	49	No	2 mo	N
39	0	1 term	M	3,620	49	No	3 mo	N
	0	2 term	F	3,000	49		2 y	N
40						No		
			F	2,525	48		1 mo	N
41	0	1 term	M	3,180	52	No	2 y	N
	0	2 term	F	3,000	49		3 y	N
42						No		
			F	2,525	48		1 mo	N
43	0	1 term	M	3,795	52	No	7 mo	N
44	0	1 term	F	2,980	53	No	4 mo	N
45	0	1 term	F	3,250	49	No	10 mo	N
46	0	1 term	M	2,700	47	No	15 mo	N
47	0	1 term	M	2,980	49	No	1 mo	N
48	0	1–6 months	M	1,425	36	No	10 mo	*

F= female, M= male, N= normal, X= no information, A= accidental, I= induced
* premature - ** renal artery stenosis

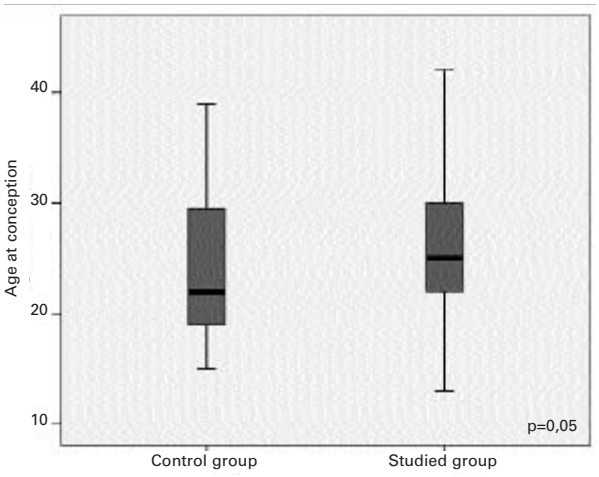

Figure 1. Age distribution of the women at delivery.

ed one month after the last radioiodine administration in the first month of pregnancy and patient nr. 29, 2 years after the last radioiodine administration in the second month of pregnancy) and two (50%) were for unknown reasons (patient nr. 6 who refused to answer the telephone and patient nr. 9 who was lost to follow-up).

Another five pregnancy events occurred: nr. 12 had placental insufficiency in the eighth month of her second pregnancy and delivered a preterm child with low birth weight; nr. 30 had a hypertensive crisis controlled with drugs; nr. 31 had risk of miscarriage, controlled with drugs and rest, nr. 33 had placental detachment, controlled with rest and nr. 48 had preterm labour. Nowadays, these children are healthy.

There were normal term births in the studied group (96.7%) and in the control group (88.7%). The chi-square test revealed no statistical difference between the two groups (p= 0.09) (figure 3).

Fourteen conceptions (21.2%) occurred within the first twelve months after the last radioiodine administration and of these, 1 (7.1%, nr. 33) presented a pregnancy event. Among the 51 conceptions (77.2%) that occurred after 1 year of the last ^{131}I administration, 7 (nr.: 4, 9, 12, 29, 30, 31, 48) presented pregnancy events.

Out of the 27 patients (56.3%) that received up to 100 mCi, five (18.5%) presented pregnancy events and out of the 21 (43.7%) that received more than 100 mCi, only four (19.1%) presented pregnancy events.

Mean birth weight for the offspring of the studied group (3,217 ± 491 grams) was not statistically different from that of the control group (3,207 ± 619 grams), p= 0.923.

There was no statistical difference between the mean birth length of the offspring of the studied group (49.0 ± 2.9 cm) and that of the control group (49.4 ± 4.1 cm), p= 0.538.

All the mothers stated that their children had normal neuropsychomotor development (time to crawl, to sit down, first teething, to walk) and good school performance. There was one case of congenital

Table 3. Control group.

Case	Age	Weight (gr.)	Length (cm)	Term (months)
1	15	2,830	50	8
2	32	2680	50	9
3	21	2,750	50	8
4	22	3,880	52	9
5	25	3,270	49	9
6	20	3,000	50	9
7	33	2,940	48	9
8	29	2,540	49	9
9	31	2,800	47	9
10	15	2,700	50	9
11	18	3,220	53	9
12	39	1,900	32	8
13	25	3,800	53	9
14	21	2,500	51	9
15	32	3,900	51	9
16	18	2,790	46	9
17	18	3,046	46	9
18	21	2,500	44	9
19	20	3,550	52	9
20	33	1,200	40	
21	19	3,300	50	9
22	25	2,820	48	9
23	19	3,800	52	9
24	23	2,730	48	9
25	22	3,000	50	9
26	35	3,240	48	9
27	36	3,650	53	9
28	22	3,600	48	9
29	21	3,790	53	9
30	24	3,690	50	9
31	19	3,930	50	8
32	20	2,960	53	9
33	24	2,765	45	9
34	23	3,320	41	9
35	17	3,300	52	9
36	34	3,245	54	9
37	28	3,275	49	9
38	31	3,156	52	9
39	18	2,750	49	9
40	16	3,450	49	9
41	28	3,000	52	9
42	24	3,660	52	9
43	35	4,200	52	9
44	16	4,100	51	9
45	20	4,060	52	9
46	30	3,500	49	9
47	19	3,735	42	9
48	22	2,160	47	8
49	17	4,310	53	9
50	18	3,850	52	9
51	22	2,840	46	9
52	35	4,200	58	9
53	27	2,775	54	9
54	31	*		11 weeks
55	17	*		4
56	35	*		3
57	25	*		2
58	21	*		6
59	18	*		3
60	19	*		3

* abortion (7), preterm (6), term (47).

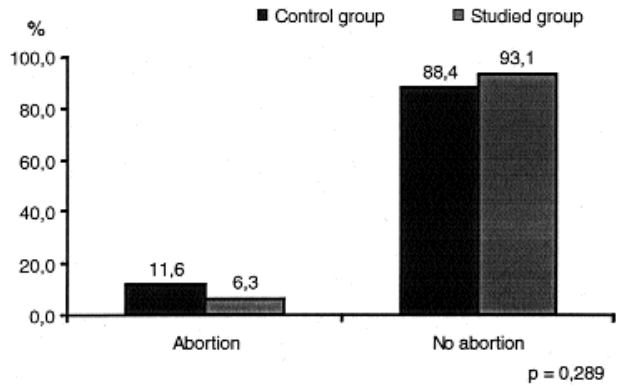

Figure 2. Abortions according to group.

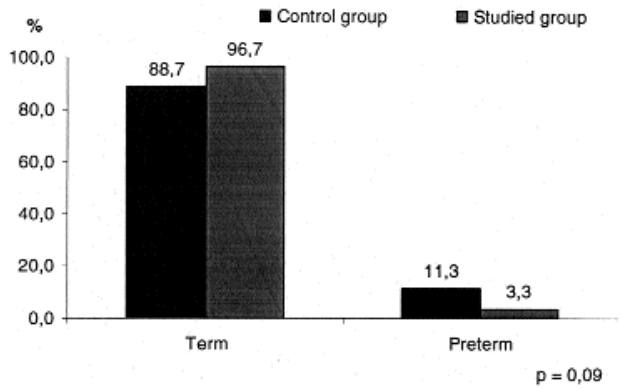

Figure 3. Birth status of the children according to group.

anomaly (renal artery stenosis, 1.6%) in patient nr. 20 and two cases of preterm birth with low birth weight (3.3%) in patients nr. 12 and 48. There were no cases of stillbirths, neonatal deaths or deaths in the first year of life.

DISCUSSION

This study involved women followed from 2000 to 2005 at the public hospitals in Rio de Janeiro, who became pregnant after thyroidectomy and radioiodine therapy for differentiated thyroid carcinoma. Congenital anomalies and abortion rates were evaluated.

The present study showed no evidence of genetic damage in the offspring. The incidence of miscarriage, preterm births and congenital anomalies in patients that received ^{131}I was not statistically different from that observed in the general population, which ranges from 1–2% (16).

We believe that radioiodine therapy did not induce the congenital anomaly (renal artery stenosis) since the patient in question conceived this child six years after the last administration of ^{131}I and had had a normal child before. Ayala (1) observed three cases of congenital anomalies in children that were conceived within one year of the last administration of ^{131}I: a male suffering Trisomy 18 (Edward's syndrome), a female with constitutional aplastic anemia, and a male with a congenital hip dysplasia. In our study, fourteen conceptions occurred within the first year of the last administration of ^{131}I and there were no congenital anomalies. Only one pregnancy event was observed: placental detachment.

Some studies demonstrate a higher rate of chromosomal aberrations in the peripheral lymphocytes of patients treated with ^{131}I (17). Amenorrhea due to temporary ovarian dysfunction (18,19) and depression of spermatogenesis (20) after radioiodine treatment have been observed.

Spontaneous abortion rates range from 15 to 20%. For some authors, abortion by itself has little relevance hardly deserving further investigation. Three or more consecutive abortions are called recurrent and warrant investigation for etiologic factors, namely genetic, hormonal, immunological or other factors (21,22).

A higher rate of abortions or congenital anomalies when compared with the general population was not found in other studies (2,23-26).

The incidence of miscarriage between the two groups was not statistically significant in our study, different from what has been observed by Schlumberger et al. (24), who reported a higher incidence of miscarriage when conception occurred within one year of the last ^{131}I administration.

The mean birth length and birth weight of the newborns in the two groups were not statistically different. So far, the offspring are in good health and perform well in school, except for the case with renal artery stenosis, which requires medical attention.

Our findings are in agreement with previous studies. We cannot conclude that radioiodine therapy is safe, but may confirm that it does not preclude pregnancy. Yet, some cautions should be taken in women at child-bearing age. First, these women need to be advised on menses and condom use. If the woman has irregular menses or is not sure about its regularity, a pregnancy test should be done. We recommend an interval of at least one year between the last administration of ^{131}I and conception, when the thyroid hormone levels have come under control.

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