Radioiodine Treatment of Hyperthyroidism in a Pregnant Woman

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We describe the effects of radioiodine treatment of a pregnant thyrotoxic woman. **Methods:** The woman received 500 MBq of ^{131}I in her 20th gestational week. The pregnancy was discovered 10 days after radioiodine administration. A gamma camera examination of the abdomen at that time showed a distinct focus of activity, which was interpreted as the fetal thyroid. Gamma camera examinations of the mother and fetus were performed at 10, 11, 12, 13 and 18 days after administration of the therapeutic activity and were the basis of dose calculations. The child was examined by hormone tests and mental performance tests, up to 8 yr after birth. **Results:** The uptake at 24 hr postadministration was calculated to be 10 MBq (2%) in the fetal thyroid gland. The effective half-life was 2.5 days, giving a calculated absorbed dose to the fetal thyroid gland of 600 Gy, which is considered to be an ablative dose. The calculated absorbed dose to the fetal body, including brain, was about 100 mGy, and 40 mGy to the fetal gonads. Doses were estimated taking contributions from radioiodine in the mother, the fetal body and the fetal thyroid into consideration. The woman was encouraged to continue her pregnancy and received levothyroxine in a dose to render her slightly thyrotoxic. At full term, an apparently healthy boy, having markedly raised cord blood serum thyroid-stimulating hormone concentration and subnormal thyroxine (T4) and low-normal triiodothyronine (T3) concentrations, was born. Treatment with thyroxine was initiated from the age of 14 days, when the somatosensoric evoked potential latency time increased to a pathological value and hormonal laboratory tests repeatedly confirmed the hypothyroid state. At 8 yr of age, the child attends regular school. A neuropsychological pediatric examination showed that the mental performance was within normal limits, but with an uneven profile. He has a low attention score and displays evidently subnormal capacity regarding figurative memory. **Conclusion:** Radioiodine treatment in pregnancy in the 20th gestational week does not give a total absorbed dose to the fetal body that justifies termination of pregnancy. A high absorbed dose to the fetal thyroid, however, should be the basis of the management of the pregnancy and offspring.

Key Words: radioiodine; pregnancy; fetal thyroid; hyperthyroidism

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Radioiodine treatment of hyperthyroidism is, for obvious reasons, not performed when the patient is pregnant, and there are only few reports of administration of radioiodine in pregnancy. In most cases, the treatment was given early in the pregnancy, and information on dosimetry and follow-up is scarce (*1–8*). An excellent summary of the scarce information in the literature has recently been given by Zanzonico and Becker (*9*).

In this article, we describe a hyperthyroid woman who was treated with radioiodine in the 20th gestational week of a previously undetected pregnancy. Information is presented on radioiodine uptake and effective half-life in the fetal thyroid and absorbed doses to fetal organs. Although the woman was treated with levothyroxine in doses high enough to render her slightly thyrotoxic during the remaining part of her pregnancy, there was evidence of thyroid dysfunction of the child at birth. The child, during an 8-yr follow-up, including neuropsychological testing, had presented signs of subnormal brain function, with a short attention score and subnormal capacity regarding figurative memory.

CLINICAL EVENT

A 43-yr-old woman contacted her gynecologist in 1987 because of nervousness, tiredness, tachycardia and gastrointestinal problems. She had had regular contacts with this physician for 2 yr because of infertility problems. She was of Hispanic origin and did not speak Swedish; hence, an interpreter was present at visits. The woman reported not having had any menstrual bleeding for 3 mo. Clinical examination and a urinary pregnancy test performed in the gynecologist's office did not indicate pregnancy. She was told that she was in the menopausal transition period and that she probably suffered from hyperthyroidism. The woman was referred to an internist, who noted her symmetrically enlarged thyroid gland as well as typical clinical findings of hyperthyroidism. This diagnosis was confirmed biochemically, with a free T4 concentration of 49 pmol/liter (Amerlex free T4, Amersham International Plc, Amersham, United Kingdom; normally 10.8–23.0 pmol/liter) and a total T3 concentration of 5.0 nmol/liter (T3 RIA "double antibody," Diagnostic Products Corp., Los Angeles, CA; normally 1.5–3.0 nmol/liter). Thyrostatic (thiamazole) medication was then initiated as a preliminary regime before definitive treatment of her hyperthyroidism.

With the intention of radioiodine treatment, a physician examined the patient after withdrawal of thiamazole for 7 days. Gamma camera examination after intravenous administration of 150 MBq [^{99m}Tc]pertechnetate confirmed the clinical diagnosis of toxic diffuse goiter (Graves' disease), showing an even distribution of the radionuclide in a moderately enlarged thyroid gland. A radioiodine uptake test was performed after oral administration of 0.5 MBq ^{131}I and showed an elevated uptake value of 59% after 24 hr.

After being advised of the therapeutic alternatives, the patient chose surgery instead of radioiodine therapy because she was hoping to become pregnant in the near future. Thus, radioiodine treatment was not given at that point of time. The patient was referred for surgery and the thiamazole medication was reinstituted.

The patient subsequently changed her mind and was again referred for radioiodine treatment, now 3 mo after the initial diagnosis. After withdrawal of thiamazole for only 3 days, another uptake for radiation dosimetry was performed. A

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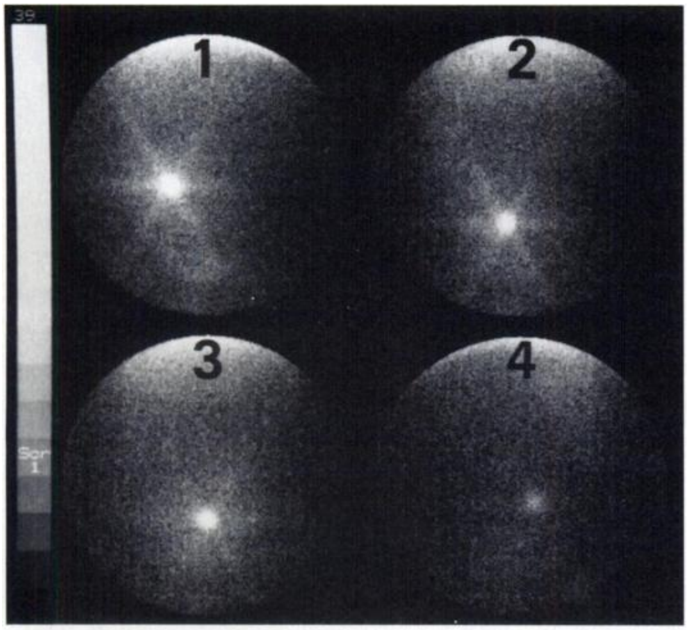

FIGURE 1. Gamma camera images of the abdomen of the woman 10 (panel 1), 11 (panel 2), 12 (panel 3) and 13 (panel 4) days after administration of radioiodine, showing the fetal thyroid.

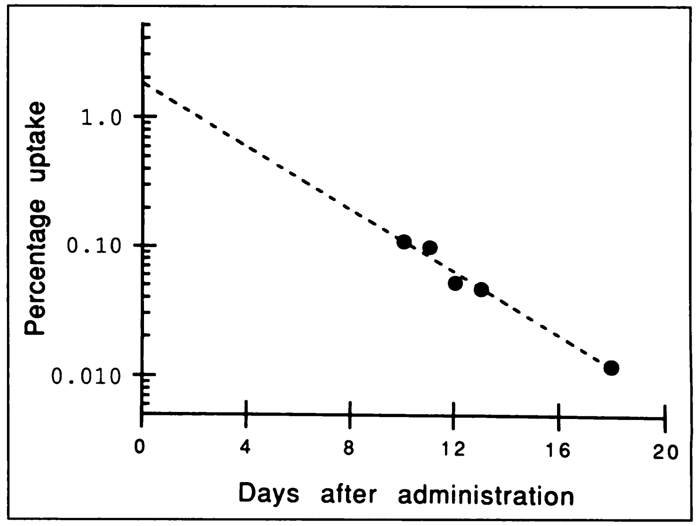

FIGURE 2. Uptake values in the fetal thyroid gland measured from the scintigraphic images 10, 11, 12, 13 and 18 days after radioiodine administration.

renewed uptake test for dose calculation indicated an uptake of 35% at 24 hr. With an effective half-life of 6 days calculated from serial uptake measurements, 500 MBq ^{131}I were administered 4 days later, to achieve a prescribed thyroidal absorbed dose of 100 Gy (*10*).

Dosimetry

Ten days after radioiodine administration, it was discovered that the patient was pregnant. Ultrasonography demonstrated a fetus with a size compatible with gestation week 22. The gestational age was calculated to be 20 wk at the time of radioiodine treatment, the fetal age was, therefore, 18 wk and, correspondingly, the fetal age at the first visit to the gynecologist was 7 wk.

As soon as the diagnosis of the pregnancy was established, the patient was referred for a gamma camera examination. At 10, 11, 12, 13 and 18 days after administration of the therapeutic ^{131}I dose, a gamma camera examination of the abdomen (General Electric 400 A/T, Milwaukee, WI) equipped with a medium-energy collimator and using an energy window of 365 keV, ±10% showed a distinct focus of activity that was interpreted as the fetal thyroid (Fig. 1). Quantification of the ^{131}I uptake in the fetal thyroid was by the conjugate view technique (*11*). At the first measurement at day 10, the activity was 0.6 MBq and then declined, with an effective half-life of 2.5 days. After extrapolation to the time of administration, the initial uptake was calculated to be 10 MBq, i.e., 2.0% of the administered activity, and the cumulated activity was calculated to be 900 MBq·hr (Fig. 2). Assuming a fetal thyroid mass of 143 mg (*12*) at fetal age 18 wk and using an S-value of 0.65 Gy/MBq·hr (*13*), the absorbed dose to the thyroid was calculated to be 600 Gy.

The mean absorbed doses to the fetus and to the certain fetal tissues from radioiodine in the mother, extrathyroidal fetal tissues and the fetal thyroid are presented in Table 1 (*14–18*).

Clinical Follow-Up

The woman was encouraged to continue her pregnancy, although the dose calculations had clearly indicated that the fetal thyroid should be ablated. Thyroxine substitution to the woman was initiated (0.1 mg, starting 14 days after radioiodine administration, and increasing to 0.125 mg after 6 wk). With this medication, the woman was intentionally kept slightly thyrotoxic during the remaining pregnancy, with free T4 concentrations of about 30 pmol/liter.

At full term, the woman gave birth to a healthy boy (Apgar score 10 after 10 min) with a weight of 3150 g, length of 49 cm and head circumference of 35 cm. Analysis of cord blood serum at delivery showed a markedly increased thyroid stimulating hormone concentration, but free and total thyroid hormones were normal compared to a reference population of 24 newborn healthy children (Table 2). Free T3 and total T3 concentrations were, however, in the lower range of the normal reference interval. The child had initial problems maintaining body temperature, which decreased from 36.8°C to 35.7°C in 3 hr. Examination by x-irradiation of the left knee joint 7 days after birth showed normal development. At gamma camera examination of the newborn child, using 4 MBq ^{123}I, the thyroid was only poorly visible (Fig. 3), and the estimated uptake was only 0.2% after 24 hr. The child was followed by repeated electroencephalographic examinations of the response to light stimuli

TABLE 1
Mean Absorbed Dose (mGy) of Iodine-131 to the Fetus

Source	Body	Brain	Gonads
^{131}I in the mother*	13	13	13
^{131}I in the fetus†	18	18	18
^{131}I in the fetal thyroid‡	65	75	10
Total	96	106	41

*Pharmakokinetic data are taken from ICRP 53 (*15*) for 35% thyroid uptake. The dose calculation was made using specific absorbed fractions for the gamma radiation according to Stabin et al. (*14*)

†The ^{131}I concentration in the fetus was estimated using data from Aboul Khair et al. (*16*) and Dyer and Brill (*17*) for fetal ages around 18 wk (an exponential fit to these data indicates an initial radioiodine concentration of 0.64×10^{-3}%/g with an effective half-life of 37 hr). The dose calculation was made using an absorbed fraction of unity for the beta radiation and ignoring the contribution from the gamma radiation.

‡Our own quantification of the ^{131}I activity in the fetal thyroid was used (10-MBq initial uptake and 2.5-day effective half-life). The dose calculation was made using point isotropic absorbed fractions (*18*) and assuming the body to be within a distance of 1.0–7.5 cm, the brain to be within 2.7–6.0 cm and the gonads to be 7.5 cm from the thyroid. Estimation of distances in the fetus was made from measurements of aborted fetuses of similar age.

FIGURE 3. Gamma camera image of the newborn child 24 hr after administration of 4 MBq ^{123}I. Uptake in thyroid was 0.2%.

with registration of the somatosensoric evoked potentials (latency time), the first examinations giving normal results; the examinations were conducted by Hrbek et al. (*19*). Within 14 days, the latency time increased to pathological values, and repeated peripheral thyroid hormonal determinations showed decreasing concentrations (Table 2); it was decided to initiate thyroxine treatment, which the boy has received since then.

The child was followed by an experienced pediatric endocrinologist. He had normal height and weight development, and at 8 yr of age, he is 126.5 cm tall and weighs 24.5 kg. His present height is 1.3 s.d. below the population mean (expected from parent data: 2.0 s.d. below the mean). Thus, he is short in stature but taller than would be expected considering the height of his parents.

During follow-up, he has appeared clinically euthyroid, although serum thyroid stimulating hormone and free T4 concentrations occasionally have indicated noncompliance. The child has been treated with thyroxine in doses increasing with age (initially 0.025 mg daily; now 0.075 mg daily as judged from thyroid stimulating hormone determinations, aimed to be within normal reference limits). He now lives with his mother and attends regular school. Due to language problems, the boy speaks neither Swedish nor Spanish perfectly, it has been difficult to evaluate his mental capacity. However, results from a neuropsychological test performed in October 1995, information from school and experience from the pediatric follow-up together indicate partially subnormal brain function. He has a good verbal capacity but a low attention score and displays evidently subnormal capacity regarding figurative memory.

DISCUSSION

Fetal Thyroid Function

The fetal thyroid is capable of forming colloid at 10–11 wk of age, and at about the same time, it is capable of concentrating iodine and synthesize thyroid hormones (*4,20*). In the present case, the fetus was exposed to radioiodine at an age of 18 wk. Thus, he would be expected to be fully capable of concentrating iodine in the thyroid, and this was clearly demonstrated by gamma camera imaging.

In vitro studies of aborted fetuses have shown 24-hr uptake values of 0.8%–2.1% in fetuses aged 17–19 wk (*21,22*). These uptake values are in good agreement with our in vivo registrations which, although extrapolated to 24 hr, indicate an uptake of about 1.4%. Model calculations have indicated a biological half-life as long as 30 days (*4,13*). However, estimations by Elsasser et al. (*12*), based on measurements on fetuses aborted at various times after ^{131}I administration (*16*), give a half-life of 3.2 days, i.e., a value similar to our finding of 3.6 days. However, it should be noted that the effective half-life measured in the present case was made in a nonphysiological situation with radioiodine-induced thyroiditis.

Previously published calculations of the absorbed dose to the fetal thyroid show discrepant results of 0.13–1.2 Gy per MBq given to the mother (*4,12,13,17,23*). This discrepancy is mainly due to different assumptions concerning uptake, half-life, thyroid mass and the absorbed fraction in the thyroid of the emitted beta particles. Our calculation, based on the measured uptake, gives 1.2 Gy/MBq with the mass estimation as the greatest source of error. The two mass formulas reported in the literature (*4,12*) give a discrepancy of almost a factor of two, indicating the high degree of uncertainty.

Radiation Risk for the Fetus

Effect on the Brain. The mean absorbed dose to the fetal brain was calculated to be 100 mGy. Although earlier data suggest that a threshold for radiation effect may exist (*24*), data on Japanese atomic bomb survivors exposed in utero at fetal ages 8–15 wk suggest the possibility of a non-threshold-type response for the induction of severe mental retardation (*25*). This has not, however, been conclusively established although the data have been interpreted by ICRP as representing a loss of 30 IQ points per Gy (low linear energy transfer). The somewhat higher age of the presently reported fetus makes the risk of brain damage in our child lower, perhaps by a factor of 4 (*25*). This means that the predicted IQ loss would have been less than 1 IQ point and, of course, undetectable on an individual basis. It may even be that, in fetal week 18, there is a threshold of

TABLE 2
Thyroid-Related Hormones During the First Two Weeks after Delivery*

Day after delivery	TSH (milli units/liter)	T3 (nmol/liter)	T4 (nmol/liter)	Free T4 (pmol/liter)	rT3 (nmol/liter)
0 (cordblood)	298	0.37	88	10.5	2.9
6	607	1.06	49		
11	768	1.42	32		
13	810	1.42	25		
Levothyroxine substitution initiated					
15	737	1.30	23		
18	628	2.29	92		
24	39	2.48	177		

*Reference intervals based upon 24 newborn healthy children: TSH = 0–25 milli units/liter; T3 = 0.3–1.3 nmol/liter; T4 = 70–150 nmol/liter; Free T4 = 9–17 pmol/liter; rT3 = 1.2–3.2 nmol/liter.

600–700 mGy, under which there is no radiation-induced mental retardation at all (*26*).

Effect on Thyroid. Radioiodine administration to adults in ablative doses is not associated with an increased risk of thyroid malignancy (*27*). This might be due to a radiation-induced permanent devitalization of the thyroid tissue. The Chernobyl experience indicates, however, that the young thyroid is much more at risk for thyroid cancer after radiation. We can, therefore, not make any definite conclusions as regards risk for thyroid malignancy in this case report. The possibility of thyroid malignancy should, of course, be kept in mind in the lifelong follow-up of the child.

Risk for Radiation-Induced Malignancy. The stochastic effects of the irradiation in the form of cancer induction and hereditary effects will affect the number of excess lethal cases (leukemia and solid tumors) in the childhood after irradiation in utero, estimated to be 3% per Gy (*24*), i.e., 0.3% per 100 mGy. Estimations of the lifetime risk coefficient for in utero irradiation are very uncertain and may exceed that for the childhood period by a factor of 2–4 (*25*). An in utero dose of 100 mGy will significantly increase the natural risk of fatal cancer in childhood, and will only result in a lifetime fatal-cancer risk of 1–2%. This should be compared with the natural level of risk of 20%–25%.

Thyroid Hormone and Brain

The subnormal mental development in this case might have been the result of inappropriately low thyroid hormone concentration to the fetus during the development of the central nervous system. The absorbed dose to the fetal gland was estimated to be 600 Gy, which may be considered to be an ablative dose. The mother received thyroxine during her pregnancy in a dose high enough to render her slightly thyrotoxic, in the hope of promoting sufficient placental passage of thyroxine to the fetus. This procedure was thoroughly discussed with Dr. Gerald N. Burrows (Toronto General Hospital, Toronto, Canada) at the actual time of decision and was later described by Glinoer et al. (*28*).

It has been proposed that the fetal lack of thyroxine in athyreotic fetuses might be compensated by maternal thyroxine passing the placenta (*29–34*). Here, cord blood analysis at birth verified the passage of thyroxine to the fetus, although in inadequate amounts, as judged from the elevated thyroid stimulating hormone concentration and subnormal (T4) and low-normal (T3), respectively, thyroid hormone concentrations. The high normal concentrations of reverse triiodothyronine (rT3) might reflect an increased transplacental passage of rT3 from maternal blood, where this metabolite would be expected to be present in increased concentrations due to the high intake of thyroxine. Thus, although the mother was kept slightly thyrotoxic, the transplacental passage of thyroxine was not sufficient to maintain normal hormone levels in the fetus, and it is possible that this deficiency of thyroid hormone during the fetal development was of importance. In fact, it is now realized that a significant number of children with neonatal hypothyroidism, who were diagnosed and treated even earlier than 14 days after delivery, show signs of impaired psychomotor development (*35,36*). Although the delay of 14 days in therapy in the present case may have been unfortunate because adequate thyroid hormone concentrations are vital to the neurological development during the first weeks of life (*33*), the slight mental development defects observed in the present case might already have been present at birth.

Pregnancy Testing

The absence of a positive result from pregnancy testing in the office of the referring physician is notable, but we cannot offer any explanation for this result. It should, however, be noted that routine pregnancy testing by previously common procedures may give misleading results at later stage of pregnancy due to concentrations of chorionic gonadotropin being below the detection limits of these tests. In this case, ultrasonographic examination would have given reliable information of pregnancy at the time of radioiodine treatment.

General Aspects

Thyroid blocking by administration of KI, given in direct association to radioiodine exposure, is considered to reduce the fetal thyroid uptake by a factor of 100 (*9*). In this case, however, the pregnancy was discovered 10 days after radioiodine exposure, and at that late time, blocking with KI would not significantly prevent fetal radioiodine uptake.

Intrauterine administration of levothyroxine is of theoretical interest once the athyreotic state of the fetus is known, but present available techniques are not possible because the drug (levothyroxine) must be administered repeatedly, and chronic installation of a catheter involves considerable risks for infections.

COMMENT

The case was brought to the attention of the Swedish National Board of Health who concluded that none of the physicians involved should be accountable. All medical clinics in Sweden, however, were informed of the incident, and new procedures were introduced. A pregnancy test by a high-detectability method is mandatory in women in fertile age before treatment, regardless of the patient's information about possibility of pregnancy.

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Variability of Perceived Defect Size in Virtual Lung Scintigraphy

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The diagnosis of pulmonary embolism is based on the presence of mismatched segmental or subsegmental defects. An important axiom is the classification of defect sizes into small, moderate and large. Little information about the recognition and classification of such defects has been published. We undertook a study of the perception of defect size using a model of the virtual scintigraphic anatomy of the lungs to address this issue. **Methods:** Segmental anatomy of the lungs was modeled with CT, cadaveric lungs and standard anatomical tests. The emission, scatter and attenuation of photons were modeled within these virtual lungs and the surrounding tissues. Single segmental lesions, each 100% of a segment, were created in eight projections and submitted for blinded reporting by four experienced nuclear medicine physicians to obtain their assessment of the size of each defect on two occasions. **Results:** Of the 144 defects submitted for reporting, 15% were reported as <25% of a segment, 35% were reported as 25%–75% and 50% were reported as 75%–100%. The accuracy of each reporter and the intraobserver agreement were calculated; the weighted kappa value ranged from 0.34 to 0.60. The segmental defects that were most likely to be underestimated in size were in the right lower lobe. **Conclusion:** It is clear that segmental defect sizes were underestimated, particularly in the right lower lobe. Although the intraobserver agreement in reporting was fair, the accuracy of estimation was only 50%. The variability and inaccuracy might be reduced by the use of a guide to segmental anatomy.

Key Words: Monte Carlo simulation; lung scintigraphy; perception; defect size

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Evaluation of lung scintigrams for the diagnosis of pulmonary embolism is based on the recognition of segmental anatomy and the extent of mismatched defects in perfusion. The combination of these two observations yields an estimate of the probability of the diagnosis of pulmonary embolism. Currently accepted criteria for such a diagnosis are derived from the PIOPED study (*1*), to which progressive refinements have been added through further analysis of the various subsets of the original data (*2–4*).

The PIOPED study divided defects into small (<25% of a segment), moderate (≥25%–75% of a segment) and large (>75% of a segment). The accurate and reproducibility of the assessment of defect sizes are assumed to be fundamental for the criteria to be clinically valid. However, little information has been published to confirm that assumption. Morrell et al. (*5*) demonstrated consistent underestimation of defect size in over 50% of cases and poor interobserver agreement for those observations. That study, however, suffered from the limitations of radiation exposure of normal volunteers and the acquisition of limited projections. We undertook a study with similar aims but used eight standard views produced in a virtual scintigraphic model of the segmental anatomy of the lungs.