AFTER IODINE-131 THERAPY FOR DIFFERENTIATED THYROID CANCER, INFERTILITY IS LOW AND OBSTETRICAL AND NEONATAL OUTCOMES ARE VERY GOOD

Sioka C, Fotopoulos A. **Effects of I-131 therapy on gonads and pregnancy outcome in patients with thyroid cancer.** Fertil Steril 2011;95:1552–9.

SUMMARY

BACKGROUND

Although radioactive iodine (^{131}I) therapy is usually well tolerated, side effects that impact future pregnancies can occur such as transient or chronic hypospermia, early onset of menopause, and menstrual cycle abnormalities. The authors reviewed all of the published reports concerning the effects of 131I therapy on female and male gonads and on pregnancy and offspring.

METHODS

Publications related to ^{131}I effects were identified using PubMed and Medline. Among the abstracts reviewed, 146 full-text articles related to side effects of ^{131}I were selected, and eventually 54 were used. The criteria used for final selection were the report of the effects of ^{131}I therapy for thyroid cancer on female and male gonads, lactation, or pregnancy outcome. The review was divided into sections according to the effects of ^{131}I on female or male gonads, lactation, and pregnancy outcome.

RESULTS

^{131}I and Ovarian Function

The authors systematically analyzed 16 articles that included data from 3023 women of child-bearing age who had differentiated thyroid cancer (DTC), examining the gonadal and reproductive effects of radioactive iodine therapy. Transient absence of menstrual periods occurred in 8% to 27% of women within the first year after radioactive iodine therapy, particularly in older women. In addition, the ^{131}I-treated women experienced menopause at a slightly younger age than women not treated with radioactive iodine. Although administration of 3.7 GBq of ^{131}I may still cause earlier menopause, doses over 3.7 GBq were more likely to increase such a risk. Overall, most studies have demonstrated that, apart from a possible slightly earlier menopausal age, postsurgical administration of ^{131}I for ablation of residual thyroid cancer remnants (up to 3.7 GBq activity) resulted in only transient menstrual cycle abnormalities, lasting up to a year, but no permanent ovarian failure. However, repeated doses for recurrent or persistent disease may slightly increase the risk for permanent ovarian failure.

^{131}I and Testicular Function

Significant irradiation is delivered to the testes after administration of a single ablative dose to patients who have undergone thyroidectomy. The authors reviewed 8 studies with a total of 306 men of reproductive age receiving doses of ^{131}I ranging from 1.1 GBq up to 9.2 GBq, with 1 study repeatedly using doses over 22.2 GBq. In most, but not all studies, serum follicle-stimulating hormone (FSH) levels increased between 2 and 6 months after therapy; they very seldom remained elevated by 18 months after therapy. Spermatogenesis was reduced for up to 18 months in all but one study, but permanent impairment was reported only with repeated doses of ^{131}I. These changes could be significant in subjects with preexisting impairment of fertility.

^{131}I and Pregnancy Outcome

Eight articles reported the obstetrical outcomes of women treated for DTC. The number of deliveries varied from 49 to 2673. In the largest study (2673 pregnancies), miscarriages rates of 10% before any treatment, 20% after surgery only, and 19% after ^{131}I treatment were reported. Miscarriages were not significantly more frequent in women treated with radioiodine during the year before conception, not even in women who had received >370 MBq during that year. The incidences of stillbirths, preterm births, low birth weight, congenital malformations, and death during the first year of life were not significantly different before and after ^{131}I therapy. The incidences of thyroid and nonthyroidal cancers were similar in children born either before or after the mother's exposure to radioiodine. Overall, the studies showed

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no evidence that exposure to radioiodine affected the outcomes of subsequent pregnancies and offspring.

A comparison of 356 pregnancies from 173 fathers before thyroid cancer diagnosis with 114 pregnancies from 63 fathers with thyroid cancer who received ^{131}I and with 23 from 17 fathers who had only surgery showed no differences in rates of miscarriage or congenital malformation of offspring before or after the diagnosis of thyroid cancer or after the administration of ^{131}I.

The above studies provide evidence that previous ^{131}I therapy in male or female patients did not significantly affect the subsequent pregnancy outcome and did not increase congenital anomalies in the offspring. Avoidance of conception for 6 to 12 months after ^{131}I therapy is recommended for both male and female patients, to allow for complete replacement of irradiated spermatozoa and reversal of the transient ovarian damage. However, ^{131}I therapy may still result in a reduced ability to conceive, especially in male patients, in older patients, and in patients treated with multiple doses of ^{131}I. In such cases, referral to physicians specializing in fertility management may be required.

^{131}I and Lactation

Reports of the transfer of radioiodine into human milk are rare. Radioiodine uptake is rarely observed in normal breast tissue, but it does occur in the lactating breast. Accumulation of ^{131}I in the breast may be an undesirable effect of ^{131}I ablation. Patients should be instructed to avoid both pregnancy and breast-feeding for 6 to 12 months after radiotherapy.

CONCLUSIONS

Transient amenorrhea or menstrual irregularities, which usually resolve within 1 year, can be expected in about 30% of patients who have received therapeutic ^{131}I. Male patients demonstrate transient impairment of spermatogenesis associated with elevation of FSH, which is reversed within 18 months after ^{131}I therapy. However, the risk of persistent male or female gonadal dysfunction may be increased in some patients after repeated or high cumulative radioiodine activities. No effects of ^{131}I on subsequent pregnancy outcomes and on offspring have been documented in either fathers or mothers. Although ^{131}I therapy is safe overall, most authorities recommend withholding pregnancy until 1 year after ^{131}I ablation therapy to allow enough time for complete replacement of irradiated spermatozoa and reversal of transient ovarian damage.

COMMENTARY

One common concerned of women and men who need ^{131}I ablation therapy after thyroidectomy for DTC is the risk of maternal and neonatal complications in future pregnancies. The other, almost universal, question is the effect of therapy on fertility. The complete review of the literature by Sioka and Fotopoulos, showed a remarkable consistency of results and conclusions among the investigators reporting on the subject. There are very few studies on the effect of ^{131}I therapy on lactation, but the recommendation is to not offer ^{131}I therapy to nursing women or that lactation be discontinued 1 to 2 months before ^{131}I therapy, but the minimal time is several days (1,2). The advice commonly given to women who want to become pregnant is to wait for 6 to 12 months, until remission of thyroid cancer is confirmed. Fairly good studies support this recommendation. Birth control should be strongly advised until the end of this waiting period. Another important basis for recommending a waiting period before becoming pregnant is to achieve the target thyrotropin value. Perhaps something not usually discussed with male patients is the potential effect on fertility, since men with unknown reduced fertility could be exposed to ^{131}I therapy. It has been suggested that sperm banking should be considered in those requiring cumulative doses of ^{131}I (3). Finally, the indications for ^{131}I therapy after thyroidectomy for DTC should be carefully reviewed and the guidelines from the ATA task force should be followed (4).

— Jorge H. Mestman, MD

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