Thyroid Functions of Newborn Babies Born to Mothers with Differentiated Thyroid Carcinoma Following Radioiodine Treatment at a Tertiary Hospital

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ABSTRACT

Objective: The aim of the study was to investigate thyroid function of newborn babies of mothers with differentiated thyroid carcinoma (DTC) after receiving radioactive iodine (^{131}I) therapy (RAIT). Materials and methods: During the period of 2009 to 2014, a total of 1620 women had been treated with 131I in the thyroid division of National Institute of Nuclear Medicine & Allied Sciences (NINMAS). Patients were followed up at regular intervals systematically and were allowed to conceive with confirmation of disease free condition. A retrospective review of the medical records was done in this study. Out of 1620 patients, 1370 (84.6%) were in the reproductive age group (18-44 years). Among 1370 patients, 111 patients became pregnant after 2 years of the RAIT. Age at pregnancy ranged between 20 to 32 years (24.8 ± 4.8). All pregnant mothers were disease free and well supplemented by levothyroxine and maintained their Thyroid Stimulating Hormone (TSH) at a low normal range (0.1-1.0 mIU/L). Average serum thyroglobulin (Tg) level were below <0.02 ng/dl. Would be mothers were requested to estimate TSH of the newborns by 7 to 15 days after birth and report to us. They immediately reported the TSH test results of the babies. Results: One hundred fourteen mothers with DTC had received RAIT and conceived at a mean age of 24.8± 4.8 years (19-38 yrs). Out of 114 patients, 110 (96.5%) patients were papillary thyroid cancer (PTC) and 4 (3.5%) was follicular thyroid cancer (FTC). Patients were treated by 30-100 mci. The outcome of 111 pregnancies after RAIT was 108 (97.30%) delivered the healthy euthyroid babies and 3 (2.70%) had miscarriages. TSH range from 0.52 -16 mIU/L (3.69 ± 3.19)

Conclusion: This study showed that RAIT in young women did not have any deleterious effects on subsequent pregnancies. All babies born by mothers with DTC after radioiodine treatment showed normal thyroid function evaluated by TSH.

Key words: Differentiated thyroid carcinoma, radioactive iodine (^{131}I) therapy, pregnancy risk.

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INTRODUCTION

Radioactive iodine (^{131}I) therapy (RAIT) has been used for decades in the diagnosis and treatment of well-differentiated thyroid carcinoma (DTC). It is worldwide accepted as the treatment of DTC due to its effectiveness in preventing relapses and treating metastases (1–6). Since the 1980s, National Institute of Nuclear Medicine & Allied Sciences (NINMAS) started RAIT for thyroid patients in Bangladesh.

The majority of female DTC patients were treated with RAI (^{131}I) for post-operative thyroid remnant ablation and distant metastases (7-9). Pregnancy after the treatment of thyroid carcinoma is not uncommon for female patients of reproductive age. Furthermore, studies have demonstrated that previous administration of high doses of ^{131}I does not appear to be an effective reason to avoid pregnancy due to the genetic effect, which is rare, and no such reproductive abnormality is also seen (10–11). However, an increased frequency of miscarriage has been reported within one year of RAIT (12). So RAIT might not affect the outcome of any subsequent pregnancy after 2 years (13).

The thyroid gland is a rare site of carcinoma, with female preponderances affecting 0.6% males and 1.6% of females respectively (14, 15). However, if the age distribution is analyzed, a significant number of patients in their younger years are found. The maximum age for developing papillary carcinoma is about 30 years of age and for follicular carcinoma, 45 years of age, and both types are about three times more frequent in women (16). Most of the young female patients may be considered cured after thyroidectomy and RAIT, and they are anxious about their future family life, so their desire to have a child is therefore normal. During pregnancy, well-defined changes in thyroid

hormone physiology reflect an increased demand for thyroid hormone for thyroid hormone production. For this reason, one third of the patients required an increased dose of levothyroxine. which can also affect the pregnancy outcome (16, 17, 18). The objective of the study was to investigate the thyroid functions of newborn babies of mothers with DTC after receiving 131I RAIT.

PATIENTS AND METHODS

During the period of 2009 to 2014, a total of 1620 women of reproductive age had been treated with ^{131}I in the thyroid division of NINMAS. They have been followed up at regular intervals, systematically, after RAIT. According to the follow-up protocol of NINMAS, all patients were given Levothyroxine doses capable of suppressing thyroid stimulating hormone (TSH). Serum TSH levels were routinely measured, and suppression doses were adjusted individually based on the results. This was done in order to obtain optimal suppression with the smallest amount of thyroxine and avoid probable iatrogenic hyperthyroidism. At the same time, all patients of reproductive age are instructed to avoid pregnancy for one year after their last RAIT. According to the protocol for follow-up after one year, whole body diagnostic scintigraphy was performed 72 hours after the administration of ^{131}I (1–5 mCi). Thyroxin stimulation therapy was discontinued four weeks prior to the whole body scintigraphy to determine the Tg and anti-TgAb levels. Later during the follow-up period, patients who were planning for pregnancy were allowed to conceive in a disease-free condition (Dx WBS: negative, thyroglobulin and anti-TgAb: within normal limits). All pregnant women were disease-free and well-supplemented with levothyroxine during routine regular follow-up, and their TSH remained in the low normal range (0.1-1.0 mIU/L). Their serum thyroglobulin (Tg) levels were below 0.02 ng/dl. During the first trimester of pregnancy, Levothyroxine dosage and TSH levels are carefully monitored for dosage adjustment since there is an increased demand for thyroid hormone production during that period. Mothers in their last trimester were requested to estimate the TSH of the newborn baby's blood at the 1st–2nd week of birth. They appropriately reported the TSH report of babies.

RESULTS

A retrospective review of the medical records was done in this study. Out of 1620 patients, 1370 (83.2%) were in the reproductive age group (18-44 years). Among 1370 patients, 114 (8.1%) patients became pregnant after 2 years of the RAIT. Age at pregnancy ranged from 15 to 38 years (mean ± SD; 24.8 ± 4.8). Distribution of studying patient was ≤20 years 25 patients, 21 – 30 years was 79 patients and > 30 was 10 patients.

Table 1: Distribution of the stydy patients by age (n=114)

Age	Number of patients	Percentage
≤20	25	21.9
21-30	79	68.4
>30	10	8.8
Mean± SD	24.8± 4.8	
Range (Min-max)	15-38	

The mean age was found 24.8±4.8 years with range from 15-38 years. Histologically, 66 (58%) tumors were found to be papillary thyroid carcinoma, 24 (21.1%) papillary carcinoma with lymph node metastasis, 18 (15.8 %) follicular variant of papillary carcinoma (FVPTC), 4 (3.5%) follicular carcinoma, 1 (0.9%) FVPTC with lymph node metastasis and 1(0.9%) PTC with lymph node and lung metastasis.

Table 2: Histopathological types of differentiated thyroid carcinoma among the study population (n=114)

Type of carcinoma	Number of patients	Percentage
Papillary Thyroid Carcinoma	66	58.0
Papillary Thyroid Carcinoma with Lymph Nodes Mets	24	21.1
Follicular variant of Papillary Thyroid Carcinoma	18	15.8
Follicular Thyroid Carcinoma	4	3.5
Follicular variant of Papillary Thyroid Carcinoma with LN Mets	1	0.9
Papillary Thyroid Carcinoma with Lymph Nodes Mets then lung Mets	1	0.9

After initial surgery, an ablation dose ranging between 30-450 mCi of radioiodine (single to multiple therapies) was administered. Among them, 88 (77.2%) patients received ≤ 100 mCi (30 – 100 mCi) and 26 (22.8%) patients were treated with more than 100 mCi . Single dose was administered to 106 (93%) and only 8 (7%) patients needed more than one dose.

Table 3: Radioiodine ablation doses administered to the female differentiated thyroid carcinoma patients of child bearing age (n=114)

Ablation dose (mCi)	Number of patients	Percentage
≤100	88	77.2
>100	26	22.8
Mean ±SD	106.1±53.6	
Range (min-max)	30-450	

During follow up period, all patients were disease free and supplemented by levothyroxine for maintaining the level of Thyroid Stimulating Hormone (TSH) at a low normal range (0.1-1.0 mIU/L) i.e. suppression. The outcome of 114 total pregnancies that occurred after RAIT was uneventful and 111 (97.3%) newborn were euthyroid. The remaining three (2.7%) pregnancies ended in miscarriage.

Figure 1: Outcome of the study patients after radioiodine therapy for differentiated thyroid carcinoma (n=114)

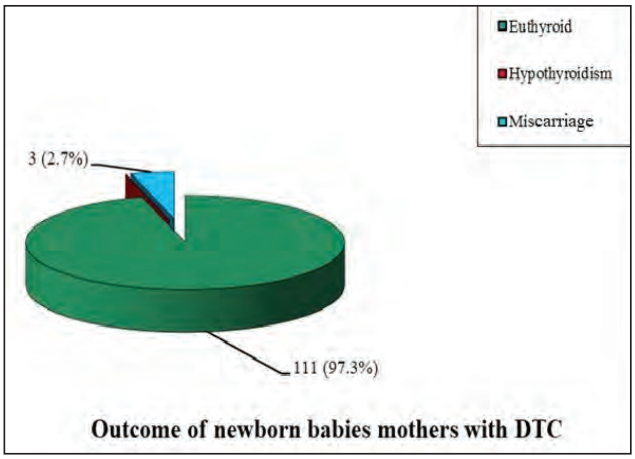

Table 4: Thyroid function status of newborn babies (n=111) born to radioiodine treated differentiated thyroid carcinoma mothers

Out come	Number of newborns	Percentage
Euthyroid	111	100%
Hypothyroid	0	0.0

** all newborns were euthyroid at the time of examination.*

DISCUSSION

Radioactive iodine treatment (RAIT) after thyroidectomy for differentiated thyroid carcinoma is commonly used for remnant ablation and adjuvant therapy and is intended to improve disease-specific and disease-free survival. Radioactive iodine (RAI; sodium iodide ^{131}I, or Na^{131}I) affects ovarian tissue, and common adverse effects of RAIT include oligomenorrhea, temporary secondary amenorrhea, and/or an earlier onset of menopause. Radiation exposure is also a risk factor for mutagenic abnormalities. This may represent an additional burden for patients of reproductive age (10).

In 2015, the American Thyroid Association released guidelines that strongly recommended women of childbearing age who are scheduled to receive RAIT have a negative screening result for pregnancy before RAI administration and avoid pregnancy for 6 to 12 months after receiving RAIT. In its 2017 guidelines, the American Thyroid Association updated its recommendation for deferring pregnancy, reducing the interval to 6 months after RAIT; however, the quality of the evidence supporting this recommendation remains relatively low. Five guidelines from the European Association of Nuclear Medicine Therapy Committee recommend that pregnancy be avoided and effective contraception be used for 6–12 months after receiving RAIT (10). In this study, patients have been deferred from pregnancy after 2 years of RAIT.

ME. Dottorini et al. emphasized the risk of fertility impairment and its effects on the offspring, which was assessed by selecting all female patients with a pathologic diagnosis of differentiated thyroid carcinoma under the age of 43years at the time of diagnosis, who had been followed-up for at least 2 years. A total of 814 selected patients were then divided into two groups: Group I (n = 627) with the patients treated with surgical, hormonal and ^{131}I therapy and Group II (n = 187) made up of the patients treated only with surgical and hormonal therapy (without ^{131}I therapy). Sixty-five children (45 males and 20 females) were born from 49 females of Group I and 19 children (12 males and 7 females) from 15 females of Group II. Two premature births at the seventh month of pregnancy and three spontaneous abortions by the third month were registered in the females treated. One spontaneous abortion at the second month was registered in the group of females not treated with ^{131}I. Among the children born from treated females, only one case of ventricular septal defect (VSD) and patent ductus arteriosus (PDA) was registered. All other children, born from the females of Group I and Group II, were in good health and achieved normal development parameters regularly. Females treated with ^{131}I are not discouraged from becoming pregnant at 1 year after the completion of

RAIT. Only one case of VSD and PDA was detected. No significant difference in the number of abortions or premature births in between the two groups was registered. All females had normal pregnancies and delivered children who were normal on follow-up. Their clinical data suggest that the use of ^{131}I for therapeutic purposes does not affect the fertility in females (11).

Ayala, E. Navarro, and colleagues studied 26 women with differentiated thyroid cancer who became pregnant after receiving therapeutic doses of ^{131}I in order to document the possibility of a greater risk for disorders in these pregnancies. There were a total of 39 pregnancies, six of which occurred during the first year after therapy. In three cases, the following anomalies were encountered: a male suffering from trisomy 18 (Edward's syndrome), a female with constitutional aplastic anemia, and a male with congenital hip dysplasia. There were two spontaneous abortions and one male with ureteral stenosis among the 33 pregnancies that occurred after the first year of RAIT. Although it cannot be confirmed that these congenital disorders are due to the ^{131}I therapy based on these data, authors recommend to avoid pregnancy in the first year after therapy. Their clinical data suggest that the use of ^{131}I for therapeutic purposes does not reduce fertility in females (17).

Esfahani AF et al. studied the outcome of pregnancy in females with DTC and evaluated the genetic risks and health status of their offspring. In a retrospective study on 111 women hospitalized (between 1999 and 2004) for high doses of RAIT (100mCi) they found 653 in their reproductive period and at least 100 of them got pregnant after RAIT. Authors demonstrated following observations after meticulous follow up of 126 pregnancies among these patients: a) there was no evidence of increased spontaneous abortions b) Increase interval between the last RAIT and time to plan pregnancy might be beneficial for reducing risk of abortions c) Treatment with ^{131}I had no obvious risk of congenital anomalies (18).

Bal CS et al. studied 1282 women between 1967 to 2002 after RAIT for DTC and found 692 (54%) in their reproductive age. Among them, forty women had a total of 50 pregnancies after a single high-dose therapy in 30 cases, two therapies in 7 patients, 3 therapies in 2 women and 4 doses were needed by a patient with lung metastases. The interval between RAIT and pregnancy ranged between 7 to 120 (37.3 ± 28.2) months. Three spontaneous abortions occurred in two women. Out of 47 newborns (F=20, M=27), normal birth weight and normal developmental milestones were reported in 44 (93.6%). Authors observed, female fertility to be unaffected by high-dose radioiodine treatment, and the therapy does not appear to be associated with any genetic risks to the offspring (19). Present study of 114 pregnancies after RAIT for DTC found 109 (95.6%) euthyroid babies and uneventful pregnancies. However, two miscarriages and three induced abortions were reported.

Out of 1620 patients of this retrospective analysis, 1370 (83.2%) were in the reproductive age group (18–44 years) and 114 (8.1%) out of 1370 patients became pregnant after two years of RAIT. Ages of pregnancy appeared earlier (24.8 ± 4.8) in comparison to the studies of Bal CS et al. and Esfahani AF et al. Following the initial surgery, a radioiodine ablation dose of minimum 30 and maximum 450 mCi (in multiple therapies) were recorded. The majority of the patients, 88 (77.2%), received 100 mCi (30–100 mCi), and 26 (22.8%) received > 100 mCi. One hundred and sixty patients (93%) received a single RAIT, while only eight (7%) needed multiple therapies.

During the follow-up period from 2009 to 2014, 114 (8.1%) patients subsequently became pregnant. We maintained routine follow-up throughout the pregnancy, and all pregnant women were disease-free, well-supplemented with levothyroxine, and their Thyroid Stimulating Hormone (TSH) remained in the low normal range (0.1-0.5 mIU/L). In 114 total pregnancies that occurred after radioiodine therapy, 111 (96.5%) children were born, and all babies are euthyroid, The thyroid status and abortion rate in the study suggest that radioiodine had no effect on pregnancy outcome. Previous administration of ^{131}I in women of reproductive age diagnosed with DTC failed to show immediate adverse effects during subsequent pregnancies since only 3 of 114 patients (4.4%) who conceived within 6 months after the last administration of ^{131}I had 2 miscarriages and 3 induced abortions.

No difference in outcome between the low and high total RAIT groups ($p = 0.273$) were observed in this study. Also, no difference was noted in the gender distribution ($p=0.823$). Stillbirths, congenital abnormalities, and first-year neonatal mortality were not included.

CONCLUSION

This study with a good number of DTC patients treated with radioiodine showed no evidence of thyroid carcinoma altering female fertility or appear to be related with genetic risks. So, it should not cause concern for the prospective mothers who desire to plan pregnancy. However, increasing the interval between the last dose of ^{131}I treatment and pregnancy might be beneficial for

decreasing the possible risk of abortions cause gonadal irradiation contributing to the occurrences of malformations, thyroid, and nonthyroid malignancies are still unknown. The induced abortions were mostly related to mothers' concern of possible neonatal anomalies and not maintaining the recommended time interval.

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