Successful pregnancy after radiotherapy with 131I for differentiated thyroid cancer. A case report and review of the literature

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Summary

Background: Radioactive iodine has been used effectively in the diagnosis and treatment of thyroid diseases. Since radiation is delivered to the whole body, including the ovaries, there is reasonable concern as to whether there is a possibility of mutagenic effect on germ cells. *Case Report:* A 33-year-old woman with a differentiated papillary carcinoma. (T2N0M0), underwent radiotherapy three weeks after surgery and one year afterwards she became pregnant. At the 38th week of gestation she delivered vaginally a healthy female neonate weighing 3100 g. The child at the age of five years is healthy with no signs of malignancy or other disease. *Discussion:* Washout of 131I of the whole body takes place in a few days. Nevertheless, most guidelines recommend avoiding pregnancy for four to six or even 12 months after RAI treatment or scanning. As reported in our case a normal uncomplicated pregnancy can follow an operative and complementary treatment of thyroid cancer.

Key words: Radiotherapy; Differentiated thyroid cancer; Pregnancy.

Introduction

Radioactive iodine (131I) has been used effectively in the diagnosis and treatment of thyroid diseases. It is mostly used in differentiated thyroid cancer (DTC) [1, 2], where it has been proven to prevent relapses and treat metastases. DTC has a female predominance and more than 50% of cases occur in the reproductive years. It seems that certain reproductive and hormonal factors that occur during pregnancy and during the first years after giving birth may predispose to the development of the thyroid cancer. The prognosis for DTC is good [3, 4], and treatment with 131I prolongs life, even when distant metastases occur [5, 6]. Since radiation is delivered to the whole body, including the ovaries, it is a reasonable concern as to whether there is a possibility of mutagenic effect on germ cells. The relevance of the mutagenic effects of radiation as assessed by untoward pregnancy outcomes, such as miscarriages, congenital abnormalities and malignancies in offspring, remains to be clarified in humans. One extensive study of Japanese atomic bomb survivors and two large studies of patients who had been exposed to abdominal radiation during childhood and adolescence did not detect any statistically significant effects of radiation on pregnancy outcome [7-9]. Despite that, the relevance of the mutagenic effects of radiation on the fertility and well-being of the offspring is still debated and discussed in cases of high-dose 131I treatment for DTC because large and conclusive data have not yet arisen. Hence, further research in this field is urgently needed so that a significant body of data can be collected. It is interesting that a recent study reported increased risk of leukemia in offspring whose fathers were exposed to radiation preconceptionally [10].

The radiation dose delivered to the ovary is approximately 0.14 cGy after administration of 37 MBq (1 mCi) 1311 in normal subjects [11]. Thyroid cancer patients receive diagnostic doses of I131 ranging from 1-5 mCi and therapeutic doses ranging from 30 to 150 mCi or more. In many cases functioning metastases are in close proximity to the ovary having as a consequence greater doses of radiation delivered to them. Furthermore, many patients during radiotherapy exhibit hypothyroidism due to insufficient thyroid hormone replacement therapy. This condition decreases renal iodine clearance, resulting in prolonged gonadal exposure [12].

Case Report

We report the case of a 33-year-old woman who complained of local pain in the glandular thyroid location. She also complained of weight loss during the previous few months. Ultrasound and scintigraphy examinations revealed a mass of 2.5 cm in the thyroid gland and fine needle aspiration (FNA) was suggested. The results of the FNA were suggestive of a differentiated papillary carcinoma. Thyroid hormone levels at that time were as follows: TSH: 2.1 mU/l, T4: 7.3 μg/dl, T3: 110 ng/dl, CEA: 3.5 ng/ml, calcitonin:18 pg.ml.

The patient underwent a chest and abdominal computed tomography (CT) scan and a body scintigram, but neither metastases nor nodules were found. Also, the capsule of the thyroid gland did not seem infiltrated. According to the TNM classification it was a T2N0M0 tumor. The woman underwent a total thyreoidectomy and pathological examination confirmed FNA findings and preoperative classification, adding that it was a grade 3 papillary carcinoma.

The case was discussed in the oncologic council and it was concluded that thyroid hormone replacement therapy should be

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prescribed and that surgery should be followed by percutaneous radiotherapy.

The woman underwent the radiotherapy three weeks after the surgery. The dose was 80 mCi (= 2960 MBq) of 131I. Afterwards thyroid hormone replacement therapy was started. TSH values were evaluated to confirm the expected TSH suppression, since TSH seems to reflect the growth of tumor cells of the thyroid. TSH values were lower than normal range.

Three months after surgery the following parameters were checked: lung parenchyma (chest X-ray), thyroid hormone levels, TRH test, erythrocyte count and TKE, and there were no indications of metastases. Six and 12 months after surgery this checkup was repeated without any remarkable findings.

One year after finishing her therapy the patient became pregnant. She had a normal and uncomplicated pregnancy and at the 38th week of gestation she delivered vaginally a healthy female neonate weighing 3100 g. The apgar score was 9 at the 1st and 10 at the 5th minute. During the pregnancy the woman did not undergo any radioactive examination. After delivery follow-up of the above-named parameters was continued every six months. The child at the age of five years is healthy with no signs of malignancy or other disease associated with radioactive therapy.

Discussion

The most important limitation in any study trying to clarify the effect of radiotherapy with 131I on pregnancy outcome is to eliminate all other cofactors that could influence mother or the infant. Age at conception, socioeconomic class, alcohol intake, and smoking, as well as adequacy and fluctuation of thyroid hormone replacement and radiation dose to the ovaries are biases difficult to overcome. The physical half-life of 131I is 8.04 days [13], and the median effective half-life is at least 14 hours [14], with substantial variations. Consequently, washout of 131I of the whole body takes place in a few days. Nevertheless, most guidelines recommend avoiding pregnancy for four [15] to six [16] or even 12 months after radioactive iodine (RAI) treatment or scanning [17, 18]. Despite instructions to patients unexpected pregnancies may occur. If radiotherapy followed conception with an interval of less than ten weeks it is essential to estimate the dose to the fetal thyroid and whole body and counsel the couple regarding their options. The tendency to adopt the recommendation for avoiding pregnancy up to one year after radiotherapy is based on two facts. The first one is that a greater miscarriage rate [18] and some untoward pregnancy outcomes such as birth defects [19], Edward's syndrome [20], and aplastic anemia [20] have been described to occur in pregnancies conceived within the first post-RAI year. The second one is that during that annual interval complete remission of the disease can be confirmed and the thyroid hormonal status controlled [18]. Therapeutic abortion has been a quite common approach for accidental RAI administration in the first trimester of pregnancy [21]. Knowledge of the timing of fetal thyroid development and the potential effect on the fetal thyroid and whole body irradiation on a developing embryo can guide management. The fetal thyroid begins to develop and differentiate into follicles at ten weeks of gestation. Consequently, if maternal RAI is administered after the 10th week of gestation it is quite possible that fetal hypothyroidism will appear [22]. To avoid such inadvertent events, patients should be strongly counseled to avoid pregnancy before radiotherapy, while determining the date of the woman's last menstrual period and contraception practice, and providing pregnancy testing within 48 hours before RAI administration are good procedural safeguards [23]. Since, DTC is considered a malignancy with a very good prognosis and slow growth rate, guidelines recommend delaying thyroid surgery and any RAI investigations until after delivery [15]. Some authors support the concept that hCG binds to the TSH receptor, stimulating the growth of benign and malignant thyroid tissue. Endogenous estrogen binding activity in neoplastic thyroid cells is described by some researchers. Diethylstilbestrol also was shown to have a relationship to thyroid neoplasia in C57BL/6 mice. Pregnancy termination or thyroidectomy during pregnancy is considered a rare approach, and mostly employed when diagnosis is made in the first trimester. The most commonly adopted approach is to keep the pregnancy, deferring thyroidectomy to either the second trimester or even until after delivery. The most important prognostic factors seem to be maternal age at the time of diagnosis. Tumor size, grading and other pathologic findings are of less importance. Thyroid cancer during pregnancy is reported to be associated with increased fetal loss, especially if more extensive surgery, including neck lymph node dissection is performed. Although most of the studies have failed to reveal any statistically significant effect of radiation such as 131I on fertility [24-26], ovarian [27] or testicular function [28], childhood cancers [29], congenital malformations [30], chromosomal abnormalities [31], or, some studies have demonstrated a greater frequency of chromosomal aberrations in the peripheral lymphocytes of patients treated with 131I [10, 32] or suggested an association between ionizing radiation of the father and an increased risk of congenital abnormalities [33] and leukemia [10]. Women previously irradiated for Wilms' tumor or other cancers with abdominal doses of 20 to 30 Gy are reported to have an increased rate of miscarriages, but this increase was attributed mostly to somatic damage to the abdominopelvic organs [34]. Recently controversial reports have been published showing an apparent increase in the number of leukemias in young people, whose fathers worked at the Sellafield nuclear reprocessing plant in Northwest England and were occupationally exposed to radiation [10], raising new concerns about these effects at low doses. It is quite interesting that the most profound reproductive effect of the Chernobyl accident was a sharp increase in elective terminations of pregnancy in Europe, which most of the time was unjustified after negligible exposure [32]. Therefore, the importance of clarifying the effect of 131I on pregnancy outcome is important not only for the management of patients with DTC, but also for assessment of the impact of ionizing radiation on human health in general.

Conclusion

Although the number of children born to mothers exposed to radioiodine is relatively small, there is no reason for patients exposed to radioiodine to avoid pregnancy. Radioiodine treatment of differentiated thyroid cancer does not affect female fertility nor is it associated with any genetic risk to the offspring. A washout period of one year is a reasonable approach. During pregnancy, thyroid function needs to be closely monitored and given these precautions RAI is a safe treatment method in young women.

As reported in our case a normal uncomplicated pregnancy can follow an operative and complementary treatment of thyroid cancer. Non differentiated thyroid carcinomas, as in our report, can be treated by total thyroidectomy followed by percutaneous radiotherapy, and the dose of thyroid hormone replacement therapy has to be very high in order to develop TSH suppression, since TSH seems to have a growth effect on the thyroid tumor cells. Our report is in accordance with the recent medical literature, stating that a one-year interval between radiotherapy with 131I for DTC and pregnancy is a safe option.

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