Pregnancy Outcome after Treatment with Radioiodine for Differentiated Thyroid Carcinoma

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ABSTRACT

The aim of the study was to investigate the influence of radioiodine (RAI) therapy on pregnancies and the health status of children born to mothers who had received therapeutic doses of I-131 for differentiated thyroid carcinoma (DTC). Gestational histories of 76 women treated for DTC from 1971–2005 were retrospectively analyzed. The outcome of 49 pregnancies after RAI was: 35 children (72%), 5 (10%) miscarriages and 9 (18%) induced abortions. RAI did not adversely affect the rate of successful delivery and live birth demographics. Congenital malformation and first year mortality were not observed. The children’s ages range from 1 month to 29 years (X±SD=8.0±8.4). A higher therapeutic dose (>100 mCi) did not significantly alter the pregnancy outcome. There is no reason to discourage females treated with I-131 from becoming pregnant. Patients should avoid pregnancy after RAI administration for 1 year.

Key words: differentiated thyroid carcinoma, radioiodine, dose, pregnancy

Introduction

Radioactive iodine I-131 (RAI) has been used for decades in the diagnosis and treatment of well differentiated thyroid carcinoma (DTC). It is an effective treatment of DTC, both in preventing relapses and treating metastases. Following total thyroidectomy, patients are administered a diagnostic dose of 37–185 MBq I-131 and subsequently a therapeutic dose, varying from 1.85 to 3.70 GBq I-131 for the ablation of the thyroid remnant or even more for the therapy of the metastatic disease, if necessary.

The thyroid gland is an uncommon site of cancer, accounting for 0.6% and 1.6% of cancers among men and women, respectively. However, if the age distribution is analyzed, a considerable number of patients in their younger age are found. The peak age for developing papillary carcinoma is about 30 years of age, for follicular carcinoma 45 years of age and both types are about three times more frequent in women. Of all 1231 patients treated for well differentiated thyroid carcinoma from 1971–2005 at the Department of Oncology and Nuclear Medicine, University Hospital Sestre Milosrdnice in Zagreb, 956 (78%) were woman, of which 180 (19%) were younger than 35 years.

A large number of young female patients may be considered cured after thyroidectomy and radioiodine therapy and their desire to have a child is therefore normal. However, it is well known that radiation exposure induces genetic mutation, which can result in genetic abnormalities in the newborns. Therefore, beside positive effects of such therapy, great interest has been shown in the research of possible mutagenic effect on germ cells, which could result in adverse outcome of pregnancy (spontaneous abortions, congenital abnormalities, malignancies in offspring). During pregnancy, well-defined changes in thyroid hormone physiology reflect an increased demand for thyroid hormone production (in one-third of patients on L-thyroxin therapy a dosage increase is required), which can also affect the pregnancy outcome. It is difficult to assess the effect of RAI therapy due to a small number of patients (thyroid carcinoma is not a frequent disease) and their restrictive age. Also, the patients appear to be less willing to have children, particularly if they were already parents, because of their primary disease. Several studies addressing this problem did not find statistically significant associations between...
previous RAI exposure and unfavorable pregnancy outcome except for miscarriages. In our previously published data, a slight increase of miscarriages was also observed. The largest reported series by Schlumberger et al. revealed that the miscarriage rate increased from 11% to 20% after surgery for DTC, irrespective of the use of RAI. More miscarriages were observed among the women treated with RAI in the year immediately preceding conception (40%), but there was no other unfavorable pregnancy outcome. However, it is hard to estimate real radiation risk as clinical data are still insufficient to assess the low level of RAI risk, compared to other influences which have an impact on pregnancy outcome.

The aim of our study was to further evaluate the influence of radioiodine therapy on pregnancies and the health status of children born to mothers who had received therapeutic doses of I-131 for DTC, at the Department of Oncology and Nuclear Medicine, University Hospital Sestre Milosrđnice.

Patients and Methods

A group of 76 female patients, who were less than 35 years at the time when they were treated for DTC, were evaluated. They were all referred to the Department of Oncology and Nuclear Medicine, University Hospital Sestre Milosrđnice in the period from 1971 to 2005 and received regular follow-up. During routine check-ups between January 2003 and April 2005 pregnancy history, outcome and physical and intellectual condition of their children were assessed.

According to histological type of cancer, 71 patients (93%) had papillary and 5 patients (7%) follicular carcinoma. All patients were treated according to the standard protocol. After total thyroidectomy an ablation dose of 1.85–3.70 giga Becquerel (GBq) I-131 (50–100 millicuries) was administered for the ablation of thyroid remnants. Radioiodine administration was repeated in 3, 6 or 12-month intervals until significant uptake in thyroid bed had completely disappeared. One patient had lung and bone metastases at presentation and one developed lung metastases during follow-up period. They were treated with additional RAI doses and RAI treatment resulted in complete remission in these two patients. The average dose for metastatic disease at our department was 5.55 GBq (150 mCi). The numbers of I-131 administrations were the following: 41 patients received a single dose, 28 patients received two, 5 patients received three, one patient received four and one six doses. Total doses varied from 1.85 to 28.86 GBq I-131 (50–780 mCi), X±SD=5.72±3.87 GBq, median 3.70.

The age of patients at first radioiodine administration for therapeutical purposes ranged between 12 and 35 years (X±SD=25.9±5.6 years, median 26 years). All patients were recommended to avoid pregnancy after each I-131 administration for 12 months.

The patients were followed up according to the following protocol: whole body scintigraphy was performed 72 hours after the administration of 37–185 mega Becquerel (MBq) I-131 (1–5 mCi). Thyroxin substitution therapy was discontinued four weeks prior to whole body scintigraphy and TSH level confirmed to be >30 IU. Thyroglobulin level was measured and ultrasound of the neck performed, along with routine clinical examination and chest X-ray if indicated.

After the therapy, all patients were given thyroxin at doses capable of suppressing thyroid stimulating hormone (TSH). Serum TSH level was measured regularly, while suppression doses were adjusted individually according to the obtained results. This was done in order to obtain optimal suppression effect with the smallest amount of thyroxin and thus avoid possible iatrogenic hyperthyroidism. Later during the follow-up period, in the patients who were free of disease thyroxin dose was decreased until normal TSH values were obtained. In the patients who were planning pregnancy, the thyroxin dose was also decreased and serum TSH levels titrated to reach the normal range. During the first trimester of pregnancy, thyroxin dose was increased and TSH levels carefully monitored for dosage adjustment since there is increased demand for thyroid hormone production during that period. Separation of thyroxin ingestion by at least four hours from iron and calcium supplements was recommended.

Clinical data on pregnancies were obtained during a routine check-up of patients, including pregnancy details and outcome, live birth demographic data and the physical and intellectual condition of these children (the latest was assessed subjectively by their mothers by comparison with other siblings and peer group).

Statistical analysis

Numerical data were presented as mean, standard deviation, or median with range. Qualitative data were described by frequencies and percentages. Mann-Whitney test was used to compare numerical data of two independent groups, while qualitative data were compared by two-sided Fisher’s exact test. For statistical analysis, the SAS System for Windows, Release 8.02, TS Level 02M0 (SAS Institute Inc., Cary, NC, USA) was used.

Results

The mean follow-up of these 76 patients was 9.4 years, SD=7.0, median 7.7, range 1–32 years.

Seventy-six women evaluated gave birth to a total of 91 children, of which 56 were born before any treatment for DTC.

After surgery for thyroid carcinoma and administration of therapeutical activities of RAI, 45 women (58%) had no wish to become pregnant and of the remaining 31 women who declared that they were not avoiding pregnancies, 24 women (32%) gave birth, 2 (3%) had 1 miscarriage each and 5 (7%) did not conceive (Figure 1).

The outcome of 49 total pregnancies that occurred after radioiodine therapy was: 35 children (72%) were born, 5 (10%) miscarriages were observed and 9 (18%)
pregnancies ended by induced abortion. Three of these nine induced abortions were performed because they occurred during the period of 6 months after the RAI therapy, four pregnancies were terminated to prevent a feared negative outcome and reasons for other two abortions were not specified. After exclusion of pregnancies terminated by induced abortion, 5 miscarriages (12.5%) were observed in the 40 remaining pregnancies. Twenty-four women gave birth to a total of 35 children (22 males and 13 females). Nulliparous women easily decided to become, which is evident from data that 16 of these women gave birth to total of 27 children. Eight women who previously had children gave birth to one more each.

Median activity of I-131 prior to pregnancy was 3.7 GBq (100 mCi), range 2.96–28.86 GBq (80–780 mCi). The largest single dose administered was 5.55 GBq (150 mCi). Mean number of applications was 1.6 (SD=1.2, range 1–6). Patient’s ages at the time of pregnancy ranged 18 to 40 years, X±SD=28.9±5.1, median 30.0 years. The interval between the last administration of I-131 and conception ranged 0.4 to 19 years, X±SD=6.0±5.1, median 4.0 years.

We also studied whether a higher total RAI dose had any association with adverse pregnancy outcome. Pregnancies occurred after the RAI therapies were classified according to I-131 dose before each pregnancy into two groups: Group A ≤100 mCi and Group B >100 mCi (Figure 2).

The clinical characteristics of patients, pregnancy outcomes and children in each group are presented in Table 1 and Table 2.

There was no difference between the groups for the age when DTC was diagnosed (p=0.643), follow-up period (p=0.227), the maternal age at pregnancy (p=0.999) or the interval between RAI and pregnancy (p=0.267).

Stillbirths, congenital abnormalities or first year neonatal mortality were not recorded. We did not find any difference in the adverse effects on outcome between low and high total I-131 dose groups. The proportion of live births was similar and after excluding pregnancies ended by elective abortion, the incidence of miscarriage was not different between the RAI groups (13% vs. 11%, p=0.999). Also, no difference was noted in the gender distribution (p=0.680), or children’s birth weight (p=0.723) between the groups with different total I-131 dose administration. To the present, the children’s ages’ range from 1 month to 29 years, X±SD=7.8±8.1, median 6.0 years. All children had normal growth and have not been afflicted with severe disease.

**Discussion**

The diagnostic and therapeutic use of I-131 for the evaluation and management of thyroid remnants and regional and distant metastases of differentiated thyroid

**TABLE 1**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A (≤100 mCi)</th>
<th>Group B (&gt;100 mCi)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-131 Dose (mCi)</td>
<td>Median 91</td>
<td>30 Range 200</td>
<td>672</td>
</tr>
<tr>
<td>Fractions (n)</td>
<td>1 1</td>
<td>2 5</td>
<td></td>
</tr>
<tr>
<td>Maternal age at DTC* diagnosis (y)</td>
<td>23 16</td>
<td>26 20</td>
<td>0.643</td>
</tr>
<tr>
<td>Interval before pregnancy (y)</td>
<td>4 17</td>
<td>6.5 16</td>
<td>0.267</td>
</tr>
<tr>
<td>Maternal age at pregnancy (y)</td>
<td>29 22</td>
<td>30 10</td>
<td>0.953</td>
</tr>
<tr>
<td>Patient’s follow-up (y)</td>
<td>11.6 30.5</td>
<td>9 18</td>
<td>0.227</td>
</tr>
<tr>
<td>Children’s birth weight (kg)</td>
<td>3.4 1.6</td>
<td>3.3 0.7</td>
<td>0.723</td>
</tr>
<tr>
<td>Age of child at last follow-up (y)</td>
<td>8 28.9</td>
<td>1.5 4.8</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

* p<0.05, Group A:≤100 mCi I-131, Group B:>100 mCi I-131, *DTC-Differentiated Thyroid Carcinoma

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TABLE 2
CLINICAL CHARACTERISTICS OF PATIENTS ACCORDING TO PRECONCEPTION I-131 ADMINISTRATION

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A (≤100 mCi)</th>
<th>Group B (&gt;100 mCi)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies after I-131</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live births</td>
<td>36/100</td>
<td>13/100</td>
<td></td>
</tr>
<tr>
<td>Miscarriages</td>
<td>4/11</td>
<td>1/8</td>
<td></td>
</tr>
<tr>
<td>Induced abortions</td>
<td>5/14</td>
<td>4/31</td>
<td></td>
</tr>
<tr>
<td>(Therapeutic)</td>
<td>0/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Social/psychological)</td>
<td>3/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Unspecified)</td>
<td>2/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live birth – gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11/41</td>
<td>2/25</td>
<td>0.680</td>
</tr>
<tr>
<td>Male</td>
<td>16/59</td>
<td>6/75</td>
<td></td>
</tr>
</tbody>
</table>
| Group A ≤100 mCi I-131, Group B >100 mCi I-131

carcinoma (DTC) have been routine for decades. Long-term studies reported that I-131 ablation of residual thyroid tissue after surgery decreased the risk of recurrence and cancer-specific mortality rates were significantly lower than in those who did not undergo remnant ablation. Since all diagnostic and therapeutic modalities should be assessed carefully for the relative benefits and hazards, the purpose of this study was to evaluate, in a clinical setting, the impact of I-131 therapy on pregnancy outcomes and the health status of their children born.

Knowledge that radiation is mutagenic and may affect gonads (thereby resulting in genetic damage to offspring) has raised concern regarding the use of radioiodine in patients during their reproductive years. Virtually every patient treated with any dose of I-131 is exposed to some potential risk. The potential hazards that have the greatest impacts on the decision to utilize this modality are the induction of second tumors and genetic and chromosomal damage. Also, a large individual variation in the reaction to RAI exposure was observed due to differences in each individual’s features and environment.

Genetic risk of ionizing radiation in humans has been estimated in the offspring of survivors of the atomic bomb explosion in Japan, in populations living in areas of high background radiation levels, and in the descendants of persons exposed to radiation either on the job, or through diagnostic and therapeutic procedures. Studies on survivors of the atomic bomb explosion in Japan and of childhood and adolescent cancer survivors who had received radiation to the abdomen or pelvis have failed to provide any clear evidence of increased germ cell mutation subsequent to exposure, but some studies have suggested an increased risk of congenital abnormalities and leukemia in children born to occupationally exposed men.

It has been estimated that the radiation dose delivered to the ovary is approximately 0.14 cGy after administration of 37 MBq (1 mCi) of radioiodine, which correlates well with in vivo measured doses. Since the rate of congenital anomalies due to RAI exposure is low compared to the other influences that have an impact on pregnancy outcome, it is hard to estimate the risk. The rate of spontaneous birth anomalies is 800 per 100,000 pregnancies and if all 100,000 women received 370 MBq (10 mCi) I-131 before they became pregnant, the rate of congenital anomalies would increase to 803 (only 3 new congenital anomalies on 100,000 women exposed with 10 mCi I-131). In addition, there are genetic diseases that are either easily recognized but uncommon, or more frequent but difficult to detect.

So far, studies about the impact of I-131 therapy on pregnancies included small number of patients and failed to reveal any significant I-131 related effect. Even in the largest study reported, with data on 2113 pregnancies evaluated, 272 pregnancies presented referred to the period after the surgery for thyroid cancer and only 206 to the period after the RAI administration.

Our data show that all children born to mothers who had received therapeutic activities of I-131 for DTC had birth weight similar to the birth weight of healthy newborns from the Zagreb County, Croatia and were in good health. The only untoward outcome of pregnancy was 5 (12.5%) miscarriages. One miscarriage occurred when the patient was off the substitution therapy with thyroxin and in two others, miscarriages occurred within 6 month following thyrodeectomy and radioiodine therapy (subsequently these women had healthy children). Therefore, the contribution of other factors, as an inadequate control of the thyroid hormonal status, cannot be excluded (both hyperthyroidism and hypothyroidism have significant effects on estrogen metabolism, fertility and pregnancy outcome). Many factors capable of interfering with the hypothalamic-pituitary-thyroid axis may induce changes in TSH level and affect the pregnancy, so thyroid hormonal status should be carefully followed-up.

In the general population, the incidence of miscarriages in clinical recognized pregnancies is about 10%, but in prospective studies, when healthy women attempting to conceive were under medical supervision, the incidence of miscarriages was significantly higher. In the study of 221 healthy women attempting to conceive, early pregnancy loss (1 to 91 days after the implantation) was 31%. In similar studies the incidence ranges from 18% to even 63%. In the general population a great deal of early pregnancy loss remains clinically unrecognized. Patients with a diagnosis of DTC are under more strict medical control because of their primary disease and their pregnancies are usually planned and more carefully supervised.

In our group of patients, worst pregnancy outcome was not associated with higher total RAI therapy dose. Although our data do not establish that no risk exists, they indicate low level of RAI ablation risk and emphasize the importance of individual differences due to non-
uniform distribution of internally deposited radionuclides and different level of gene activity and chromosome repair in each patient. However, in the recently published Erselcan study the connection between the dose and the chromosomal damage has been established. The authors of this study have assessed the damage in the peripheral lymphocytes of 15 patients who received various doses of I-131. Acute and late effects were defined using the »damage ratio« (acute effect) and the »recovery ratio« (late effect), based on the basal, acute (3rd day) and late (6 months) data in patients treated for thyrotoxicosis or DTC. The »damage ratio« was not related to the dose administered, but a negative correlation was found between the I-131 dose and the »recovery ratio«. Results also suggested that part of the damaged lymphocytes disappear from the circulation in a dose dependent manner following I-131 treatment. These results, together with other studies indicate dose-effect relationship at the chromosomal level.

Although, previous studies do not indicate any increase in the untoward pregnancy outcome except for miscarriages, there is a need for further studies to assess biological effects and clinical impact of RAI therapy in patients receiving different therapeutic doses of I-131.

Conclusion

On the basis of the present data and data from previous studies on this subject, there is no reason to discourage patients treated with radioiodine therapy from becoming pregnant. The incidence of spontaneous abortions, still-births, congenital abnormalities or malignancies in the offspring was not increased. Also, higher therapeutic doses did not affect the outcome. However, patients should be advised to avoid pregnancy after I-131 administration for 1 year. Thyroid hormonal status should be evaluated prior to pregnancy and during pregnancy thyroxine dose carefully adjusted.

REFERENCES

TRUDNOĆE U ŽENA LIJEČENIH RADIOAKTIVNIM JODOM RADI DIFERENCIRANOG KARCINOMA ŠTITNJAČE

SAŽETAK

Cilj studije bio je utvrditi utjecaj radioaktivnog joda (RAI) na trudnoće, kao i na zdravlje djece bolesnica koje su primale terapijske doze I-131 radi diferenciranog karcinoma štitnjače (DTC). Trudnoće u 76 bolesnica liječenih radi DTC-a u periodu od 1971.-2005. g. su retrospektivno analizirane. Ishod 49 trudnoća koje su uslijedile nakon terapije RAI bio je: 35 djece (72%), 5 spontanih pobačaja (10%) i 9 arteficijalnih pobačaja (18%). Terapija radioaktivnim jodom nije negativno utjecala na stopu uspješnih poroda, niti na demografske osobine novorođenčadi. Kongenitalne malformacije i mortalitet u prvoj godini 'ivota nisu registrirani. Srednja dob djece bila je 8 godina (raspon 1 mjesec do 29 godina, SD=8.4). U bolesnica koje su primile veće terapijske doze radioaktivnog joda (>100 mCi) nije registriran lošiji ishod. Bolesnicama liječenim radioaktivnim jodom radi diferenciranog karcinoma štitnjače nije potrebno preporučivati izbjegavanje trudnoće. Preporuča se izbjegavati trudnoću u godini neposredno nakon primanja terapije I-131.