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I-131 myth bursting: association of pregnancy/infertility related adverse effects of radioactive iodine I-131 administration

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ABSTRACT

Background: There is very little knowledge on the risks of genetically transmissible diseases after the exposure to radiation. This study aimed to investigate the influence of radioiodine [radioactive iodine therapy (RAI)] on the outcome of pregnancies and the health status of children born to mothers who had received therapeutic doses of I-131 for differentiated thyroid carcinoma or for hyperthyroidism.

Methods: Gestational histories of 300 women who were treated with radioactive iodine either for the treatment of hyperthyroidism or for the treatment of thyroid cancer from 2012 to 2017 were retrospectively analyzed. Two Groups were made on the basis of administered doses of radioactive iodine. The first group was further divided into two sub groups. Sub group A consisted of the patients who were treated with radioactive iodine for hyperthyroidism with less than 30 mCi. Sub group B had patients of differentiated thyroid cancer that had been treated with doses above 100 mCi of I-131. Group 2 had patients with primary hypothyroidism and was on thyroxine replacement therapy. Control group consists of healthy young women with no co-morbidities delivered babies in this time interval.

Results: The outcome of the 200 patients were as follows: 97 live births in the group A and 10 miscarriages, while in high dose group, 85 live births and 8 miscarriages were recorded versus 44 live births and 6 miscarriages in the group who were primary hypothyroid. In the control group, there were 50 patients who had 3 miscarriage and 47 healthy babies.

Conclusion: Therefore, the present study concluded that radioactive iodine administration does not increased a women risk of infertility or early pregnancy failure.

Keywords: Pregnancy, radioactive iodine, hyperthyroidism, cancer thyroid, thyroxine.

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Introduction

Thyroid carcinoma is the commonest endocrine malignancy and accounts for approximately 1% of all malignancies. The American Cancer Society's most recent estimates for thyroid cancer in the United States for 2021 are: about 44,280 new cases of thyroid cancer (12,150 in men and 32,130 in women) and about 2,200 deaths from thyroid cancer (1,050 men and 1,150 women) [1].

Thyroid carcinoma arises from thyroid follicular cells (papillary, follicular, and anaplastic) or from other cells within the thyroid gland like lymphocytes (primary thyroid lymphoma) or neuroendocrine C cells (medullary thyroid carcinoma). Papillary and follicular carcinomas are considered differentiated carcinomas and are often managed similarly despite many differences between the two. Papillary thyroid carcinoma accounts for the majority 80%-90% while follicular 5%-10% and anaplastic

carcinomas are rare at 1%-2%. In Pakistan among thyroid carcinomas papillary is the commonest ranging from 69%% to 71% followed by follicular carcinomas from 11.6%% to 13% [2,3].

Treatment includes thyroidectomy followed by radioactive iodine ablation [radioactive iodine therapy (RAI)] therapy. There is insufficient evidence regarding the impact of RAI therapy on reproductive function. RAI has been used for decades in the diagnosis and treatment of well differentiated thyroid carcinoma (DTC) as well as for the patients having hyperthyroidism [4]. Following total thyroidectomy, patients are administered radioactive iodine. The patient remains in observation for 2-3 days, before releasing from the hospital.

The peak age for developing papillary carcinoma is about 30 years of age, for follicular cancer is 45 years and

both of the cancers are 3 times more commonly found in women. A large number of young female patients may be considered cured after thyroidectomy and radioiodine therapy and their desire to have child is within expect for their age range.

There is very little knowledge on the risks of genetically transmissible diseases after the exposure to radiation. There are two case scenarios where the women are exposed to ionizing radiation, i.e., during medical exposure (radiotherapy, radiological examinations) and accidental exposure. We have data from the studies that are being conducted on lab animals only. Radiation sensitivity also effects the oocyte survival. When exposed to ionizing radiation it results in two types of anomalies the structural chromosomal anomalies as well as in the numerical chromosome anomalies. Errors in chromosome segregation, results in aneuploidy causing genetic diseases many of which are related to mental retardation and congenital malformations [5]. 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.

Materials and Methods

This study was carried out as a retrospective study, conducted at Atomic Energy Cancer Hospital, NORI. Ethical approval was granted by the Research Training and Monitoring Cell (RTMC) of NORI, in March 2018, RTMC 3/3-34-2018, and informed consent was obtained from the patients.

A total of 1,200 female patients were treated with radioactive iodine at our hospital, between January 2012 and December 2017. Total 250 patients were included in this study. Of those, 200 female patients became pregnant after the radioactive iodine administration.

Patients were divided into two groups (Figure 1). Group 1 consists of the patients who were given radioactive iodine, they were further subdivided into two sub groups, sub group A consists of patients who were hyperthyroid belonging to benign thyroid disease and were given radioactive iodine <30 mCi, while sub group B consists of patients having differentiated thyroid cancer and were given ≥100 mCi or above with ablative intent. Group 2 consist of patients who were primary hypothyroid and on thyroxine replacement therapy. Control group consists of patients who conceived naturally and were not on any medication. Clinical data on pregnancies were obtained during a routine check-up of patients, including pregnancy details and outcome, live birth demographic data, thyroid stimulating hormone (TSH) after birth and the physical and intellectual condition of the children (the latest was assessed subjectively by their mothers by comparison with other siblings and peer groups).

Inclusion Criteria

Women of age above 20 years, non-pregnant & non-lactating at the time of treatment, and having no previous history of miscarriage or infertility were included in this study.

Results

The mean follow-up of these was 5.4 years. Group 1 conceived at a mean age of 25.93 ± 3.49 -year-old and group 2 at a mean age of 26.56 ± 2.56 . Group 3 conceived at a mean age of 24.22 ± 2.88 years as shown in Table 2. A total of 300 pregnancies were recorded during this study

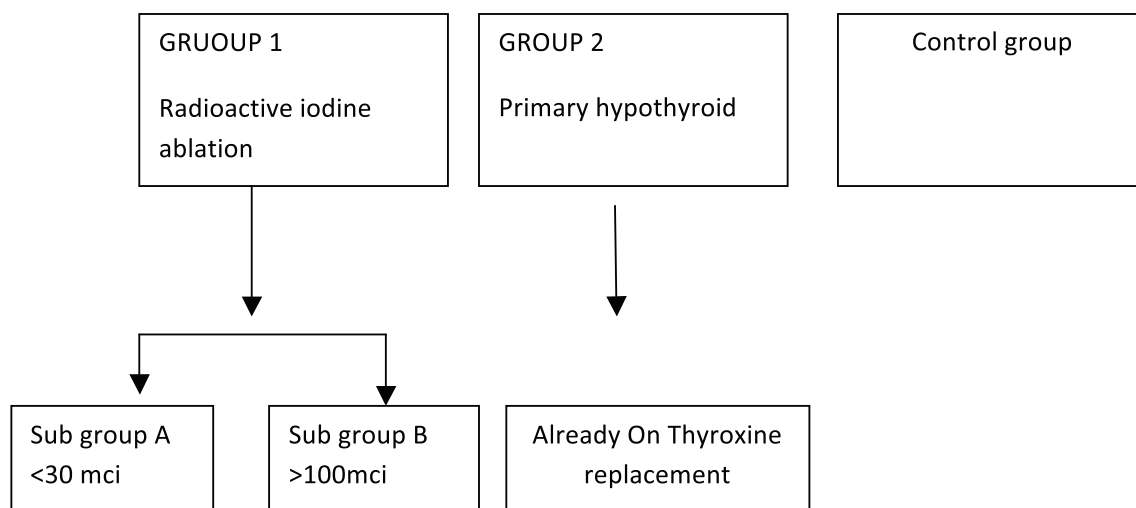


Figure 1. Division of patients into groups.

Table 1. Data of mean age on groups at conception.

Groups	Mean age at conception (years)
Group 1	25.93 ± 3.49
Group 2	26.56 ± 2.56
Control group	24.22 ± 2.88

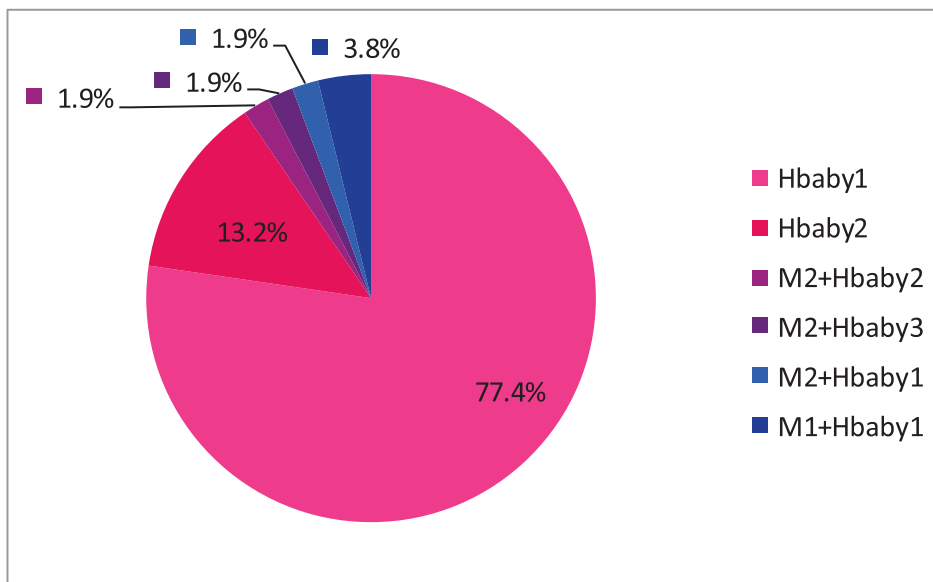


Figure 1. Pie chart showing the distribution of the patients who conceived after radioactive iodine H means healthy baby and miss means that there is miscarriage and it can be seen that majority of the pie part is taken up the healthy baby%.

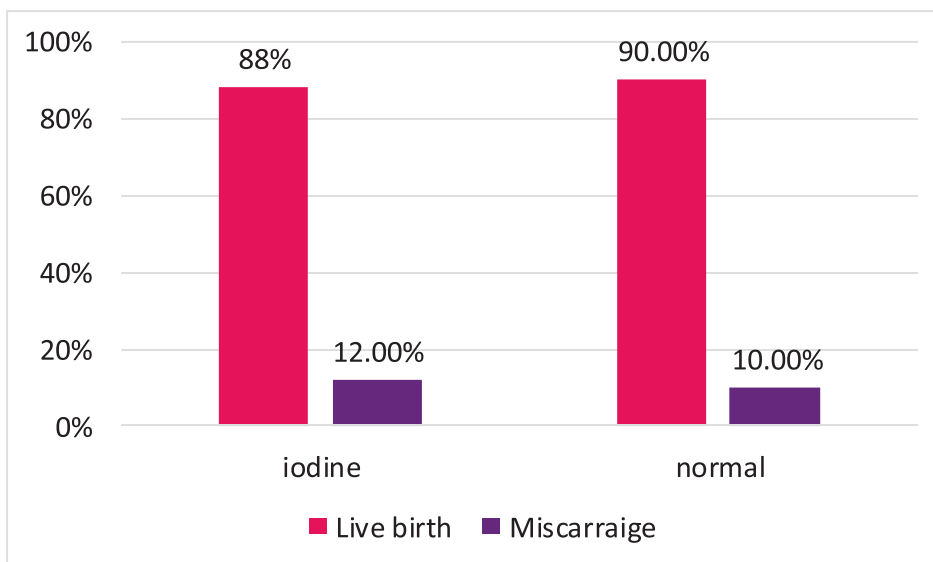


Figure 2. Bar chart showing head-to-head comparison of the patients who conceived after taking radioactive iodine and control group and one can easily identify that there is no difference in the out comes.

period. Among these 13 episodes of spontaneous abortion were observed.

The data were statistically analyzed on MS Excel and Statistical Package for the Social Sciences and *p*-value <0.005 was taken as significant. Group 1 conceived after a mean 4 months, of the last administration of ¹³¹I. The

miscarriage rate among women who underwent RAI was 26% in higher dose, 28.5% in hypothyroid versus 27% in the control group, which was not statistically different. No congenital malformations or first year mortality was noted. Odd ratio calculated was 0.66 and is considered normal. It can be easily demonstrated from the pie chart

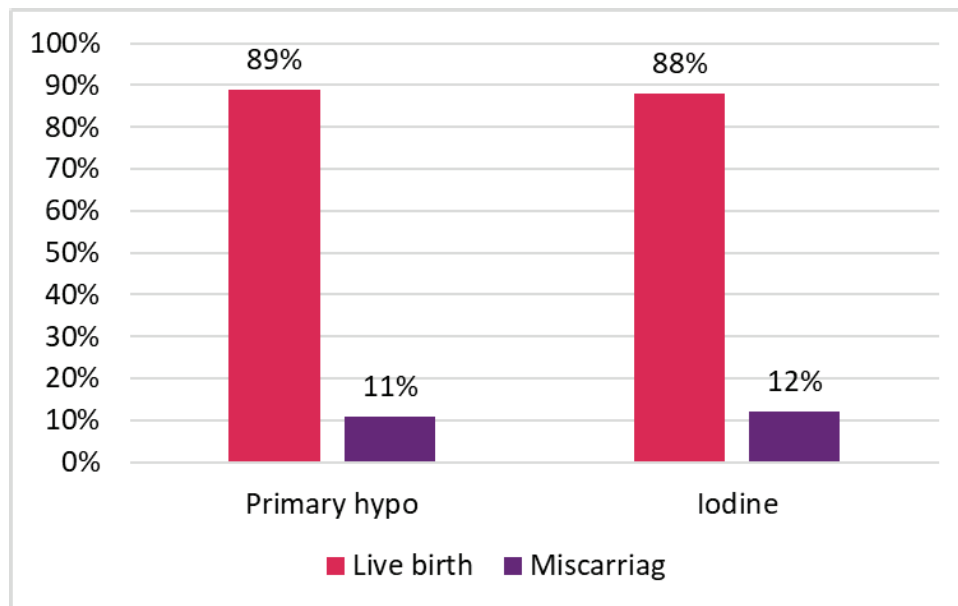


Figure 3. Bar chart showing that there is almost similar pattern of live births and miscarriage after taking radioactive iodine versus patients who are primary hypothyroid.

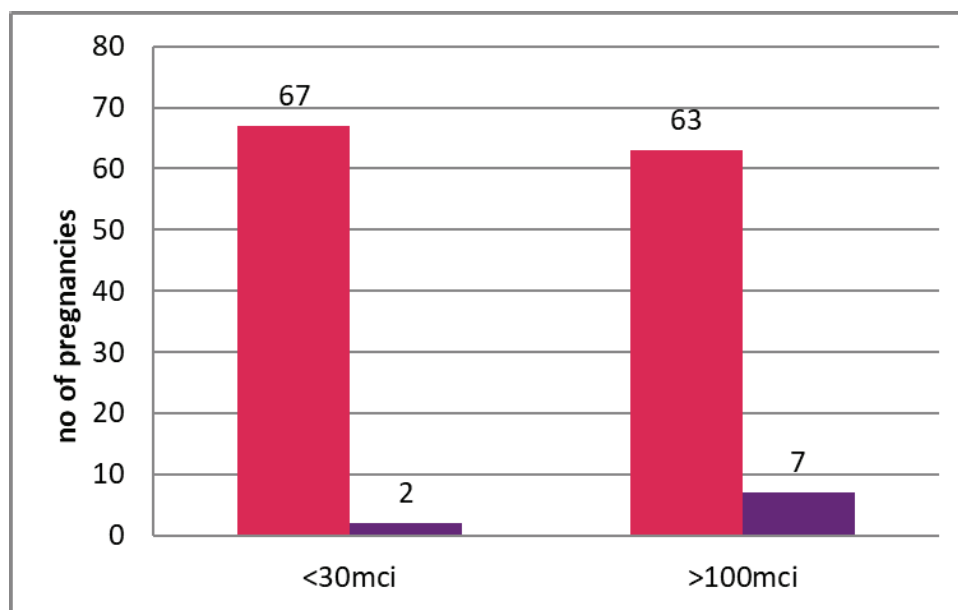


Figure 4. Live births and miscarriages in both sub groups A and B.

that majority of the pie chart is taken up by the patients who conceived after radioactive iodine and delivered a healthy baby that is 77%, while who delivered two healthy babies are 13% so a total of 90% is occupied by healthy babies. While it can also be seen in the pie chart that patients who had miscarriages, they had healthy children as well as seen by the pie chart 1. Figure 2 showing head-to-head comparison of the patients who conceived after taking radioactive iodine and control group and one can easily identify that there is no difference in the outcomes of the two groups. Figure 3 presents the results of the patients who were primarily hypothyroid and on thyroxine replacement versus those patients who took radioactive iodine both of them showed almost similar

result. Figure 4 presents head-to-head comparison in the two subgroups.

Discussion

RAI is used effectively in the treatment of hyperthyroidism and thyroid cancer, but it is contraindicated during pregnancy. RAI treatment during pregnancy can lead to fetal hypothyroidism, mental retardation, and increased malignancy risk in the infant [6]. Keeping these in mind, pregnancy tests must be performed before each and every treatment in all women of reproductive age. In pregnancy thyrotoxicosis is treated by antithyroid drugs. In the second trimester, it is safe to opt for surgery. But many women due to the risk of surgery as well as cosmetic

reasons do opt for treatment with radioactive iodine. But it is certainly not a choice during the pregnancy [7].

RAI when administered orally to a pregnant woman it crosses the placenta rapidly and reaches the fetus [8]. Physiologically after the 12th week of gestation, the fetal thyroid gland starts up taking and storing iodine [9]. If accidentally a pregnant woman had taken radioactive iodine the fetal serum RAI level reaches 75% of mother's serum level and RAI can persist in the fetal thyroid gland for approximately 70-75 days. All fetal tissues, and especially the thyroid tissue, are 2-3 times more sensitive to radioactivity as compared to adult tissues. RAI concentrated in the thyroid gland causes ablation [10].

RAI can create a lethal effect on the embryo and can negatively affect brain development both directly by its radioactive effect and indirectly by creating hypothyroidism [11,12]. Besides hypothyroidism, a fetus when exposed to RAI can have mental retardation, malformations, as well as an increased cancer risk in the later years of its life [13,14]. In some reported cases, hypoechoic thyroid nodules were also detected and that were later on resolved with thyroxine therapy [15]. Radiation can impair the developmental events occurring at the time of exposure. The potential risk depends on the radiation dose absorbed and the sensitivity of the tissue. Data from atomic bomb survivors indicate that ionizing radiation at 8-15 weeks of gestation may significantly affect brain development leading to intelligence quotient (IQ) loss or mental retardation [16]. The average IQ loss is approximately 25-30 points per Gy. In the 16-25-week stage of gestation, the brain is less sensitive and the average IQ loss is estimated to be 13-20 points per Gy above 70 rad [17]. After about 26 weeks, the fetal brain becomes all the more less sensitive to radiation exposure. An incident is reported that a figurative memory was found to be impaired in a patient who was inadvertently exposed to 500 MBq, of I-131 at 20 weeks of gestation [18].

The risk of congenital malformation is considered to be minimal after in utero exposures of 5 rad or less but rises significantly over control levels at doses above 15 rad. The type of malformation is determined by the stage of development at which the radiation exposure occurs. Permanent impairment of physical growth has been noted in atomic bomb survivors who receive radiation doses above 100 rad particularly when exposure occurs in the first trimester of pregnancy. This results in a 3%-4% reduction in height at aged 18 years for radiation doses greater than 100 rad [17]. While ¹³¹I administration to adults is not associated with an increased risk of thyroid cancer, data from the Chernobyl accident suggest that in utero exposure may be associated with a small increased risk [19]. In a cross-sectional study of 2,582, Ukrainian mothers pregnant at the time of the accident, 7 cases of thyroid carcinoma and 1 case of Hurthle cell cancer were identified amongst the offspring by screening.

To prevent RAI exposure during pregnancy, it is crucial to perform a proper pregnancy test in every female thyroid patient and not just rely on medical history. For this purpose, the American College of Radiology has prepared a guideline listing four different clinical situations that eliminate the possibility of pregnancy [19]. These are:

- A negative result in a pregnancy test performed within the past 72 hours.
- History of hysterectomy.
- State of menopause for at least 2 years.
- Pre-menarche child aged 10 years or younger.

There is 17%-31% chance of having miscarriage or spontaneous pregnancy loss in all gestations. [20]. A spontaneous pregnancy loss is usually defined as one occurring at less than 20 weeks of gestation. The risk of miscarriage varies and it depends upon the certain clinical factors such as maternal age, family history, environmental exposures, and medical comorbidities [21]. Pregnancy losses have a significant emotional burden, especially on the females but it can result in bleeding, infection, pain, and may even need a surgical intervention.

Recurrent pregnancy loss is defined as either two consecutive spontaneous losses or three or more spontaneous losses, and it may occur in up to 1% of all women [22]. Causes of recurrent pregnancy loss may include the parental chromosomal anomalies, immunologic derangements, uterine pathology, and endocrine dysfunction [23].

The risk of infertility in women with overt hypothyroidism is less well studied. In a study of 171 hypothyroid women with TSH concentrations >15 mU/l, 68% reported having irregular menses, far higher than the 12% rate of menstrual irregularities reported by euthyroid controls. In one cross-sectional study among 129 infertile women, 5% had serum TSH levels >4.5 mU/l [24]. Thyroid dysfunction is also reversible, and treatment is generally safe and may exert a positive effect on fertility.

Persistent maternal hypothyroidism has consistently been shown to be associated with an increased risk of adverse pregnancy related complications [25,26] and is also known to show the detrimental effects upon fetal neurocognitive development. The adverse outcomes associated with it are risks of premature birth, low birth weight, pregnancy loss, and lower offspring IQ. Abalovich et al. [27] demonstrated that women with overt hypothyroidism carry an estimated 60% risk of fetal loss when not adequately treated.

The detrimental effects of maternal thyroid hypofunction on fetal neurocognitive development are less clear. In support of an adverse impact attributable to maternal hypothyroidism, data from a large case-control study demonstrated a seven-point reduction in IQ among children born to untreated overtly hypothyroid women compared to euthyroid controls [28,29]. Findings also

supported a delay in motor skill development, language development, and attention at 7-9 years of age.

What we concluded from the histories and the mother experiences 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 control group. The only untoward outcome of pregnancy was miscarriages. Deep when we asked the patients the reasons, we got for the miscarriages are as follows:

- People who stopped thyroxine
- Use of different brand of thyroxine
- Not complaint with thyroxine
- No regular check up with the endocrinologist/gynecologist

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.

Conclusion

There is no reason to discourage patients treated with RAI therapy from becoming pregnant. The incidence of spontaneous abortions, stillbirths, congenital abnormalities, or malignancies in the offspring was not increased. Also, higher therapeutic doses did not affect the outcome. Patients should be advised to avoid pregnancy after I-131 administration for a period of at least 6 months. Thyroid hormonal status should be evaluated prior to pregnancy and during pregnancy and thyroxine dose should be adjusted cautiously. The gynecologist and the nuclear physician should be on same page for the treatment of their patient. Beta human chorionic gonadotropin test should be performed before every dose of radionuclide therapy.

List of abbreviations

B HCG	beta human chorionic gonadotropin
DTC	differentiated thyroid cancer
Gy	Gray
RAI	radioactive iodine

Conflict of interest

None.

Funding

None.

Consent to participate

Not applicable.

Ethical approval

Ethical approval was granted by the Research Training and Monitoring Cell (RTMC) of NORI, in March 2018, RTMC 3/3-34-2018.

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