Effects of marginal iodine deficiency during pregnancy: iodide uptake by the maternal and fetal thyroid

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Versloot, P. M., J. P. Schröder-van der Elst, D. van der Heide, and L. Boogerd. Effects of marginal iodine deficiency during pregnancy: iodide uptake by the maternal and fetal thyroid. Am. J. Physiol. 273 (Endocrinol. Metab. 36): E1121–E1126, 1997.—Iodide uptake by the thyroid is an active process. Iodine deficiency and pregnancy are known to influence thyroid hormone metabolism. The aim of this study was to clarify the effects of iodine deficiency and pregnancy on iodide uptake by the thyroid. Radioiodide was injected intravenously into nonpregnant and 19-day pregnant rats receiving a normal or marginally iodine-deficient diet. The uptake of radioiodide by the thyroid was measured continuously for 4 h. The absolute iodide uptake by the maternal and fetal thyroid glands at 24 h was calculated by means of the urinary specific activity. Pregnancy resulted in a decrease in the absolute thyroidal iodide uptake. Marginal iodine deficiency had no effect on the absolute iodide uptake by the maternal thyroid. The decreased plasma inorganic iodide was compensated by an increase in thyroidal clearance. A similar compensation was not found for the fetus; the uptake of iodide by the fetal thyroid decreased by 50% during marginal iodine deficiency. This can lead to diminished thyroid hormone production, which will have a negative effect on fetal development, especially of the brain.

Iodine deficiency is known to affect various physiological conditions, for instance, food deprivation (24), pregnancy (10, 11, 12), and iodine deficiency (19, 23). Iodide is an essential element for the production of thyroid hormones. The uptake of iodide by the thyroid gland is an active process that is regulated by thyroid-stimulating hormone or thyrotropin (TSH) (26) and the thyroidal blood flow (3). Alterations in the thyroidal uptake of iodide can cause changes in the production of thyroid hormones.

Iodine deficiency affects the physical and mental development of humans in large areas of the world (13). In rats it has been shown that during iodine deficiency the plasma thyroxine (T₄) level decreased while the 3,5,3'-triiodothyronine (T₃) level remained unchanged (23). The weight of the thyroid and the T₃-to-T₄ ratio in the thyroid of rats on a low-iodine diet increased (19, 23). Studies of 10-day-old rats have shown that the thyroidal iodide uptake was considerably higher in iodine-deficient rats than in controls (31).

Physiological changes in thyroid function also occur during pregnancy. Normal pregnancy in humans is accompanied by a rise in T₄-binding globulin and total T₄ and T₃ (12). However, the free T₄ level is decreased at the end of gestation (29). The availability of iodide for the maternal thyroid is decreased because of increased renal clearance (1) and transport to the fetoplacental complex during the late phase of gestation (10). The maternal thyroid is enlarged and the radioiodide uptake, expressed as a percentage of the dose, is increased during pregnancy (1, 10, 13).

In the rat normal pregnancy results in a decrease in plasma total T₄ and T₃ concentrations (4). This is comparable to the decrease in free T₄ in the third trimester of human pregnancy (29). The thyroidal uptake of ¹³¹I is decreased in the pregnant rat (9, 11, 15). No changes were found in the urinary excretion of iodide during the last days of gestation (9). Iodine deficiency induces a further decrease in plasma T₄ in the near-term pregnant rat (8). Also the weight of the thyroid is increased by iodine deficiency in the pregnant rat (7).

Most studies of the iodide uptake in rats are performed by tracer injection of a radioactive isotope of iodide (¹³¹I, ¹²⁵I, or ¹²³I). After a certain period the thyroid is removed and the percentage of the injected radioactivity is calculated (9, 11, 15, 31). In our laboratory we developed a method for measuring continuously the in vivo uptake of ¹²⁵I by the thyroid. By means of this method it is possible to study not only the amount of radioiodide taken up by the thyroid but also the kinetics of the thyroidal iodide uptake of iodide. We were also able to calculate the absolute iodide uptake by the thyroid.

The aim of this study was to clarify the effects of pregnancy and iodine deficiency on iodide uptake by the thyroid. We used four groups of rats: nonpregnant and near-term (day 19) pregnant rats receiving a normal iodine diet or a marginally iodine-deficient diet. This marginally iodine-deficient situation closely reflects the iodine status of large populations of humans in the world. As previously described, pregnancy as well as iodine deficiency affects plasma thyroid hormone levels. However, the effects on the absolute iodide uptake by the thyroid are unknown. In particular iodine-deficient, near-term pregnant rats represent an important group. What are the effects of iodine deficiency on iodide metabolism in the near-term pregnant rat? Are the low amounts of iodide available taken up totally by the maternal thyroid, or is there still iodide available for the fetuses?

MATERIALS AND METHODS

Animals. Three-month-old female Wistar rats (CPB/WU, IFKA CREDO, Brussels) were used. The rats were individually housed in metabolic cages at 22°C, with alternating 14-h light and 10-h dark periods. The animals were fed a semisynthetic American Institute of Nutrition (AIN) diet (2) mixed with distilled water (60% dry weight-40% water) and potassium iodide: 55 ng [normal iodine dose (NID)] or 2.9 ng [marginal iodine dose (MID)] per gram of feed. The margin-
ally iodine-deficient groups received 1% KClO₄ in the drinking water during the first 2 days of the MID ≥ 4 wk before measurement was started. KClO₄ was given to accelerate thyroidal depletion of total iodine stores.

After two regular estrus cycles the rats were mated. Mating was confirmed by the presence of sperm in a vaginal lavage the following morning, called day 0 of pregnancy.

Design of the study. In this study four groups of animals were studied: 1) nonpregnant rats on a normal diet (NID, C); 2) pregnant rats on a normal diet (NID, P); 3) nonpregnant rats on a marginally iodine-deficient diet (MID, C); 4) pregnant rats on a marginally iodine-deficient diet (MID, P). The pregnant rats were assessed at the end of gestation, i.e., day 19. Fetuses were delivered on day 21. The more frequently used day 20 was not suitable in this experiment, because the animals were killed and bled 24 h after the injection of radiiodide.

Daily feed intake and urinary iodide excretion were determined for all rats. The mean feed intake was 30 g, resulting in a daily iodide intake of 1.3 µg for the NID groups and 66 ng for the MID groups.

Urinary iodide was determined as described by Sandell and Kalthoff (22).

The experiments were approved by the University Committee on Animal Care and Use of the Agricultural University of Wageningen.

Thyroidal iodide uptake. The rat was anesthetized with xylazine (25 µl of 2% Rompun/100 g body wt sc), atropine (50 µl of 10% ketamine/100 g body wt ip). The anesthetized rat was fixed in a bed of plaster. The body temperature was monitored via the rectum and maintained at 38°C by a warming jacket.

The scintillation probe (type 42A NaI crystal 23 mm long × 1 mm thick, connected to mini-Assay type 6–20 (Mini Instruments, Essex, UK)) was placed as close as possible to the thyroid region.

To measure the thyroidal iodide uptake in the rat, a cannula was inserted into the right vena jugularis (20) and a 400-µl bolus of saline containing 10 µCi carrier free Na¹²⁵I (Amersham, Aylesbury, UK) was injected. The radioactivity taken up by the thyroid was measured automatically every 30 s for 4 h and calculated as a percentage of the injected dose.

The percentage dose of iodide taken up by the thyroid was measured by excising that part of the trachea containing the thyroid.

The assumption can be made that, during a steady-state situation, the specific activity of iodine (ratio of ¹²⁵I to ¹²⁷I) in urine is the same as that in the plasma from which it originated (28). The absolute iodide uptake (AIU) by the maternal and fetal thyroids, mammary gland, placenta, and fetuses minus thyroid at 24 h) was expressed as percentages of the injected dose.

The results are expressed per minute (16).

Body weight and plasma thyroid hormone concentrations. Plasma T₄ and T₃ did not change significantly during marginal iodine deficiency. Pregnancy resulted in a significant increase of T₄ and T₃ levels.

Table 1. Body weight and plasma thyroid hormone concentrations

<table>
<thead>
<tr>
<th></th>
<th>NID, C (n = 13)</th>
<th>NID, P (n = 10)</th>
<th>MID, C (n = 8)</th>
<th>MID, P (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>229 ± 4</td>
<td>300 ± 5*</td>
<td>235 ± 4</td>
<td>304 ± 6*</td>
</tr>
<tr>
<td>T₄, nM</td>
<td>31.4 ± 0.6</td>
<td>21.2 ± 1.5*</td>
<td>29.5 ± 2.4</td>
<td>16.9 ± 2.0*</td>
</tr>
<tr>
<td>T₃, nM</td>
<td>0.55 ± 0.05</td>
<td>0.49 ± 0.03*</td>
<td>0.69 ± 0.06</td>
<td>0.47 ± 0.04*</td>
</tr>
<tr>
<td>TSH, ng/ml</td>
<td>0.51 ± 0.09</td>
<td>0.48 ± 0.07</td>
<td>0.75 ± 0.05</td>
<td>0.65 ± 0.09</td>
</tr>
</tbody>
</table>

Values are means ± SE. NID and MID, normal and marginal iodine deficiency, respectively; C, control rats; P, near-term pregnant rats; T₄, thyroxine; T₃, 3,5,3' -triiodothyronine; TSH, thyrotropin. *P < 0.05, P vs. C.
decrease in plasma T4 and T3 in NID as well as MID rats (Table 1).

Feed intake and urinary iodide excretion. At the start of the experiments, the marginally iodine-deficient groups received potassium perchlorate for 2 days. The effect of this treatment on urinary iodide excretion is shown in Fig. 1. Potassium perchlorate treatment from day 0 to day 2 resulted in an increase in iodide excretion. Within 1 wk after perchlorate treatment, urinary iodide excretion had decreased to 0.4 µg/day; it remained constant during the rest of the experimental period.

The mean feed intake and urinary iodide excretion for the four groups of rats are shown in Fig. 2. No effect of MID on feed intake was found. During pregnancy, feed intake and urinary iodide excretion increased.

Thyroidal 125I uptake. Table 2 shows the data on thyroidal 125I uptake. The weight of the thyroid increased significantly in both marginally iodine-deficient groups; pregnancy had no effect on the weight of the thyroid. The 4-h 125I uptake by the thyroid increased in C and P MID rats. Pregnancy induced a decrease in 125I uptake by the thyroid in both NID and MID rats. The 4-h 125I uptake is a direct measurement of the thyroid; A and γ are the results of fitting the data to the one-exponential function %dose = A [1 - exp(-t/γ)]. Two- and three-exponential functions did not yield satisfactory results. The time constant (γ) of the 125I uptake was unchanged in all groups. The mean fitted thyroidal 125I uptake is given in Fig. 3, where we also see that the thyroidal 125I uptake was lower in P rats and increased in the MIDs groups.

Perchlorate discharge test. No discharge of radiiodide from the thyroid was found for any of the four groups. The radioactivity of the thyroid remained unchanged (results not shown).

Iodide kinetics in plasma. Table 3 shows the parameters of iodide kinetics in plasma. No significant changes were found except for A1 in pregnant rats.

AIU after 24 h. Table 4 shows the specific activity of urine and the results of calculations of the AIU by the maternal thyroid, PII, Cth, and CR. The urinary specific activity was unchanged during pregnancy, but marginal iodine deficiency caused an increase in specific
activity. The AIU by the thyroid was decreased by pregnancy, whereas marginal iodine deficiency had no effect on the AIU. PII was decreased in the MID groups, whereas pregnancy had no effect. Unidirectional iodide $C_{Th}$ was increased in the MID groups. C$_R$ was increased by pregnancy, whereas MID resulted in a decrease in $C_R$ in C and near-term P rats (Table 4).

The AIU values at 24 h by the maternal thyroid, placentas, fetal thyroids, remaining part of the fetuses, and mammary gland are shown in Fig. 4. Whereas MID had no effect on the AIU by the maternal thyroid, a pronounced decrease was found for the fetal thyroids and the remaining part of the fetuses. The amount of iodide taken up by the mammary gland was also decreased by MID, whereas no significant effect was found for the placentas.

**DISCUSSION**

The process by which the thyroid gland adapts to an insufficient iodine supply is to increase the trapping of iodide. When iodine intake is low, adequate secretion of thyroid hormones may still be achieved by marked modifications of thyroid activity. The thyroid is stimulated by an increased thyroid blood flow (3) and TSH (19, 23). The T$_3$-to-T$_4$ ratio of iodothyronines secreted by the thyroid is increased during iodine deficiency, especially because of a decrease in T$_4$ production (23).

Marginal iodine deficiency was induced in our rats by feeding them a MID diet. Within 2 wk of the start of the MID diet, urinary iodide excretion remained at the same level. So, at the moment of measurement, 2 wk after start of the MID diet, the rats were in a steady state. The fact that only a marginal iodine-deficient state was achieved, and not a severe iodine-deficient state, is demonstrated by the unchanged plasma T$_4$ and T$_3$ levels. Despite a slight increase in plasma TSH, the weight of the thyroid had already increased by 50%. The unchanged number of fetuses during pregnancy also demonstrates that the induced iodine deficiency was not severe (8).

In this study we were able to measure thyroidal radioiodide uptake continuously. For the kinetic analysis of radioiodide uptake in the human thyroid, a three-compartmental model is used (3, 14, 30). In this model, a plasma iodide pool and an inorganic and an organic thyroidal iodide pool can be distinguished. We tried to fit our data to this model; however, our data could only be fitted to a one-exponential function. Therefore, we assume that, even in euthyroid rats, iodide transport from plasma into the thyroid is unidirectional because of an extremely avid iodine organification. This idea is confirmed by the total absence of a perchlorate discharge in all rats, meaning that there is no efflux of inorganic iodide from the thyroid (17).

The thyroidal uptake of radioiodide was stimulated by marginal iodine deficiency. The kinetic analysis shows that the time constant for thyroidal radioiodide uptake was not affected by iodine deficiency, meaning that the time needed to achieve the maximum effect remained the same. However, the AIU by the thyroid remained normal. This was achieved by an increased $C_{Th}$ resulting from the increased thyroid volume and thyroidal blood flow (3).

The urinary specific activity was increased, whereas the radioiodide activity in plasma was not altered by marginal iodine deficiency. This resulted in a PII that was significantly lower, such as is found in humans residing in areas of iodine deficiency (5) and in 10-day-old iodine-deficient rats (31).

Our observations emphasize the need for caution in interpretation of results obtained by studies measuring the thyroidal radioiodide uptake only. We have demonstrated that a decrease or increase in radioiodide uptake does not automatically mean that the AIU has changed.

**Table 3. Parameters of iodide kinetics in plasma**

<table>
<thead>
<tr>
<th></th>
<th>NID, C (n = 13)</th>
<th>NID, P (n = 10)</th>
<th>MID, C (n = 8)</th>
<th>MID, P (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1$, %dose/ml</td>
<td>7.05 ± 0.42</td>
<td>4.92 ± 0.13*</td>
<td>7.01 ± 0.16</td>
<td>5.34 ± 0.22*</td>
</tr>
<tr>
<td>$\lambda_1$, 1/min</td>
<td>−1.78 ± 0.13</td>
<td>−2.32 ± 0.24</td>
<td>−2.47 ± 0.13</td>
<td>−2.28 ± 0.21</td>
</tr>
<tr>
<td>$A_2$, %dose/ml</td>
<td>1.14 ± 0.15</td>
<td>1.19 ± 0.13</td>
<td>1.12 ± 0.07</td>
<td>1.22 ± 0.16</td>
</tr>
<tr>
<td>$\lambda_2$, 1/min</td>
<td>−0.066 ± 0.014</td>
<td>−0.085 ± 0.013</td>
<td>−0.059 ± 0.004</td>
<td>−0.072 ± 0.009</td>
</tr>
<tr>
<td>$A_3$, %dose/ml</td>
<td>0.806 ± 0.067</td>
<td>0.762 ± 0.049</td>
<td>0.837 ± 0.055</td>
<td>0.767 ± 0.069</td>
</tr>
<tr>
<td>$\lambda_3$, 1/min</td>
<td>−0.0019 ± 0.0003</td>
<td>−0.0022 ± 0.0007</td>
<td>−0.0025 ± 0.0003</td>
<td>−0.0034 ± 0.0007</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05, †P vs. C.

**Table 4. Urinary specific activity, absolute iodide uptake by thyroid at 24 h, plasma inorganic iodide, and clearance of iodide from plasma by thyroid and kidneys**

<table>
<thead>
<tr>
<th></th>
<th>NID, C (n = 7)</th>
<th>NID, P (n = 12)</th>
<th>MID, C (n = 5)</th>
<th>MID, P (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine, %dose/ng</td>
<td>0.022 ± 0.003</td>
<td>0.023 ± 0.003</td>
<td>0.034 ± 0.005</td>
<td>0.037 ± 0.005†</td>
</tr>
<tr>
<td>AIU, µg/24 h</td>
<td>1.29 ± 0.09</td>
<td>0.87 ± 0.16</td>
<td>1.57 ± 0.35</td>
<td>0.89 ± 0.14*</td>
</tr>
<tr>
<td>PII, ng/ml</td>
<td>24.5 ± 4.6</td>
<td>19.9 ± 2.4</td>
<td>11.7 ± 3.6†</td>
<td>9.11 ± 2.3†</td>
</tr>
<tr>
<td>$C_{Th}$, ml/min</td>
<td>0.079 ± 0.014</td>
<td>0.079 ± 0.015</td>
<td>0.367 ± 0.172†</td>
<td>0.164 ± 0.044</td>
</tr>
<tr>
<td>$C_R$, ml/min</td>
<td>0.149 ± 0.010</td>
<td>0.228 ± 0.040</td>
<td>0.081 ± 0.019†</td>
<td>0.173 ± 0.032*</td>
</tr>
</tbody>
</table>

Values are means ± SE. AIU, absolute iodide uptake; PII, plasma inorganic iodide; $C_{Th}$ and $C_R$, clearance of iodide from plasma by thyroid and kidneys. *P < 0.05; †P vs. C; †MID vs. NID.
Also, during normal pregnancy, changes in iodide metabolism are found. The urinary iodide excretion was higher for P than C rats of the NID as well as MID groups. This can be explained by the increased feed intake and the increase in CR. Galton (11) also found an increased urinary iodide excretion for pregnant rats during the last days of gestation.

At the end of gestation the percentage of radioiodide taken up by the thyroid was significantly decreased. This has also been reported for rats with a normal iodine intake (9, 11, 15). Because the urinary specific activity was not altered by pregnancy, this also resulted in a decrease in the absolute iodide uptake by the maternal thyroid at the end of gestation in NID as well as MID rats. It seems that the thyroid of the near-term P rat has less iodide available for the production of thyroid hormones. However, no change in thyroid hormone production is found at the end of gestation (27). This would seem to imply that the use of iodide in the thyroid of the near-term P rat is more efficient or that the thyroglobulin stores are depleted.

The difference in thyroidal iodide uptake between C and near-term P rats cannot be attributed entirely to the increase in urinary iodide excretion. We suggest that the remaining part of the iodide is used by the mammary glands and the feto-placental compartment. For lactating rats it has been shown that, 4 h after injection, the mammary glands contain as much radioiodide as the thyroid, and it was suggested that during pregnancy radioiodide was already being transported to the mammary glands (15). The latter was contradicted by our measurements. One gram of the mammary gland had only taken up 6.5 ng iodide at 24 h; this is less than 1% of the thyroidal uptake.

The placenta possesses a mechanism for actively transporting iodine (21). Therefore, it is to be expected that a certain amount of radioiodide is transported to the fetal compartment. Our results, collected 24 h after injection, show that the fetal thyroid is capable of concentrating iodide on day 20 of pregnancy. The thyroidal region of the fetus contained as much iodide as the rest of the fetus. However, the total amount of iodide in placentas and fetuses could not explain the decreased uptake of iodide by the maternal thyroid. Therefore, the feto-placental compartment and the mammary glands are not the only factors responsible for the difference in maternal thyroidal iodide uptake.

During marginal iodine deficiency the AIU of the maternal thyroid remained normal. However, there was already a tendency toward a shift in thyroid hormone synthesis; T4 decreased and T3 remained normal. In contrast to the maternal thyroid, no compensation by an increased thyroid clearance for the decreased PII concentration was found for the fetal thyroid. The AIU by the fetal thyroid was decreased by 50%. This pattern can lead to lower T4 availability for the fetus. This is supported by kinetic studies of marginally iodine-deficient, near-term pregnant rats showing that the maternal transfer of T4 and T3 to the fetuses is decreased during marginal iodine deficiency (unpublished data). As long as the increase in type II deiodinase is sufficient to maintain normal T3 values in the fetal brain, problems need not be expected (18). If this is not achieved, defects in brain development will occur.

In conclusion, during pregnancy the AIU by the maternal thyroid gland is decreased. Marginal iodine deficiency does not affect the maternal thyroidal AIU. The low availability of iodide was compensated by increased activity of the maternal thyroid, whereas fetal thyroidal uptake of iodide decreased by 50%. The fetus is apparently not able to regulate its iodide metabolism in case of marginal iodine deficiency. Therefore, this level of marginal iodine deficiency, despite the near euthyroid status of the mother, already has an effect on the availability of iodide for the fetus. This can mean that fetal T4 production is markedly diminished at a time when it is of eminent importance for the normal development of many organs, especially the brain.

We are grateful to J. S. Goense for setting up the measurements and G. van Niftrik (Gelderse Vallei Hospital, Bennekom, The Netherlands) for designing the measuring bed for the rats. We thank M. van Lieshout for contributing to the experiments, T. Viets for performing the iodide measurements, Dr. R. Bakker for developing the mathematical model, and G. P. Bieger-Smith for correcting the text.
REFERENCES


