

Article

The Safety of Radioiodine Therapy for Women of Reproductive Age

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A B S T R A C T

Radioiodine (^{131}I) is an essential adjuvant treatment after thyroidectomy in patients with differentiated thyroid carcinoma as well as Graves' disease (hyperthyroidism). Generally, ^{131}I is safe. It has some side effects. Infertility is one an important issue for patients who will consider receiving the therapy, especially for a woman in reproductive age. This is reviewed in this paper. Studies reported, in hyperthyroidism and thyroid cancer patients who received ^{131}I therapy, demonstrated no significant radiation effect, some of the patients may have experienced short-term reproductive organs disfunction and changes generally resolve. There is no effect of ^{131}I on subsequent pregnancy documented.

I. INTRODUCTION

Radioiodine (^{131}I) is a radionuclide emits β and γ particles. β particle is used for therapy purpose and γ particle for diagnostics. It has a physical half-life of 8.1 days with β -particle energy 0.61 MeV and γ -particle energy 364 keV. Radioiodine therapy is administrated by oral to treat papillary and follicular thyroid cancer, hyperthyroidism, or nontoxic nodular goiter [Silberstein, 2012].

^{131}I is captured and accumulated in thyroid cells to damage the cell. ^{131}I therapy was introduced around 70 years ago for the treatment of benign thyroid diseases. ^{131}I has been used as second-line therapy 20 years ago for Graves' disease in case of recurrence after antithyroid drugs (ATD) therapy [Wartofsky,1991. Vaidya,2008. Bonnema,2012]. Recent data in the United States reported, ATD seems to replace by ^{131}I as a first-line choice and cure rate of patients who received ^{131}I within one year was 50%-90% [Emiliano,2008. Bonnema,2012]. However, hypothyroidism condition is an inevitable side effect and some related with to the radiation dose and predisposed individuals. So, longer follow-ups are needed after receiving ^{131}I therapy.

In the management of differentiated thyroid cancer (DTC), ^{131}I has been used for adjuvant therapy after near-total thyroidectomy for ablation microscopic residual tissue, distance metastases, persistence and recurrence tumor, and nonresectable tumor. Ten years of survival

for patients who received ^{131}I therapy is estimated 85% [Sioka 2011]. The US Air Force Registry and the Ohio State University Registry reported, that postoperative radioiodine (RAI) therapy reduced compare surveillance in 15-year recurrence (16% vs 38%), and mortality (3% vs 8%). [Mazzaferrri,1997. Anderson 2017].

Radiation phobia causes fear for patients when deciding to get radioiodine therapy for the treatment of thyroid diseases. Is radioiodine therapy-induced infertility? The statement often arises when patients are offered radioiodine for thyroid cancer as well as hyperthyroid disease. Infertility and sex dysfunction are important issues related to radioiodine. In the present review paper, we discuss publish reports of the radioiodine therapy effects focus on fertility for subsequent pregnancy planning.

II. METHODS

Studies of radioiodine effects were identified using Pubmed. The searching database was using keyword radioiodine effect, ^{131}I , pregnancy, infertility. The related papers and abstracts were downloaded and reviewed.

III. RESULT

^{131}I therapy on ovarium function

Infertility effect of ^{131}I treatment is an important consideration for most of the patients in reproductive age. The treatment may be affected by reproductive organs from blood circulation that contain ^{131}I . A systemic review study reported that 8 to 27% of 3,023 patients who received radioiodine for thyroid cancer had a transient of menstrual period absence within the first year after the therapy [Sioka,2011]. A study reported 20% of patients who received 4.24 MBq of ^{131}I experienced amenorrhea and increasing of FSH level for one year [Sioka,2011].

From four hundred- nine subject of DTC subjects, thirty-four (38%) of them who received ^{131}I experienced amenorrhea for four to ten months after the treatment and, four of them reported subsequently to pregnant 16-30 months after the treatment. Forti-nine (12%) of the subjects experienced a menstrual cycle irregularity, and 19 of them subsequently to be pregnant and one suffered from abortion [Vini,2002]

Another study reported that menstrual cycle irregularities increased significantly after received ^{131}I therapy, 83 (17%) of 322 patients received 3 GBq single ablation dose of ^{131}I reported experienced amenorrhea and transient menstrual cycle irregularities for 10 months after therapy, but no reports for ovarian failure permanently [Sioka,2011].

A review of 159 female DTC patients who received ^{131}I therapy reported no signs of changing of luteinizing hormone (LH), Follicle-stimulating hormone (FSH), estrogen and progesterone levels, and no sexual dysfunction, abortion, infertility during one year of follow-up [Sioka,2011].

Another study, also reported earlier menopause to compare to control [Raymond, 1989]. However, another study reported, there was no association between ^{131}I and early menopause [Sioka,2011].

Pregnancy after ^{131}I therapy

A study review 66 pregnancy women after received ^{131}I therapy (14 women within one-year therapy and 51 women after one year) from 2000 to 2005. Variation doses of ^{131}I from 1.11 GBq to 20.35 GBq and range of conception with last administrations of ^{131}I were 1 month to 10 years. The result of the study showed no evidence of genetic damage and no congenital anomaly reported in 14 pregnancies which occurred within one year after received ^{131}I .

Furthermore, there was no significant association between miscarriage, preterm birth in patients who received ^{131}I therapy from the general population [Brandão,2007. Dottorini, 1995). Another study reported that miscarriage incidence is higher within one year of the last ^{131}I therapy [Schlumberger M 1996].

A retrospective study in 257 Graves' disease patients reported that, no significant differences between patients who received ^{131}I therapy and anti-thyroid drug (ATD) or 166 the healthy women in intrauterine growth restriction, neonatal gender, premature birth. However, the higher abortion rate was found in Graves' disease patients who received both ^{131}I and ATD [Zhang 2016].

A cohort study indicated that ^{131}I treatment is associated with decreased pregnancy and successful delivery rates [Ko 2016]. The underlying mechanism seems beside the impact of the therapy, likely involves by a physician recommendation, patient's psychological issue, the stage of disease especially, and un control of thyroid hormone level.

^{131}I therapy on testicular function

^{131}I therapy may be associated with a reduction in sperm counts, it also elevated the level of FSH transiently. Therapeutic doses up to 1.85GBq (50mCi) may be elevated FSH levels and follow with testicular damage [Fard-Esfahani, 2014]. Higher cumulative therapy doses of 18.5–29.6 GBq (500–800 mCi) in a male are associated with increased risk of elevation of FSH levels. However, fertility and risk of miscarriage or congenital abnormalities in subsequent pregnancies are almost the same with moderate ^{131}I doses (7.4GBq /200mCi) [Fard-Esfahani,2014]. There are no reports of permanent infertility in male with a single ablative dose. Clinically, oligospermia occurs when male gonadal receiving doses excess of 50–100 rad. Spermatogenesis might be recovered within 20–48 months, but it is not always reversible [Fard-Esfahani,2014]. Gonadal complications can reduce with the lowest dose as possible, well hydration, frequent urinate, and avoid constipation. Sperm banking also can be offered to a male patient if he was planning to have a baby very soon or will receive a multiple of ^{131}I doses [Fard-Esfahani,2014]. Another study reported that the probability of infertility or birth defects offspring of a male patient who received ^{131}I up to 9.25 GBq (250 mCi) was the same from the general population [Fard-Esfahani 2014].

IV. DISCUSSION

Over five decades, ^{131}I therapy has been accepted and proven to be effective for thyroid diseases. Graves' disease mostly identified in women in reproductive age. Therefore, the effects and safety of ^{131}I are important issues. Adverse effects of ^{131}I therapy were correlated to the cumulative dose [Clement,2015].

Ovary radiation source of ^{131}I exposure are the blood, bladder, bowel, and possibly functioning metastases foci which close to the ovaries. It is recommended to have a lot of drink, urinate frequently and avoid constipation when received ^{131}I exposure. Each ovary receives 0.14 cGy/37 MBq administered a dose of internal radiation dose [Vini,2002]. The caution should be taken in patients with hypothyroid and decreased renal function during ^{131}I administration because it will cause prolonged gonadal exposure. Furthermore, the ovaries received about threefold higher dose in a hypothyroid patient. [Vini,2002]. Thyroid cancer patients who received 10–11 GBq of ^{131}I may be experienced amenorrhoea, and radiation absorbed dose had no significant difference with patients without menstruation cycle disturbance [Vini,2002]. A cohort study of Taiwanese National Health Insurance (NHI) program database during 1998-2010, reported amenorrhoea occurred in 8% to 27% of women within the first year after radioactive therapy [Ko 2016].

Older patients were likely to have more experiences in amenorrhoea. This is indicating that ovarian sensitivity to radiation increases with increasing age. Young women who received 4Gy

external beam radiotherapy had amenorrhoea experiences around 30% compare with women above 40 (100%) [Vini 2002]. However, ovaries of young women who have been receiving a high dose of internal radiation more tolerate up to 20 Gy. Experiences of resumption of menstruation cycle have been reported [Vini,2002].

Amenorrhoea with a transient increase of gonadotrophins level (FSH and LH) occurred one to three months after radioiodine. The absence of menstrual cycle for few months after radioiodine exposure might indicate the effect on the developing oocytes in future cycles. A study reported, in women under 40 years no evidence of decreased fertility after received ¹³¹I treatment and no adverse outcome on subsequent pregnancies [Vini, 2002].

V. CONCLUSION

Studies of ¹³¹I therapy in hyperthyroidism and thyroid cancer patients demonstrated no significant radiation effect. Around 30% of patients may have experienced short-term reproductive organs disfunction and the changes generally resolve. There is no effect of ¹³¹I on subsequent pregnancy documented. Overall, ¹³¹I therapy is safe, however, is recommended holding pregnancy until one year after received ¹³¹I therapy to allow irradiated spermatozoa and ovarian complete recovery for patients without undergone gonadal function and thyroid hormone under control.

REFERENCES

- Andresen NS, Buatti JM, Tewfik HH, Pagedar NA, Anderson CM, Watkins JM. Radioiodine Ablation following Thyroidectomy for Differentiated Thyroid Cancer: Literature Review of Utility, Dose, and Toxicity. *Eur Thyroid J*. Vol. 6, No. 4, 2017, pp.187–196.
- Balenovic A, Vlastic M, Sonicki Z, Bodor, Kusic Z. Pregnancy Outcome after Treatment with Radioiodine for Differentiated Thyroid Carcinoma, *Coll. Antropol*. Vol 30, 2006, pp 743–748
- Bonnema SJ, Hegedüs L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. *Endocr Rev*. Vol. 33.2012, pp.920-80
- Brandão Carmen DG, Miranda AE, Corrêa ND, Netto LS, Corbo R, Vaisman M. Radioiodine therapy and subsequent pregnancy. *Arq Bras Endocrinol Metab*. Vol. 51. 2007. pp. 534-40
- Clement SC, Peeters RP, Ronckers CM, Links TP, van den Heuvel-Eibrink MM, Nieveen van Dijkum EJ, et al. Intermediate and long-term adverse effects of radioiodine therapy for differentiated thyroid carcinoma--a systematic review. *Intermediate and long-term adverse effect of radioiodine therapy for differentiated thyroid carcinoma- as systematic review. Cancer Treat Rev*. Vol.41, 2015.pp. 925-34
- Dottorini ME, Lomuscio G, Mazzucchelli L, Vignati A, Colombo L. Assessment of female fertility and carcinogenesis after iodine 131 therapy for thyroid carcinoma. *J Nucl Med*. Vol 36. 1995. pp.21-7.
- Emiliano AB, Governale L, Parks M, Cooper DS. Shifts in propylthiouracil and methimazole prescribing practices: antithyroid drug use in the United States from 1991 to 2008. *J Clin Endocrinol Metab*. Vol. 95. 2010. Pp. 2227–33
- Fard-Esfahani A, Emami-Ardekani A, Fallahi B, Fard-Esfahani P, Beiki D, Hassanzadeh-Rad A, et al. Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma. *Nuclear Medicine Communications*. Vol. 35, 2014, pp. 808-17
- Hamada N, Momotani N, Ishikawa N, Noh JY, Okamoto Y, et al. Persistent high TRAb values during pregnancy predict increased risk of neonatal hyperthyroidism following radioiodine therapy for refractory hyperthyroidism. *Endocrine Journal*, Vol 58,2011, pp 55-58
- Ko, K. Y., Yen, R. F., Lin, C. L., Cheng, M. F., Huang, W. S., & Kao, C. H. (2016). Pregnancy Outcome After I-131 Therapy for Patients With Thyroid Cancer: A Nationwide Population-Based Cohort Study. *Medicine*.2016.Vol. 95.e2685.
- Mazzaferri EL: Thyroid remnant I ablation for papillary and follicular thyroid carcinoma. *Thyroid* . Vol 7, 1997. pp.265–271.
- Raymond JP, Izembart M, Marliac V, Dagousset F, Merceron RE, Vulpillat M, et al. Temporary ovarian failure in thyroid cancer patients after thyroid rem- nant ablation with radioactive iodine. *J Clin Endocri- nol Metab*. Vol. 69.1989. pp.186–90.
- Silberstein EB, Alavi A, Balon HR, Clarke SEM, Divgi C, Gelfand MJ, et al. The SNM Practice Guideline for Therapy of Thyroid Disease with ¹³¹I 3.0. *Journal of Nuclear Medicine*. 2012; 53: 1-19
- Sioka, Fotopoulos. Effects of I-131 therapy on gonads and pregnancy outcome in patients with thyroid cancer. *Fertility and Sterility*. Vol. 95.2011. pp.1552-9
- Schlumberger M, De Vathaire F, Ceccarelli C, Delisle MJ, Francese C, Couette JE, et al. Exposure to radioactive iodine-131 for scintigraphy or therapy does not preclude pregnancy in thyroid cancer patients. *J Nucl Med*. Vol. 37, 1996, pp. 606-12.

- Tran P, DeSimone S, Barrett M, Bachrach Bert. I-131 Treatment of Graves' Disease in an Unsuspected First Trimester Pregnancy; the Potential for Adverse Effects on the Fetus and a Review of the Current Guidelines for Pregnancy Screening. *International Journal of Pediatric Endocrinology*. Vol 2010 .
- Vaidya B, Williams GR, Abraham P, Pearce SHS 2008 Radioiodine treatment for benign thyroid disorders: results of a nationwide survey of UK endocrinologists. *Clin Endocrinol (Oxf)*. Vol. 68. 2008. pp. 814–820
- Vini L, Hyer S, Al-Saadi A, Pratt B, Harmer C. Prognosis for fertility and ovarian function after treatment with radioiodine for thyroid cancer. *Postgrad Med J*. Vol. 78. 2002. pp. 92–93
- Wartofsky L, Glinoe D, Solomon B, Nagataki S, Lagasse R, Nagayama Y, Izumi M. Differences and similarities in the diagnosis and treatment of Graves' disease in Europe, Japan, and the United States. *Thyroid*. Vol. 1, 1991. pp.129 –135
- Zhang Li-Hua, Li Jing-Yan, Tian Qi, Liu Shuang, Zhang Hong, Liu Sheng, et al. Follow-up and evaluation of the pregnancy outcome in women of reproductive age with Graves' disease after Iodine-131 treatment, *Journal of Radiation Research*. Vol. 57, 2016, pp. 702-8.

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