Radioiodine treatment complications to the mother and child in patients with differentiated thyroid carcinoma

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Abstract

Radioiodine (^{131}I) has been widely used in the treatment of differentiated thyroid carcinoma (DTC). Since radiation can carry a known risk of mutagenic abnormalities, we decided to study the outcome of pregnancy in females with DTC and evaluate the genetic risks and health status of their offspring. We retrospectively studied the medical records of these patients in our Institute from 1999 to 2004. *A total of 1110 women* were hospitalized for treatment with high doses of ^{131}I, at least 3700MBq. During this period, 653 of these women were in their reproductive period. A hundred of them who had at least one pregnancy after ^{131}I treatment, were studied. These women had a total of 126 pregnancies (1-6 pregnancies each) after treatment and 101 pregnancies before treatment. We also reviewed the ^{131}I dose administered last, as well as the cumulative dose of ^{131}I. *Our results* show that the incidence of abortions before ^{131}I treatment was 16.83% (all were spontaneous abortions) and increased to 26.19% after ^{131}I treatment (15.87% induced and 10.3% spontaneous abortions). Spontaneous abortions were decreased. There was no significant difference between the mean last ^{131}I dose and the cumulative dose in patients with or without a history of abortions. Mean interval between the last dose of ^{131}I treatment and abortions versus the last dose and live child births showed a significant difference. All children had normal birth weight. Three congenital anomalies: Down's syndrome, cardiac abnormalities and macrocephaly were diagnosed. Three episodes of intrauterine death were also recorded. *In conclusion*, our findings indicate that in women with DTC, treated with high doses of ^{131}I: a) There was no evidence of increased spontaneous abortions, b) Increasing the interval between the last dose of ^{131}I treatment and time to pregnancy might be beneficial for decreasing the entire risk of abortions and c) It appears that ^{131}I treatment had no obvious adverse effects on the risk of congenital anomalies.

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Introduction

Differentiated thyroid cancer (DTC), although accounts for less than 1% of all cancers, is the most frequent malignancy of the endocrine system [1, 2]. DTC is more prevalent in women and particularly evident during the reproductive years [1-3]. It is usually curable when discovered at an early stage. After performing total or near total thyroidectomy, ^{131}I is widely employed for the ablation of residual thyroid tissue and the treatment of metastases [1-3]. Radioiodine treatment may damage radiation-sensitive tissues such as salivary glands, lung, gut, bone marrow and gonads [1-4]. The notion that radiation is mutagenic, may affect germ cells and result in abortions, premature birth, stillbirth and genetic damage to the offspring, including congenital abnormalities or malignancies, has raised concern regarding the use of therapeutic doses of ^{131}I in women during their childbearing years [5-6]. The deleterious effect of gonadal irradiation could be directly related to cumulative dose absorbed by the gonads. It is also influenced by patient's age, tumor proximity to the gonads, constipation and hydration [4]. In an extensive study on Japanese atomic bomb survivors, no untoward pregnancy outcomes were found [7]. Studies on pregnancy outcomes and the offspring of patients treated with ^{131}I are not many and are not conclusive [5, 6, 8-10]. The objective of this study was to assess the pregnancy outcome, the health status and possible congenital malformations of the offsprings, in DTC patients treated with high doses of ^{131}I.

Patients and methods

From 1999 to 2004, a total of 1110 women with DTC had been treated with ^{131}I at Shariati Hospital, Research Institute for Nuclear Medicine, Tehran. Of these patients, 653 were in the

reproductive age group aged 15-45 years, mean age 30.06±4.69 years. A hundred of these women had at least one pregnancy after ^{131}I treatment and were enrolled in the study. Those with a history of external irradiation or radiographs of the abdomen or pelvis were excluded so that ^{131}I was considered the only medical source of gonadal irradiation after the diagnosis of DTC. No patient had received external beam radiotherapy. Patients with a history of any potential risk of abortion due to other uterine or pelvic inflammatory diseases were also excluded from the study. Any possible complaints of not achieving conception were recorded. The pretreatment pregnancies of these patients were considered as the control for the exposed to^{131}I patients. The 100 women studied were asked about possible complications of their pregnancies including abortion, stillbirth, premature labor and the exact date of these happenings in both pre- and post-treatment pregnancies. If they had child birth(s), they were asked about general health status, sex, birth weight, height and head circumference of their neonates. Also questions were asked about any congenital abnormalities and cancer in their offspring compared to those before ^{131}I treatment. We also collected data about histology and the extent of DTC, the history of tumor recurrence and/or metastases and all ^{131}I related information, as date and dose of the last treatment, times of treatment (1-4) and cumulative dose. All patients after their ^{131}I therapeutic doses were under suppression treatment.

The statistical software, version 10.0 SPSS was used for data analyses. Frequency, mean, range of the data and association between the ^{131}I dose and the occurrence of adverse events, were calculated. Mann-Whitney U test was used to compare the means. The significance of differences in the clinical parameters was shown by P-values and $P<0.05$ was considered statistically significant.

Results

Among the 100 women studied after ^{131}I treatment, a total of 126 pregnancies were recorded. There were no complaints about not achieving pregnancy. Seventy eight women 78/100 (78%) had one pregnancy, 21/100 women (21%) had 2 pregnancies and 1/100 woman had 6 pregnancies. Among these 126 pregnancies we noticed 33 abortions in 29 women. Of these, 27/33 had one abortion each, 1/33 had two abortions, and 1/33 four abortions. Only 13/33 abortions occurring in 10 women were spontaneous. Nine women had one abortion each, and one had 4 abortions. The remaining 20/33 were induced abortions. Before ^{131}I treatment 58/100 of the women studied had a history of 1-6 pregnancies and a total of 101 pregnancies.

A total of 33 abortions among 126 pregnancies (26.19%) after ^{131}I treatment were reported. The incidence for spontaneous abortions after ^{131}I treatment was 10.3% (13/126) and for induced abortion was 15.87% (20 /126). The total abortion rate before ^{131}I treatment was 17 episodes (17 out of 101 pregnancies: 16.83%) and all of them were spontaneous.

Total abortions increased from 16.83% before ^{131}I treatment to 26.19% after ^{131}I treatment; however spontaneous abortions decreased from 16.83% to 10.3%. After ^{131}I treatment, induced abortions among total abortions were 20/33 (69.7%) and this ratio for spontaneous abortions was 13/33 (30.3%) while the percentage of induced abortions among the total abortions before ^{131}I treatment was zero.

Patients had 1 to 4 radioiodine treatments. Mean cumulative dose before pregnancy was 6510±3811 MBq; 3700-22200 MBq. Mean cumulative dose in women without a history of any kind of abortions was 6895±3996 MBq; 3700-22200 MBq which was not different in patients with history of abortions (5754±2871 MBq, $P=0.93$ by the Mann-Whitney test). Mean cumulative dose in patients with history of spontaneous abortions was 5846±2964 MBq, while in patients without history of spontaneous abortions, was 6644±3808 MBq which again showed no statistically significant difference ($P=0.44$).

The mean last ^{131}I doses administered before pregnancy in patients with a history of spontaneous abortions was 4.18±1.41 GBq as compared to patients without a history of abortions (4.72±0.98 GBq) showed no statistical difference: (P value=0.26).

Mean time interval between last dose and spontaneous abortions was (16.20±10.97, range: 3-36, median: 7.5 months). Compared to that in patients with successful childbirth (32.10±18.22, range: 3-115, median: 27 months) was significantly different ($P=0.001$).

Mean interval between the last dose and induced abortions (10.11±10.83 months, range of 2-48 months) compared to the patients with a history of spontaneous abortions (16.20±10.97 month, range: 3-36 months), was significant ($P<0.001$).

Only one woman had more than one abortion (4 abortions), thus the incidence of recurrent abortions or habitual abortions was 1%. She had received 5550MBq ^{131}I and her first pregnancy was two years after ^{131}I treatment. One woman became pregnant one month after receiving 5550MBq and delivered a healthy baby.

All children in our study who were born after ^{131}I treatment had normal birth-weight, height and head circumference. In total, 3 anomalies: one case of Down's syndrome, one case of macrocephaly and one case of heart anomaly were recorded (3.9% in total).

Three intrauterine deaths out of 126 pregnancies had occurred (2.38%). One of these three women had bilateral pulmonary metastases, received 5550MBq and conceived 18 months after ^{131}I treatment. The other two women had received 3700 and 5550MBq and conceived one year after ^{131}I treatment.

Discussion

Radiation is a known mutagen. Radioiodine-131 is frequently used in DTC both to ablate thyroid remnants and to treat metastases [1-4]. Every dose of ^{131}I in patients can affect germ

cells and offspring. In thyroid cancer patients, the radiation from ^{131}I to the gonads has induced side effects including menstruation irregularities [11, 12] temporary amenorrhea with elevated FSH and LH values but no permanent ovarian failure [4, 6, 13-15]. However, one study suggested that ^{131}I treatment for DTC might lead to an earlier onset of menopause [16]. In many studies the fertility rate in ^{131}I treated women was not reduced [5, 8, 9, 11, 13, 17-19].

Miscarriage risk is another complication of radiation which was of concern in our study. Others have shown an increase in miscarriage in the first year after ^{131}I treatment [6]. Other studies suggest that previous administration of ^{131}I in female patients with DTC does not result in demonstrable adverse effects in subsequent pregnancies [5, 8, 10, 12, 17]. Spontaneous abortion rate was normal (6%) and the incidence of miscarriages was not different from that in women treated before pregnancy with ^{131}I [5, 8]. On the contrary the incidence of preterm delivery was greater in those women with a history of ^{131}I treatment ($P = 0.03$) [8].

In our study, the incidence of abortions in the unexposed to ^{131}I group, increased from 16.83% to 26.19% after ^{131}I treatment; however this increase was totally related to the induced abortions, while the risk for spontaneous abortions did not increase but was reduced from 16.83% to 10.3%. Induced abortions consisted of 69.71% of all abortions while 30.29% were due to spontaneous abortions. The reason declared for the induced abortions in most cases was the mother's concern about possible offspring complications. Other women underwent abortions because they didn't wish to have any more children. In Schlumberger's study (1996) induced abortions were also more frequent, as in our study [6]. The worldwide frequency of clinically recognized abortions is within the range of 12% in young women, to 26% in women older than 40 years [20]. In a study in Iran, the lifelong occurrences of induced and spontaneous abortion were 9.4% and 33.9%, respectively [21].

The relation between ^{131}I therapeutic doses with pregnancy outcome is another matter of concern. In our study, neither the mean last dose nor the mean cumulative dose of ^{131}I in women with or without a history of spontaneous abortions, were significantly different. In another study the rate of total abortions was 11% before any treatment and almost doubled after surgery (19%) and doubled again (40%) after ^{131}I treatment with more than 3.7GBq [6]. Abortions were not categorized into induced and spontaneous, so changes in the rate of spontaneous abortion were not reported [6]. Other studies show no significant adverse effects of high doses of ^{131}I on subsequent pregnancies [8, 10] as in our study. Higher therapeutic doses of ^{131}I in DTC patients of >3.7 GBq and of >2.96 GBq did not significantly alter the pregnancy outcome [8, 10]. All our patients were treated with ^{131}I doses higher than 3.7GBq and no comparison was made with doses below 3.7GBq. An unremarkable effect of the cumulative therapeutic ^{131}I doses on the incidence of abortion was also reported by others [6].

Recurrent miscarriage is also a distressing problem that affects 1% of all women [22]. In our study one woman had 4 abortions (1%), thus the incidence of recurrent abortions in our patients was not more than that of the normal population. All women who wished to conceive achieved conception. No adverse effects on fertility were demonstrated which is in concordance with other studies [5, 8, 9, 11, 13, 17-19].

Another major concern in the treatment with high doses of ^{131}I is that whether treating children or women during the childbearing years, the risk of congenital abnormalities increases. The genetic risk is supposed to increase with the increase of the gonadal dose. The radiation dose that would double the rate of spontaneous mutation is 1Sv [23, 24]; however, current information regarding the mutagenic effects of radiation on germ cells is based mainly on experimental evidence in animals, since only scant data are available in humans [10]. In fact, only disorders that are single-gene, highly penetrant, autosomal dominant or x-chromosome-dominant, are readily detected with certainty on the first generation of the exposed population and are useful in confirming the possible causative relationship between exposure and mutations [5]. Besides, the radioiodine dose received by the ovaries depends on morphological and kinetic factors specific to each individual and influenced by many factors [25].

The overall incidence of congenital anomalies in our study was 3.9% for all child births which was not different from that of the general population (3%) [20].

Other studies have also failed to reveal any statistically significant congenital abnormalities on the offspring [5, 6, 8, 11, 17, 26]. As to our knowledge, in other studies abnormalities after ^{131}I treatment are diverse and include leukemia [10], one translocation of the 7-14 [24] ventricular septal defect [9, 27], Edward's syndrome, aplastic anemia, and hip dysplasia [26], at a rate similar to that of normal population. In addition, three intrauterine deaths occurred in our studied group (2.38%) which is less than the percentage reported for normal population (5.1%) [20]. Stillbirths were also not reported in other studies [6, 27].

All born neonates in our study were in normal health status with normal weight / height and head circumference. These data were similar to the results reported by other studies [5, 6, 8, 9, 27].

Balenović et al. (2006) reported that radioactive iodine did not adversely affect the rate of successful delivery and live birth demographics. Congenital malformation and first year mortality were not observed in their study. They concluded that a higher therapeutic dose: >3700 MBq did not significantly alter pregnancy outcome; however they recommended that patients should avoid pregnancy for 1 year after treatment [28].

Although the rate of spontaneous abortions did not increase after ^{131}I treatment, the mean interval between the last dose of ^{131}I treatment and spontaneous abortions was lower than between the last dose and live child birth (16.20 ± 10 months vs 32.1 ± 18.22 months, $P < 0.001$). Increased incidence of miscarriages early after the administration of ^{131}I, was also reported and was suggested to be related to gonadal irradiation or to insufficient control of to hormonal thyroid status [6].

However, as our patients were on effective levothyroxine suppression treatment, the role of irradiation should be considered more noteworthy. The shorter than one year, interval between ^{131}I treatment and conception, did not significantly alter pregnancy outcome [8]. To reduce the possible adverse effects of radiation on gonads and subsequently on the neonates, some authors recommend avoiding pregnancy for at least one year after ^{131}I treatment [6, 8, 9, 26]. We recommend this interval to be increased. The determination of the optimal interval could be a subject for further studies.

In conclusion, although the total rate of abortions showed a significant increase after ^{131}I treatment, this was mostly related to increased risk of induced abortions because of mothers' concern of possible neonates anomalies. There was no clear evidence in favor of an increased rate of spontaneous abortions. However increasing the interval between last dose of ^{131}I treatment and pregnancy might be beneficial for decreasing the possible risk of abortions. It also appears that ^{131}I treatment had no obvious adverse effect on the risk of congenital anomalies.

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