ORIGINAL ARTICLE

Prognosis for fertility and ovarian function after treatment with radioiodine for thyroid cancer

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The aim of this study was to review the outcome of ablative radioiodine treatment on ovarian function in young women treated for differentiated thyroid carcinoma. Of 1398 patients with differentiated thyroid cancer, 496 were women under the age of 40 at the time of diagnosis who had received radioiodine therapy. Of these, 322 received a single 3 GBq ablation dose of radioiodine while the remainder received subsequent treatment with ^{131}I with a cumulative activity of 8.5–59 GBq for residual, recurrent, or metastatic disease. Transient amenorrhoea or menstrual irregularities lasting up to 10 months were experienced in 83 patients (17%). No cases of permanent ovarian failure were recorded. There were 427 children born to 276 women; only one patient wishing to achieve a successful pregnancy outcome has been unsuccessful. Four premature births and 14 miscarriages occurred but no congenital abnormalities were reported. The risk of permanent damage to the ovaries after ablative radioiodine treatment appears to be low and patients can be reassured they can have normal pregnancies after this treatment.

Menstrual irregularities have been reported in up to 30% of young women after administration of high activities of radioiodine (^{131}I) and a smaller number of women experience amenorrhoea usually lasting for less than six months.[1] An increased incidence of miscarriage has also been reported within one year of radioiodine administration.[2] Nevertheless, radioiodine treatment does not appear to affect the outcome of any subsequent pregnancy.[3] However, there remains concern that fertility may be impaired because of irradiation received by the ovaries.

Since the majority of patients with differentiated thyroid cancer are young and may wish to have children, we wanted to review the outcome of ovarian function and fertility for these patients and now report our experience.

PATIENTS AND METHODS

Between 1949 and 1997, 1398 patients with differentiated thyroid cancer were treated at the Royal Marsden Hospital. We identified 496 women under the age of 40 at presentation who were treated with surgery followed by radioiodine and had a minimum follow up of two years.

All surviving patients were interviewed during clinic attendance or contacted by post. A full obstetric history was taken and details of the menstrual cycle were noted. Measurements of follicle stimulating hormone, luteinising hormone, and oestradiol were undertaken in patients in whom menstrual abnormalities arose. Patients were asked if they had had all the children they wished to have. Those who had not had a subsequent pregnancy were asked whether this was by choice.

The median age at diagnosis was 31 years (range 8–40); 381 tumours were papillary and 115 were follicular. A near-total thyroidectomy had been performed in 323 patients while the remainder had undergone hemithyroidectomy.[4]

The majority of patients had early disease confined to the thyroid gland (pT1–3). Extension beyond the gland with infiltration of surrounding tissues (pT4) was documented in 23 patients and lymph node involvement in 55 (ipsilateral in 41). Distant metastases in the lungs at presentation were discovered in 11 (2%).

After initial surgery, an ablation dose of radioiodine (1.1 or 3 GBq) was administered to 322 patients. A further 174 patients received subsequent therapeutic ^{131}I (cumulative activity 8.5–59 GBq for residual, recurrent, or metastatic disease).[5] Patients were advised to maintain a high fluid intake and void urine frequently after treatment. They were instructed to avoid pregnancy for one year after the last iodine dose.

RESULTS

With a median follow up of 18 years (range 2–48), 31 patients (6%) had died of their disease and 10 of unrelated causes. A further 46 patients had been lost to follow up. The remaining 409 were interviewed or contacted by post.

Ovarian function and numbers of women achieving conception are shown in table 1. Of the 409 women in the

Table 1 Ovarian function and women achieving conception after radioiodine therapy

	Normal menses	Irregular menses	Transient amenorrhoea
No of patients	326	49	34
Mean age (years)	31	28	36
Median (range) cumulative radiation dose (GBq)	3 (1.1–36)	14 (1.1–30)	14 (8.5–59)
No who wish to conceive	253	19	4
No who achieve conception	253	18	4

study, 34 (8%) reported amenorrhoea lasting between four and 10 months; four of them became pregnant 16–30 months after radioiodine treatment. Of the 409, 49 women (12%) experienced menstrual irregularities comprising either lighter menses or changed duration of cycle; 19 subsequently became pregnant but one suffered three miscarriages and has so far been unable to conceive. Patients experiencing menstrual disturbances had received greater cumulative radiation doses compared with those with normal menses (table 1). This was because of more extensive or recurrent disease.

No patients in the study developed permanent ovarian failure. In patients with amenorrhoea, there was a temporary marked increase of serum follicle stimulating hormone and luteinising hormone indicating transient ovarian failure. Patients who developed amenorrhoea were older (mean age 36) compared with those with milder menstrual irregularities (mean age 28) or no menstrual changes (mean age 31).

Altogether 133 patients had no desire to become pregnant and were using contraception. A total of 427 children were born to the 276 women wanting to conceive. All 253 women with regular menses wishing to conceive, achieved conception. There were four premature births and 14 miscarriages but no fetal abnormality was reported.

DISCUSSION

In this study, we observed transient amenorrhoea in 34 patients (8%) and lesser degrees of menstrual disturbance in a further 49 patients (12%) consistent with previous reports.[1] Few patients with amenorrhoea wished to conceive after treatment for their cancer. This is a reflection of their uncertainties regarding their prognosis as these patients had more extensive disease. They were also older than patients with regular menstruation and many had already had their children. We found that older patients were more likely to experience amenorrhoea, possibly indicating greater ovarian sensitivity to irradiation with increasing age. Experience with external beam radiotherapy suggests that the risk of infertility rises with age: treatment with 4 Gy produced infertility in 30% of young women compared with 100% of those over 40.[4] This could simply reflect decreasing fertility in older women. However, young patients have been reported to tolerate high doses to the ovaries and doses as high as 20 Gy in adolescents have been associated with resumption of menstruation.[5]

Amenorrhoea with a transient rise in serum gonadotrophins (follicle stimulating hormone and luteinising hormone) occurred one to three months after radioiodine when patients were receiving thyroxine replacement treatment. The delay of a few months after radioiodine might indicate an action on the developing oocytes involved in future cycles rather than the maturing follicle.

Sources of radiation to the ovary after radioiodine are the blood, bladder, bowel, and possibly functioning metastases close to the ovaries. The absorbed dose received by each ovary is 0.14 cGy/37 MBq administered dose based on the medical internal radiation dose.[6] However, the kinetic model used to calculate this dose assumes euthyroid status.

Patients treated with radioiodine are severely hypothyroid at the time of administration and renal radioiodine clearance is decreased, resulting in more prolonged gonadal exposure.

Learning points

- Temporary amenorrhoea lasting for up to 10 months occurs in about 8% of patients after ablative radioiodine.
- Permanent ovarian failure is rare after radioiodine treatment and fertility does not appear to be reduced.
- Patients receiving large doses of radioiodine should drink plenty of fluids and avoid constipation to avoid unnecessary radiation to the ovaries.

A more realistic estimate of the dose to the ovaries in the hypothyroid patient will be about threefold higher.[7] Applying this model to patients with thyroid cancer metastases receiving 10–11 GBq radioiodine, Izembart *et al* reported that patients developing amenorrhoea had no significant difference in the calculated dose received by the ovary compared with those with normal ovarian function.[7] Nevertheless, in this study, patients with menstrual disturbances had received a greater cumulative radiation dose compared with patients having regular post-therapy menstruation.

Measures to reduce exposure of the ovaries to radiation include generous hydration with frequent micturition, and avoidance of constipation. In vivo dosimetry to measure the absorbed dose received by metastatic disease is also suggested as a means of optimising the administered radioiodine dose.[8]

In summary, we found no evidence of decreased fertility in young women under the age of 40 years who were trying to conceive after radioiodine treatment. In keeping with other studies, we found no adverse outcome on subsequent pregnancies.[3]

We selected women under the age of 40 years because these patients have the best prognosis from their thyroid cancer.[4] We did not investigate older women and further studies will be needed to ensure that radioiodine treatment does not adversely affect their fertility. Young patients can be reassured that they can still conceive and have healthy children after radioiodine treatment for thyroid cancer.

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