

Outcome of pregnancy after radioactive iodine treatment for well differentiated thyroid carcinomas

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ABSTRACT. This study sought to determine the outcome of pregnancy in female patients with differentiated thyroid carcinoma who became pregnant after radioactive iodide treatment. A total of 779 female thyroid cancer patients were treated at Chang Gung Medical Center in Linkou between January 1977 and December 1995. The medical records of these patients were reviewed retrospectively. Thirty-seven of these patients had well differentiated thyroid carcinoma receiving ^{131}I treatment and conceived at a mean age of 27.97 ± 3.49 year-old. A total of 58 pregnancy episodes were recorded during this study period. Among these 37 patients, 3 episodes of artificial abortion, 8 episodes of spontaneous abortion and 2 threatened abortions were observed. These patients delivered a total of 47 babies including 3 premature babies. Seven of these patients con-

ceived within 6 months after the last administration of ^{131}I , including 2 cases within 1 month, 4 cases within 4 months, and 1 patient within 5 months. Of these 7 patients, only one patient who conceived within 6 months after the last administration of ^{131}I (14.3%) had a spontaneous abortion. The present results suggest that previous administration of ^{131}I in female patients with well differentiated thyroid cancer does not result in demonstrable adverse effects in subsequent pregnancies. However, further studies involving long-term follow-up of children delivered by mothers who became pregnant within 6 months after the last administration of ^{131}I is needed to further elucidate the possible chronic effects and sequelae of ^{131}I therapy on subsequent pregnancies. (J. Endocrinol. Invest. 21: 662-667 1998)

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INTRODUCTION

Young females compose the majority of patients with well differentiated thyroid carcinomas (1-3). Radioactive iodine (^{131}I) has been used for postoperative thyroid remnant ablation and treatment for distant metastases in papillary and follicular thyroid carcinoma patients for over 50 years (4-6). Among female patients of reproductive age, pregnancy after the treatment of thyroid carcinomas is not uncommon. Furthermore studies have demonstrated that previous administration of high doses of ^{131}I do not appear to be a valid reason to avoid pregnancy (7, 8). However, more data are needed to convince both doctor and patients that the complications of planning pregnancy are not increased in patients previously treated with ^{131}I . To further

explore the pregnancy outcome in well differentiated thyroid carcinoma patients after ^{131}I treatment, we retrospectively reviewed the medical records of 37 female patients who became pregnant after ^{131}I treatment for well differentiated thyroid carcinoma at Lin-Kou Medical Center during the period from January 1977 to December 1995. The outcome of pregnancy after ^{131}I treatment was analyzed.

MATERIALS AND METHODS

Among 1014 patients recruited, there were a total of 910 cases of papillary or follicular thyroid carcinoma. Nearly total thyroidectomy or modified radical neck thyroidectomy was done for 690 patients after the tumors were proven to be malignant by preoperative fine needle aspiration cytology or frozen sections. Two hundred and ten patients underwent subtotal thyroidectomy or lobectomy only. Four to six weeks postoperatively, 544 patients underwent whole body scintigraphic studies delivering 185 MBq (5 mCi) of ^{131}I . Thyroid function tests

Key-words: Radioiodine therapy, abortion, tocolysis, pregnancy.

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Table I - Clinical presentations of 37 thyroid cancer patients with pregnancy after radioactive iodide treatment.

Case no	Age of diagnosis	Age at pregnancy	¹³¹ I cumulative dose (GBq)	Radiation dose to gonads (cGy)	Months after last ¹³¹ I	Histologic type	Clinical staging
1	28	33	2.8	10.5	23	Papillary ca	II
2	27	29	1.3	4.9	16	Papillary ca	I
3	32	35	3.7	14.0	31	Papillary ca	II
4	29	32	2.6	9.8	14	Papillary ca	I
5	24	26	1.5	5.6	18	Papillary ca	II
6	19	21	1.3	4.9	12	Papillary ca	I
7	27	30	2.8	10.5	18	Papillary ca	II
8	28	29	3.9	14.7	15	Papillary ca	I
9	22	24	3.9	14.7	13	Papillary ca	II
10	26	28	1.3	4.9	14	Papillary ca	I
11	27	29	3.3	12.6	12	Papillary ca	I
12	23	24	1.5	5.6	12	Papillary ca	I
13	25	26	2.8	10.5	23	Papillary ca	I
14	16	23	3.3	12.6	23	Papillary ca	I
15	29	34	3.0	11.2	30	Papillary ca	I
16	23	28	3.9	14.7	40	Papillary ca	III
17	28	30	3.9	14.7	16	Papillary ca	I
18	20	23	2.6	9.8	4	Papillary ca	I
19	23	28	5.2	19.6	21	Hürthle's cell	I
20	25	29	1.3	4.9	44	Papillary ca	I
21	25	27	1.3	4.9	21	Papillary ca	I
22	20	24	5.4	20.3	26	Papillary ca	I
23	29	33	7.8	29.4	18	Papillary ca	I
24	27	31	1.5	5.6	6	Papillary ca	II
25	26	29	1.7	6.3	6	Papillary ca	I
26	16	23	13.1	49.7	1	Papillary ca	IV
27	25	27	1.3	4.9	4	Papillary ca	III
28	24	28	11.5	43.4	5	Papillary ca	I
29	28	32	4.3	16.1	1	Papillary ca	I
30	23	24	5.7	21.7	4	Papillary ca	I
31	25	27	5.6	21.0	12	Papillary ca	I
32	25	28	1.9	7.0	6	Papillary ca	I
33	27	29	1.1	4.2	17	Papillary ca	I
34	22	29	1.5	5.6	60	Papillary ca	I
35	21	30	6.8	25.6	21	Papillary ca	II
36	20	22	3.0	11.2	4	Papillary ca	I
37	23	31	7.0	26.6	9	Papillary ca	III

including TSH, T_4 , serum thyroglobulin (Tg), anti-thyroglobulin antibody, and chest radiography were done before ^{131}I was given. After ^{131}I imaging studies, 318 patients received 1.1 GBq or higher doses of ^{131}I for thyroid remnant ablation or treatment of distant metastases.

If distant metastatic lesions were detected by the 185 MBq ^{131}I scan or chest radiographs, 3.7 to 5.6 GBq ^{131}I was then administered. If the skeletal metastases were detected by the ^{131}I body scintigraphy, ^{131}I and $^{99\text{m}}\text{Tc-MDP}$ bone scintigraphy was used as a long-term monitor for cancer persistence every half a year. In this study, tumor staging was classified according to the clinical staging as previously described (2). Stage 1 represents a tumor with single or multiple intrathyroidal foci. Stage 2 represents tumor with cervical lymph node metastases. Stage 3 represents thyroid tumor with local cervical invasion or fixed cervical metastases. Stage 4 represents lesions metastatic outside of the neck. Postoperative serum Tg levels were detected by a Tg kit (CIS bio international, France). The detection limit of the Tg kit was 0.5 ng/ml. The interassay coefficient of variation was 8% at a Tg level of 4.9 ng/ml; 6.9% at 223.2 ng/ml, and 5.1% at 312.9 ng/ml). To determine the outcome of the pregnancy, both an interview with the mother during the follow-up period and a review of chart records were performed. A group of control subjects were selected from healthy pregnant women in the Obstetric and Gynecological Department.

RESULTS

In this study, a total of 37 patients with well differentiated thyroid carcinoma became pregnant after ^{131}I treatment. The mean age of the patients was 27.97 ± 3.49 years (range, 21-35 years). Table 1 shows the clinical features of these patients. The mean duration between conception and the last ^{131}I administration was 16.54 ± 12.69 months (range 1-60 months). Of the 37 cases, 7 became pregnant within 6 months. The mean cumulative dose of ^{131}I in these patients was 3.67 ± 2.76 GBq (range, 1.1-13.1 GBq). The estimated radiation dose to the gonads was calculated as previously described (9).

A total of 58 pregnancies episodes were documented during the study period (Table 2). Among these 37 pregnant patients, 3 episodes of artificial abortion, 8 episodes of spontaneous abortion, and 2 cases of threatened abortion were recorded. One patient (Case No. 5) experienced two artificial abortions before a full-term delivery. Of the 47 deliveries, 3 were Caesarian sections; 2 cases

had threatened abortions, 1 of which had a prolonged premature rupture; and the pregnancies of 2 patients were complicated with tocolysis. Among the 37 patients, 2 patients had 3 post- ^{131}I treatment pregnancies. One of these patients delivered 3 times smoothly. The other one was normal spontaneous delivery once after two spontaneous abortion. Five patients delivered twice smoothly except for one patient whose first pregnancy was complicated with tocolysis (no. 34). There were 3 premature deliveries among the 46 babies delivered. The birth weight of the age-matched control normal pregnancies is listed in Table 2. The mean and standard deviation of the birth weight in thyroid cancer patients and normal controls were 3319.3 ± 493.1 and 3227.6 ± 304.6 g respectively ($p=0.398$).

In the present study, 7 patients became pregnant within 6 months after the last administration of ^{131}I , including 2 patients within 1 month, 4 patients within 4 months, and 1 patient within 5 months. One of the two patients who conceived within 1 month after the last administration of ^{131}I had a spontaneous abortion; in contrast, the other gave birth to a full-term baby smoothly. Among the 4 patients who conceived within 4 months after the last administration of ^{131}I , one (25%) had preterm labor, and the other 3 patients (75%) all gave birth to full-term babies (including 2 Cesarean sections and 1 vaginal delivery). The only patient who became pregnant within 5 months after ^{131}I treatment had a normal vaginal delivery of a baby weighing 2,800 gm.

Of the 37 patients, there was one in stage IV, 3 in stage III, 7 in stage II, and the remaining 26 were in stage I at the time of diagnosis. The patient in stage IV was a 16 year-old female with papillary thyroid carcinoma who underwent total thyroidectomy. Postoperative chest X ray was normal. However, diffuse pulmonary metastases were noted by the postoperative 185 MBq ^{131}I scan. Thyroid remnants were also detected by the 185 MBq diagnostic scan. Therapeutic scan with 3.7 GBq ^{131}I 2 weeks after 185 MBq ^{131}I administration showed diffuse bilateral lung metastases. After 3 sessions of 3.7 GBq ^{131}I treatment, no metastatic lesions were detected by the following diagnostic ^{131}I scintigraphy. Serum Tg levels then substantially decreased from 92.9 ng/ml to 1.65 ng/ml without thyroxine replacement. One month after 185 MBq ^{131}I whole body scintigraphy, the patient was found to be pregnant. Insisting on keeping on pregnancy, the patient subsequently delivered smoothly. This patient was pregnant again one year later.

Table 2 - Outcome of pregnancy in 37 thyroid cancer patients and birth weight of age-matched normal control.

Case no	Birth weight (gm)	Outcome of pregnancy	Birth weight of age-matched control
1	2936	Normal spontaneous delivery (NSD)	3740
2	3620	NSD	3160
3	3584 (M)	NSD after threatened abortion at 13 weeks of pregnancy	3480
4	-	NSD of a healthy male baby	-
5	3540 (F)	Artificial abortion, NSD once after two spontaneous abortions	2880
6	-	NSD twice smoothly	-
7	3840 (F)	First delivery, NSD of a healthy female baby	3700
	3700 (F)	2nd delivery by C/S due to chronic fetal distress	3320
8	4080 (M)	NSD	3420
9	-	Smooth pregnancy 8 months follow-up	-
10	-	First pregnancy with spontaneous abortion, second pregnancy with threatened abortion	-
11	-	NSD of a healthy female baby	-
12	3160	NSD twice smoothly	3380
13	-	Spontaneous abortion twice, 3rd pregnancy with premature labor (33 weeks) and tocolysis	-
14	2500	Delivered a low birth weight male baby	2900
15	-	NSD of healthy male baby	-
16	2708 (F)	NSD of a healthy female baby	3500
17	4080	NSD 3 times smoothly	3320
18	2750 (M)	First pregnancy with premature labor, 2nd and 3rd pregnancy with NSD	3180
	2900 (F)		3400
	3500 (M)		3580
19	-	NSD	-
20	3916 (F)	NSD	3680
21	3100	NSD	2640
22	-	First pregnancy with spontaneous abortion, 2nd and 3rd pregnancy with NSD	-
23	3100 (M)	Successful vaginal delivery with vacuum, spontaneous abortion once	3060
24	3580	NSD	2760
25	3700 (F)	NSD	3220
26	2600 (M)	First pregnancy with spontaneous abortion, 2nd pregnancy with NSD, 3rd pregnancy artificial abortion	3080
27	3900 (F)	First pregnancy with C/S of a female baby, 2nd pregnancy with NSD	3120
28	2800 (F)	NSD	2940
29	3100	NSD once followed by artificial abortion in 2nd pregnancy	3160
30	2900 (F)	C/S	3300
31	3050 (F)	NSD	3460
32	2700	Premature, baby with mitral valve prolapse	3240
33	3675 (M)	NSD twice smoothly	3260
34	4120	Tocolysis in first pregnancy, NSD in secondary pregnancy	3220
35	-	Spontaneous abortion	-
36	-	NSD	-
37	3120	NSD	2500

DISCUSSION

As noted in our previous studies, well differentiated thyroid cancer usually affects women in the child bearing age (3, 10). Lower doses of ^{131}I treatment have been shown not to increase the risk of fetal malformation or abortion in women with hyperthyroidism (11, 12). However, we still have no conclusive results about the effect of ^{131}I treatment on the outcome of pregnancy in women having well differentiated thyroid carcinoma. One previous study reported that 30% of nonmenopausal women had temporary ovarian failure within the first year after thyroidectomy and ^{131}I remnant ablation (13). Another case report and a small series both reported that no increase in infertility or adverse outcomes of pregnancy occurred (8, 14). A recent study found no evidence that exposure to radioiodine affects the outcome of subsequent pregnancies and offspring (15). In our study, out of the 58 pregnancies in 37 women, there were a total of 47 live births. The birth weight and abortion rate in the study suggest that radioiodine did not influence the outcome of pregnancy. The abortion rate in this area was 15%. Contraception is usually recommended within the first half year following ^{131}I treatment for fear of genetic damage and mutations resulting in congenital anomalies. There is one case report of a normal delivery within five months of therapy with ^{131}I treatment (8). In our series, despite our recommendation of the use of contraception, there were 7 pregnancies which were conceived within 6 months of ^{131}I treatment. Although all of these patients delivered normal babies, long-term follow-up of these children is indicated to elucidate the effects of ^{131}I treatment on the children.

Case number 26 was the youngest patient in this series. As reported in previous studies about serum Tg levels in patients with distant metastases (10, 16), markedly elevated Tg levels were noted after the operation. The lung metastases of this patient were eradicated by the ^{131}I treatment. Although the estimated radiation doses to the gonads was 49.7 cGy, the patient delivered smoothly in a second pregnancy after spontaneous abortion in the first pregnancy. Unfortunately, the third pregnancy of this patient resulted in spontaneous abortion again. In this study, previous administration of ^{131}I in female patients with well differentiated thyroid cancer failed to show immediate adverse effects during subsequent pregnancies since only one in 7 patients (14.3%) who conceived within 6 months after the last administration of ^{131}I had a spontaneous abortion. Long-term follow-up of the children delivered by mothers who became pregnant within 6 months after the last administration of ^{131}I are indicated to further evaluate the possibility of long-term effects and sequelae of ^{131}I treatment.

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