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Interrelationships among Serum Thyroxine, Triiodothyronine, Reverse Triiodothyronine, and Thyroid-Stimulating Hormone in Iodine-Deficient Pregnant Women and Their Offspring: Effects of Iodine Supplementation

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ABSTRACT. Adaptation to iodine deficiency (ID) requires changes in thyroid and pituitary function that have been well characterized in animals. The present studies were undertaken to analyze the relationships between serum thyroid hormones and TSH concentrations in iodine-deficient pregnant women as well as their newborns. The broad range of iodine intake of the population studied, from very low to adequate, allowed us to describe quantitatively the relationships among iodine intake, thyroid hormones, and TSH. The interpretation of the data was supported by the effects that iodine supplementation had on these various hormones and is consistent with animal observations. About 250 pregnant women from an iodine-deficient area were studied. Fifty percent had a urinary iodine excretion of 50 μg I/g creatinine (cr) or less; 25% had 50–100 μg I/g-cr, and about 20% had 100–200 μg I/g cr. Baseline serum hormone concentrations on first examination (mean ± SD) were: T_4, 8.0 ± 0.7 μg/dl; T_3, 179 ± 45 ng/dl; rT_3, 25 ± 9 ng/dl, and TSH, 2.9 ± 1.7 μU/ml. All values were independent of the age of gestation between 10–40 weeks. Serum T_4 and urinary I correlated linearly in a double reciprocal plot ($r = 0.90$; $P < 0.001$). Serum TSH correlated with the reciprocal of serum T_4 ($r = 0.76$; $P < 0.005$). In 36 women, oral iodine supplementation (OIS; 300 μg I/day for 4–16 weeks) increased total serum T_4 from 8.7 ± 2.4 to 12.5 ± 1.8 μg/dl ($P < 0.001$), decreased TSH from 2.8 ± 1.4 to 1.5 ± 0.8 μU/ml ($P < 0.001$), and increased rT_3 from 21 ± 7 to 25 ± 9 ng/dl ($P < 0.02$; all by paired t tests); serum T_3 remained unchanged (187 ± 25 and 180 ± 46 ng/dl), as did T_4 and T_3 free fractions. The free T_4 concentration, which was lower than that in nonpregnant adults before treatment (1.63 ± 0.4 *vs.* 2.30 ± 0.4 ng/dl; $P < 0.001$), increased to 2.3 ± 0.4 with OIS ($P < 0.001$). No change in any of these variables was observed in 10 untreated controls followed for similar lengths of time. Cord serum T_4 and rT_3 were higher in the offspring of OIS mothers (11.3 ± 1.5 μg/dl and 226 ± 55 ng/dl) than in those of untreated mothers (9.3 ± 1.7 μg/dl and 183 ± 37 ng/dl; $P < 0.001$ and $P < 0.005$, respectively). Newborn serum T_4 correlated with the mothers' value ($P < 0.001$) but was found to be less affected by iodine intake than the mothers' results.

We conclude that: 1) the decrease in TSH observed with OIS was due to the increase in serum T_4, since serum T_3 was unchanged, this stressing the critical role of the reduced serum T_4 in the adaptation to ID; 2) the small difference in serum TSH was physiologically significant, since this was associated with a compensatory increase in thyroidal T_3 secretion during ID; 3) the larger increase in serum T_4 induced by OIS in maternal as opposed to corresponding cord sera suggests that the fetus is relatively protected against ID; and 4) these findings are in agreement with previous animal studies, suggesting applicability of the latter to human thyroid physiology (*J Clin Endocrinol Metab* **52:** 671, 1981)

IODINE deficiency (ID) is known to cause alterations in plasma thyroid hormone levels. Characteristically, plasma T_4 is low, T_3 is normal, and TSH is elevated (1–4) Iodine-deficient animals show no evidence of hypothyroidism (3, 4), probably a reflection of the normal serum T_3 concentration (1, 2). The latter seems to be the result of increased thyroidal T_3 secretion that compensates for the decreased extrathyroidal production consequent to the diminished availability of T_4 (3, 5). The elevated TSH and the low degree of iodination of the thyroglobulin account for this quantitative change in the source of plasma T_3 (6). Furthermore, the reduced level of T_4 seems to be responsible for the elevated serum TSH concentration (4, 7). There is evidence that this adaptive mechanism may be operative in humans as well, since, except for extremely deficient areas, subnormal serum T_3 concentrations are seldom seen in areas affected by endemic goiter (8–13).

Iodine requirements are expected to increase during

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pregnancy, since the fetal iodine pool is being formed and the renal clearance of iodide is elevated (14). It is thus possible that the above-described compensatory mechanism could be overcome, the mother, the fetus, or both could be affected by the lack of T_3 in the tissues. Although there are many reports on the levels of T_4 and TSH in mothers and newborns of endemic goiter areas, there are only three in which T_3 has been measured (15–17). In one of these studies, serum T_3 concentrations were found to be low in some women (16), but in the other studies this was not observed (15, 17). The difference might be due to the extremely low iodine intake and the presence of goitrogens in the Ubangi, Zaire subjects (16).

It was of interest to us to see whether moderate or mild iodine deficiency, such as that prevalent in Chile, has a detectable influence on serum thyroid hormone and TSH concentrations. We were particularly interested in the role of serum T_4 in TSH regulation and that of the slightly elevated serum TSH in increasing thyroidal T_3 secretion. The rather wide range of iodine intake in Chile would allow a quantitative analysis of the relationships among these various hormones which could be complemented by evaluating the effects of iodine supplementation in some of these subjects.

Methods

Subjects

Blood samples were obtained at different gestational ages in 250 pregnant women in prenatal out-patient clinics in eastern greater Santiago. These women came from various suburban and rural areas so that there were some differences in iodine intake due to factors such as iodine content in the water, sea food consumption, and access to iodized salt.[1]

After obtaining blood and urine samples, the subjects were given 10 drops daily of a 785 μg/ml potassium iodide (KI) solution so as to provide approximately 300 μg I/day. One of every four women was not treated, forming a control group. Blood samples and urine were obtained at subsequent visits and at delivery when a cord blood sample was also collected. The shortest time interval between samples during iodide supplementation was 4 weeks and the longest was 16 weeks (Table 1). In only 36 of the 160 mothers given iodide was the protocol completed successfully and adherenece to the regimen validated by urinary iodine excretion. A similar proportion of controls was lost.

Serum samples were frozen until the assays were performed. T_3, T_4, and rT_3 were measured by RIA using specific antibodies and dextran-coated charcoal to separate bound and free fractions (18, 19). T_3 and T_4 antibodies were kindly provided by P. R. Larsen (Boston, MA). The anti-rT_3 antibody was raised in our laboratory and had less than 1:8000 cross-reactivity with T_4. The normal rT_3 serum concentration in nonpregnant adults is 13 ± 4 ng/dl, a figure somewhat lower than that usually reported. The within-assay variation was less than 10% for all three iodothyronine RIAs, and the interassay variation was 15%. All samples from an individual mother and her infant were analyzed simultaneously. Free T_4 and free T_3 concentrations were estimated from total plasma hormone and the dialyzable fraction as measured by equilibrium dialysis (20). TSH was quantitated by RIA using standard and antibodies generously provided by the National Pituitary Agency. Iodine was measured in the urine by the sodium arsenite-ceric acid method in a Technicon Autoanalyzer (Technicon Instrument Co., San Francisco, CA). Total creatinine (cr) was determined in the urine by conventional methods (21).

Statistical analysis was done by paired or unpaired Student's *t* test as appropriate. Correlation analyses were done on a Hewlett-Packard calculator (model 9815A, Hewlett-Packard Co., Palo Alto, CA). Linear transformations were performed to fit the data to nonlinear functions when appropriate. Our working hypotheses were: 1) that the iodine intake was the independent variable influencing the secretion of T_4 and, therefore, serum T_4 (3, 4), and 2) that the low level of the latter was a very important, if not the most important, signal to increase TSH secretion in these women. Therefore, in fitting the data to a given general equation, urinary iodine or serum T_4 was taken as the independent variable x, and the values were arbitrarily divided into small intervals. The variable y was then averaged for each x interval (22). Provided the scatter of y around the line was reasonably uniform, the points were fitted to the model that gave the highest coefficient of correlation. This approach makes weighting of the points unnecessary (22). The variation of y is not equally dependent on the variation of x in the whole range of x, but there is no way to determine when other factors different from the change in x begin to significantly influence the variation of y. These other factors might have been overestimated by weighting the data by the number of observations at each x interval.

Results

The distribution of iodine excretion in the population examined is shown in Fig. 1. As expected, it varied widely. Since total cr in the 24-h urine in this population ranges between 0.8–1.2 g/day, the I to cr ratios are a good approximation of daily intake. Fifty percent of the analyzed population had 50 μg I/g cr or less, indicating a significant degree of ID. About 25% excreted between 50–100 μg I/day, which can be considered a moderate deficiency, and only 15% had an adequate iodine intake (23).

The serum iodothyronine and TSH concentrations are presented in Fig. 2. It is apparent that none of the variables measured between 10–40 weeks was influenced by the duration of pregnancy.

For the analysis of the influence of iodine intake on plasma levels of T_4, T_3, and TSH, urinary iodine was

[1] Not all of the salt is iodized in Chile. Fifty salt samples from southern and eastern Santiago ranged from 0–135 μg/g salt; more than 50% were below 10, and only 12% of the samples were between 60–135 (Silva, J. E., and P. Michaud, unpublished observations).

TABLE 1. Effect of iodine supplementation on serum thyroid hormones and TSH concentrations during pregnancy (mean ± SD)

	Urinary iodide (μg/g cr)[a]	T_4 (μg/dl)	T_3 (ng/dl)	rT_3 (ng/dl)	TSH (μU/ml)	Time since conception (weeks)	Observation time interval (weeks)
Treated mothers (n = 36)							
Basal	53 ± 33	8.7 ± 2.4	187 ± 25	21 ± 7	2.8 ± 1.4	9-32	
KI[b]	376 ± 456	12.5 ± 1.8	180 ± 46	25 ± 9	1.5 ± 0.8	15-40	4-16
Change	+323 ± 450	+3.8 ± 2.2	−7 ± 46	+4 ± 10	−1.3 ± 1.5		
P[c]	<0.001	<0.001	NS	<0.02	<0.001		
Untreated controls (n = 10)							
Basal	54 ± 36	9.4 ± 2.2	179 ± 33	22 ± 7	3.0 ± 2.1	11-30	
End observation	56 ± 25	9.3 ± 2.6	165 ± 36	24 ± 8	2.6 ± 1.6	21-40	4-16
Change	+2 ± 18	−0.1 ± 2.8	−14 ± 43	+2 ± 9	−0.4 ± 0.25		
P[c]	NS	NS	NS	NS	NS		

[a] Micrograms of iodine per g urinary cr.
[b] Potassium iodide (~300 μg I/day).
[c] By paired t test.

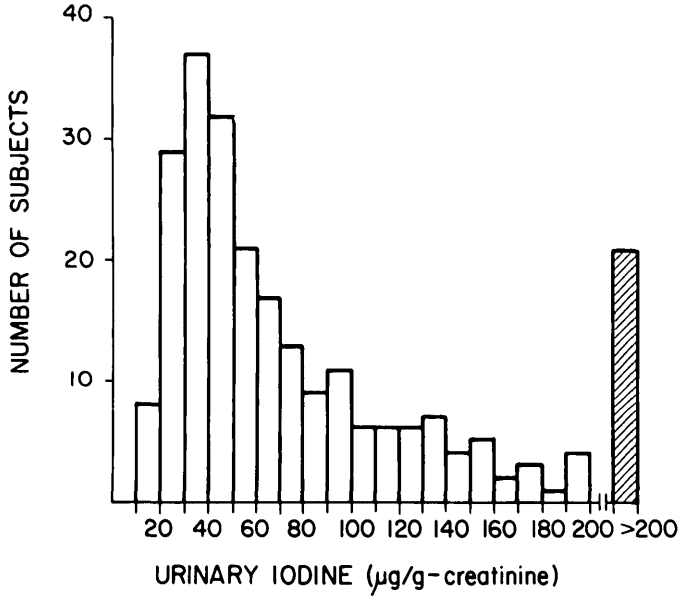

FIG. 1. Urinary iodine excretion in 250 pregnant women in an iodine-deficient area. ▨, About 8% of the subjects who had a urinary iodine level greater than 200 μg/g cr.

arbitrarily divided into 10 μg/g cr intervals. The average serum T_3, T_4, and TSH concentrations for each interval were then plotted against the average urinary iodine for the interval in the abcissa. The results are shown in Fig. 3. The serum T_4 concentrations did not bear a linear relationship to urinary iodine. Thus, T_4 values plateaued at around 100 μg I/g cr. Since it has been shown that thyroidal T_4 synthesis is dependent on iodine supply and is saturable (24), it seemed reasonable to analyze these data in a double reciprocal plot. In this plot (Fig. 3A), a high degree of correlation was found ($r = 0.90$; $P < 0.001$). The y-intercept of Fig. 3A respresents the reciprocal of the maximal T_4 concentration attainable in pregnancy at optimal iodine intake. This value was 10.4 ± 1.3 μg/dl (SD). From the same analyses, it can be calculated that at a urinary iodine of 11 μg/g cr, the concentration of T_4 in the serum should be half the maximal value. The regression curve relating T_4 and urinary iodine in the *lower portion* of Fig. 3 was calculated using these parameters.

The data in Fig. 3 also suggested that decreasing iodine supply was associated with a progressive increase in serum TSH, whereas at higher iodine intake, the serum TSH level was not influenced by further increases in iodine supply. According to the criteria described in *Materials and Methods*, the relationship was best described by a hyperbolic model: $TSH = a + b/I^-$ ($r = 0.60$; $P < 0.05$), where a = 2.2 μU/ml and b = 12.2. The parameter a represents the lowest concentration of TSH attainable by correcting the ID.

An inverse relationship between T_4 and TSH concentrations is suggested by Fig. 3, but the relationship does not seem to be a simple linear one. A plot between TSH and the reciprocal of T_4 ($TSH = a + b/T_4$, where a = 2.4 μU/ml) described the relationship ($r = 0.76$; $P < 0.005$) and is shown in Fig. 4. Thus, a steep increase in TSH would be expected in pregnant women when serum T_4 decreases below 6 μg/dl, while as the serum T_4 concentration approaches normal, TSH would not decrease greatly and would approach the value of a = 2.4 μU/ml.

Table 1 shows the effect of oral iodine supplementation (OIS) on serum concentrations of T_4, T_3, rT_3, and TSH. In the same table are shown the duration of the treatment period as well as the time since conception when the KI was started. Since the changes in T_4, TSH, and rT_3 did not correlate with the length of KI supplementation (all ≥4 weeks) or the duration of pregnancy at the time iodine was begun, all data were pooled. There was a significant increase in serum T_4 and rT_3, a decrease in plasma TSH, and no change in plasma T_3. In the untreated controls, there was no significant change in any

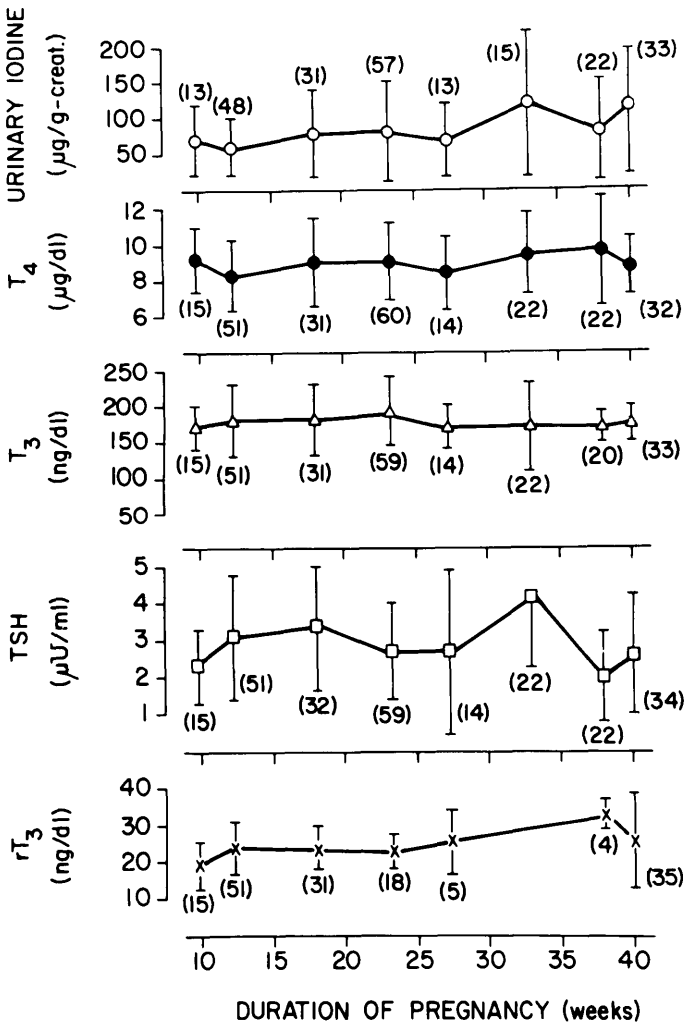

FIG. 2. Urinary iodine excretion and serum thyroid hormone and TSH concentrations as a function of time after conception in pregnant women in an iodine-deficient area. The subjects were grouped according to the duration of pregnancy at 5-week intervals. The mean ± 1 SD of each variable were plotted against the mean within each interval of time. The figures in parentheses represent the number of women at each interval.

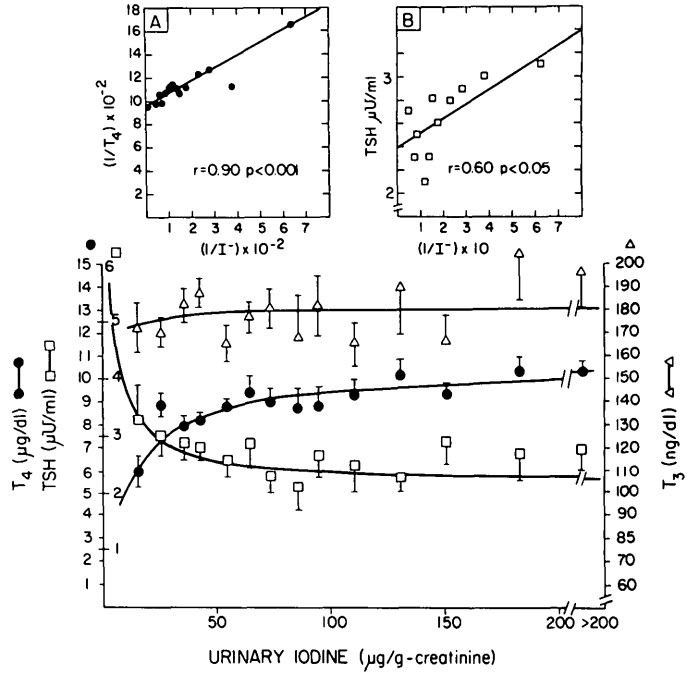

FIG. 3. Serum T_3, T_4, and TSH concentrations as a function of urinary iodine excretion in pregnant women of an iodine-deficient area. Urinary iodine secretion was arbitrarily divided in 10 μg/g cr intervals, and the mean ± 1 SEM of each variable were plotted against the mean within each interval. The *insets* are plots of the reciprocal of T_4 (A) and TSH values (B) (in the ordinates) *vs.* the reciprocal of the urinary iodine (in the abscissa). The equations obtained from these analyses were used to construct the lines shown at the *bottom*. The number of subjects at each interval of the abscissa can be obtained from Fig. 1.

of the variables studied. The agreement between the two urinary iodine measurements supports the idea that the I to cr ratio is a reproducible reflection of the iodine intake.

Table 2 shows the serum free T_4 and T_3 concentrations in 16 mothers and 14 nonpregnant euthyroid adults. In the untreated pregnant subjects, the free T_4 was reduced compared with that of nonpregnant subjects ($P < 0.001$), while serum T_3 was not different. After KI treatment, serum free T_4 increased ($P < 0.001$), becoming equal to that of nonpregnant controls. Since there was no change in the dialyzable fraction, the increase was accounted for by the increase in total serum T_4. The serum free T_3 was unaffected by iodine supplementation. In the same patients, serum TSH fell significantly from 3.0 ± 1.3 to 1.2 ± 0.6 μU/ml ($P < 0.001$).

The effect of maternal iodine supplementation on the levels of thyroid hormones and TSH in the newborn are shown in Table 3. The newborns whose mothers received iodine supplementation had higher serum T_4 and rT_3 concentrations but showed no difference in serum T_3. The difference in serum TSH was not significant because of the large dispersion of the values, presumably due to the rapid increase of TSH which occurs during the first 30 min of extrauterine life (25). There was a significant correlation between maternal serum T_4 and the corresponding value in the cord (Fig. 5). The slope of the regression line was 0.38, significantly less than 1.0 ($P < 0.001$), suggesting that the increases induced in serum T_4 by iodine intake were smaller in the fetus than in the respective mothers.

Discussion

The overall pattern of thyroid hormones and TSH found in these studies is similar to that in many previous reports of ID (8–13). Serum T_4 is low, serum TSH is increased, and serum T_3 is normal. Fewer studies have dealt with these parameters in pregnancy (15–17), but the trend is the same as that in nonpregnant adults.

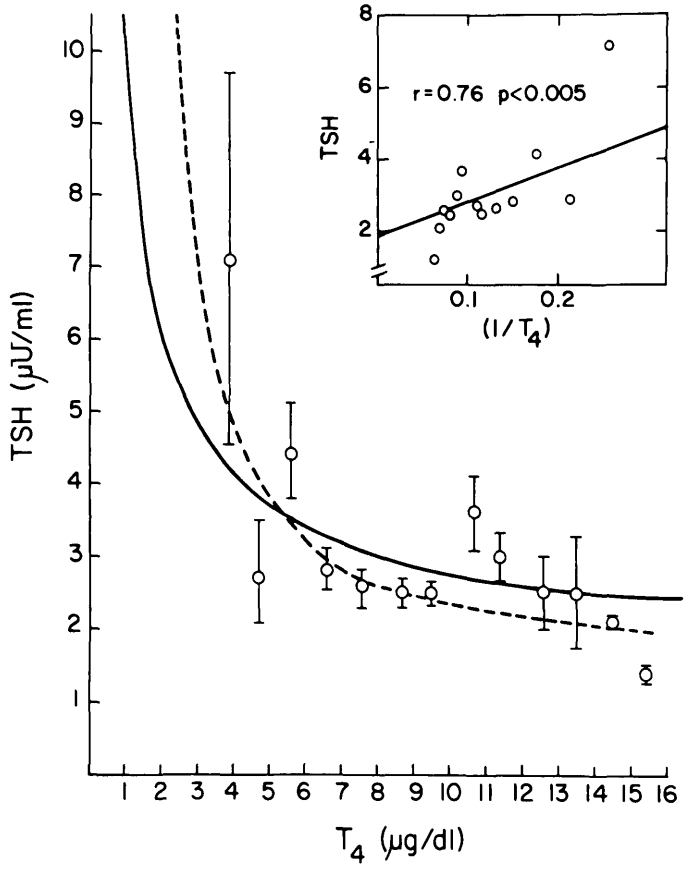

FIG. 4. Relationship between serum TSH and T_4 concentrations in pregnant women from an iodine-deficient area. Total serum T_4 was arbitrarily divided in 1 μg/dl intervals, and the mean ± 1 SD of serum TSH were plotted against the mean T_4 within each interval. The continuous curve was calculated from the linear regression shown in the *inset*. - - -, Calculated from a double reciprocal plot of both variables (not shown).

Since iodine requirements are expected to increase during pregnancy (14), iodine-deficient women might not be expected to increase their total T_4 normally in response to the pregnancy-induced increase in thyroxine-binding globulin (26). The data in Table 2 show that while serum T_4 is not higher in pregnant women than in nonpregnant controls, serum T_3 is. The failure of T_4 to increase results in a lower free T_4 concentration than that in nonpregnant controls, but, interestingly, the free T_3 concentration is not different. The assumption has been made that the fall in free T_4 is related to ID. The data shown in Fig. 3 suggest a nonlinear type of relationship between urinary iodine and serum T_4. The model that fits the data (r = 0.90) is in agreement with the fact that the rate of synthesis of T_4, as a function of iodine availability, is a saturable phenomenon (24). Pretell *et al.* (15), plotting data from different geographical areas and from endemic goitrous patients treated with iodized oil, observed that there was a correlation between urinary iodide and total serum T_4 only when the former was less than 50 μg/g cr, which is consistent with Fig. 3. The data in Fig. 3 also show that higher serum TSH concentrations are found with lower urinary iodine excretion, and further, that the low serum T_4 may be the signal for the elevated TSH secretion, since serum T_3 did not change over the observed range of iodine excretion. An inverse relationship (probably not linear) would be expected between serum T_4 and TSH concentrations. The model that best described this relationship was hyperbolic: TSH = a + b/T_4, as shown in Fig. 4.

The interactions among dietary iodine supply, plasma T_4, and TSH, suggested by the observations described in this study, were further supported by the effects that iodine supplementation had on these various hormones. Observing Fig. 3 and considering the basal level of iodine intake of the women given OIS, one would predict only a modest increase in serum T_4 and free T_4 concentrations and only a slight fall in plasma TSH with iodine supplementation in this population. Thus, the highest predictable serum T_4 and the lowest predictable serum TSH levels based on Fig. 3 are 10.5 μg/dl and 2.2 μU/ml, respectively. In addition, the lowest predictable TSH based on the relationship it bears to serum T_4 is 2.4 μU/ml, which is internally consistent with Fig. 4. With OIS, serum T_4 increased to 12.5 μg/dl, and serum TSH decreased to 1.5 μU/ml. By looking at the effect of OIS in the same subjects, the individual variation and the influence of factors other than iodine intake on T_4 and TSH alluded to in *Materials and Methods* are all minimized. Considering that these sources of variation were present in the mathematical analysis, the agreement between both observed and calculated figures is very good. On the other hand, the post-OIS values of T_4 and TSH are virtually the same as those recently found by Harada *et al.* (27) in pregnant women with sufficient iodine intake.

Since serum T_3 does not change with iodine supplementation, the increase in T_4 appears to be responsible for the decrease in TSH. The slightly increased pretreatment serum TSH (1.3 μU/ml; Table 1) disclosed only by iodine treatment is apparently sufficient to increase the thyroidal secretion of T_3 enough to compensate for the reduced extrathyroidal T_3 production from T_4. In iodine-deficient rats, the metabolic clearances of T_3 and T_4 are unchanged (3), and the increase in the intrathyroidal ratio of T_3 to T_4, due in part to the increased TSH (6), can account for the elevated T_3 to T_4 ratio in the serum (1).

Since thyroid hormones do not cross the placenta (28), the increases in cord serum T_4 levels in infants of iodine-supplemented mothers are probably the consequence of the change in maternal plasma I^-. However, the increase in the maternal serum T_4 is greater than was apparent in the newborns. In part, this observation may be due to the difference in thyroxine-binding globulin levels in

TABLE 2. Serum free T_4 and T_3 concentrations in iodine-deficient pregnant women: effect of iodine supplementation (mean ± SD)

	T_4 (μg/dl)	Free fraction (% × 10^{-3})	Free T_4 (ng/dl)	T_3 (ng/dl)	Free fraction (% × 10^{-2})	Free T_3 (ng/dl)	TSH (μU/ml)
1. Nonpregnant adult (n = 14)	7.7 ± 1.8	30 ± 5	2.3 ± 0.4	124 ± 26	28 ± 4	0.34 ± 0.14	≤5
2. Pregnant before OIS (n = 14)	8.1 ± 2.5	20 ± 4[a]	1.5 ± 0.4[a]	184 ± 25[a]	18 ± 4[a]	0.33 ± 0.06	3.0 ± 1.3
3. Pregnant after OIS	12.2 ± 1.9[a]	19 ± 3[a]	2.3 ± 0.4	177 ± 38[b]	17 ± 2[a]	0.30 ± 0.06	1.2 ± 0.6
P 2 *vs.* 3 (paired)	<0.001	NS	<0.001	NS	NS	NS	<0.001

[a] $P < 0.001$ *vs.* nonpregnant control.
[b] $P < 0.005$ *vs.* nonpregnant control.

TABLE 3. Effect of iodine supplementation during pregnancy on serum thyroid hormones and TSH concentrations in maternal and cord blood at delivery (mean ± SD)

	Maternal			Cord		
	Untreated	Treated	*P*	Untreated	Treated	*P*
T_4 (μg/dl)	8.8 ± 1.7 (32)	12.1 ± 1.9 (24)	<0.001	9.3 ± 1.7 (32)	11.3 ± 1.5 (24)	<0.001
T_3 (ng/dl)	172 ± 26 (33)	157 ± 34 (23)	NS	50 ± 23 (33)	58 ± 8 (23)	NS
rT_3 (ng/dl)	26 ± 12 (34)	24 ± 16 (25)	NS	183 ± 37 (34)	226 ± 55 (25)	<0.005
TSH (μU/ml)	2.9 ± 1.8 (34)	2.2 ± 1.2 (25)	NS	8.3 ± 7.8 (34)	5.7 ± 3.4 (25)	NS
Urinary I^- μg/g −cr)	127 ± 94	493 ± 586	<0.005			

The number of cases is in parentheses.

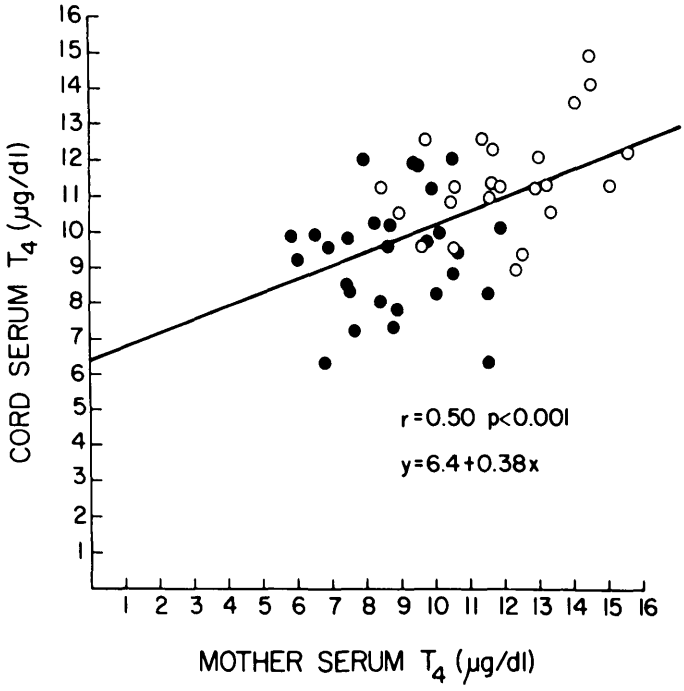

FIG. 5. Linear regression between maternal and cord serum T_4 levels in subjects living in an iodine-deficient area. ●, Untreated mother-newborn pairs; ○, those who received iodine supplementation.

mothers and newborns (26), but it may also reflect the participation of compensatory mechanisms that partially protect the fetus from the low maternal iodine intake. Whereas after correction of ID, the ratio of cord serum T_4 to maternal serum T_4 was 0.96 ± 0.16 (SD), the same ratio in the untreated controls was significantly higher (1.12 ± 0.25; $P < 0.025$, calculated from the individual data presented in Table 3). Therefore, at a same low iodine intake, fetal serum T_2 is less reduced than that of the mother. The ability of the placenta to concentrate iodine, demonstrated in other species, may be the mechanism (29).

The increases observed in maternal and cord serum rT_3 with iodine supplementation are probably a reflection of the higher serum T_4 concentration. In both cases, the relative increase in rT_3 was similar to that of T_4. This indicates that iodine did not induce a change in the capacity of the tissues to convert T_4 to T_3, since the enzyme that regulates this reaction seems to be the same 5′-monodeiodinase that catalyzes the degradation of rT_3 to 3,3′-diiodothyronine (30).

The data and their interpretation are consistent with experimental studies showing that unless the ID is extreme, plasma T_3 remains constant, probably accounting for the lack of detectable manifestations of hypothyroidism other than an elevation of TSH (3, 4, 31, 32). The fall in T_4 is likely to be responsible for the elevation of TSH, and the latter is probably the cause of the compensatory increase in thyroidal T_3 secretion. However, the lower plasma T_4 level in the fetus might not be without consequences, since it has been recently shown that, at least in the rat, plasma T_4 is an important source of intracellular T_3 in the brain (33).

Acknowledgments

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References

1. Abrams GM, Larsen PR 1973 Triiodothyronine and thyroxine in the serum and thyroid glands of iodine-deficient rats. J Clin Invest 52:2522
2. Fukuda H, Yasuda N, Greer MA, Kutas M, Greer MA 1975 Changes in plasma thyroxine, triiodothyronine and TSH during adaptation to iodine deficiency in the rat. Endocrinology 97:307
3. Silva JE 1972 Disposal rates of thyroxine and triiodothyronine in iodine-deficient rats. Endocrinology 91:1430
4. Larsen PR, Frumess RD 1977 Comparison of the biological effects of thyroxine and triiodothyronine in the rat. Endocrinology 100:980
5. Silva JE, Pineda G, Stevenson C 1974 The importance of triiodothyronine as a thyroid hormone. In: Dunn JT, Medeiros-Neto GA (eds) Endemic Goiter and Cretinism: Continuing Threats to World Health, PAHO scientific publication 292. Pan American Health Organization, Washington DC, p 52
6. Studer H, Greer MA 1965 A study of the mechanisms involved in the production of iodine-deficiency goiter. Acta Endocrinol (Copenh) 49:610
7. Larsen PR, Silva JE 1979 Sources of pituitary nuclear T3 and its influence on TSH release. In: Ekins R, Fagtia G, Penisi F, Pinchera A (eds) International Symposium on Free Thyroid Hormones, Excerpta Medica, Amsterdam, p 55
8. Delange F, Camus M, Ermans AM 1972 Circulating thyroid hormones in endemic goiter. Metabolism 34:891
9. Pharoah POD, Lawton NF, Ellis SM, Williams ES, Ekins RP 1973 The role of triiodothyronine (T3) in the maintenance of euthyroidism in endemic goitre. Clin Endocrinol (Oxf) 2:193
10. Patel YC, Pharoah POD, Hornabrook RW, Hetzel BS 1973 Serum triiodothyronine, thyroxine and thyroid-stimulating hormone in endemic goiter: a comparison of goitrous and nongoitrous subjects in New Guinea. J Clin Endocrinol Metab 37:783
11. Gosling BM, Djokomoeljanto R, Docter R, Van Hardeveld C, Hennemann G, Smeenk D, Querido A 1977 Hypothyroidism in an area of endemic goiter and cretinism in central Java, Indonesia. J Clin Endocrinol Metab 44:481
12. Chopra IJ, Hersham HM, Hornabrook RW 1975 Serum thyroid hormone and thyrotropin levels in subjects from endemic goiter regions of New Guinea. J Clin Endocrinol Metab 40:376
13. Kochupillai N, Karmarkar MG, Weightman D, Hall R, Deo MG, McKendrick M, Evered DC, Ramalingaswami V 1973 Pituitary-thyroid axis in Himalayan endemic goitre. Lancet 1:1021
14. Hollingsworth D, Fisher DA, Pretell EA 1980 The fetal maternal relationship with respect to the thyroid. In: Stanbury JB, Hetzel BS (eds) Endemic Goiter and Endemic Cretinism. John Wiley and Sons, New York, p 423
15. Pretell EA, Palacios P, Tello L, Wan M, Utiger RD, Stanbury JB 1974 Iodine deficiency and the maternal-fetal relationship. In: Dunn JT, Medeiros-Neto GA (eds) Endemic Goiter and Cretinism: Continuing Threats to World Health, PAHO scientific publication 292. Pan American Health Organization, Washington DC, p 143
16. Thilly CH, Delange F, Lagasse R, Bourdoux P, Ramioul L, Berquist H, Ermans AM 1978 Fetal hypothyroidism and maternal thyroid status in severe endemic goiter. J Clin Endocrinol Metab 47:354
17. Medeiros-Neto GA, Walfish PG, Almeida F, Maia E, Gomes EF, Kiy Y, Knobel M, Binsberg J, Chopra IJ 1978 3,3′,5′-Triiodothyronine levels in maternal and cord blood sera from endemic goiter regions of Brazil. J Clin Endocrinol Metab 47:508
18. Larsen PR 1972 Direct immunoassay of triiodothyronine in human serum. J Clin Invest 51:1939
19. Larsen PR, Dockalova J, Sipula D, Wu FM 1973 Immunoassay of thyroxine in unextracted human serum. J Clin Endocrinol Metab 37:177
20. Oppenheimer JH, Squef R, Surks MI, Haur H 1963 Binding of thyroxine by serum proteins evaluated by equilibrium dialysis and electrophoretic techniques. Alterations in non-thyroidal illness. J Clin Invest 42:1769
21. Chattaway FW, Hullin RP, Odds FC 1969 The variability of creatinine excretion in normal subjects. Mental patients and pregnant women. Clin Chim Acta 26:567
22. Riggs DS 1963 The Mathematical Approach to Physiological Problems. Williams and Wilkins, Baltimore, pp 57–66
23. Matovinovic J, Child MA, Nicham MZ, Trowbridge FL 1974 Iodine and endemic goiter. In: Dunn JT, Medeiros-Neto GA (eds) Endemic Goiter and Cretinism: Continuing Threats to World Health, PAHO scientific publication 292. Pan American Health Organization, Washington DC, p 67
24. Inoue K, Taurog A 1968 Acute and chronic effects of iodide on thyroid radioiodine metabolism in iodine-deficient rats. Endocrinology 83:279
25. Fisher DA, Odell WD 1969 Acute release of thyrotropin in the newborn. J Clin Invest 48:1670
26. Stubbe P, Gatz J, Heidemann P, von zur Mühlen A, Hesch R 1978 Thyroxine-binding globulin, triiodothyronine, thyroxine and thyrotropin in newborn infants and children. Horm Metab Res 10:57
27. Harada A, Hershman JM, Reed AW, Braunstein GD, Digman WJ, Derzko C, Friedman S, Jeweewicz R, Pekary AE 1979 Comparison of thyroid stimulators and thyroid hormone concentrations in the sera of pregnant women. J Clin Endocrinol Metab 48:793
28. Fisher DA, Dussault JH, Sack J, Chopra IJ 1977 Ontogenesis of hypothalamic-pituitary-thyroid function and metabolism in man, sheep and rat. Recent Prog Horm Res 33:59
29. London WT, Money WL, Rawson RW 1964 Placental transfer of 131 I-labelled iodide in the guinea pig. J Endocrinol 28:247
30. Kaplan MM, Utiger RD 1978 Iodothyronine metabolism in rat liver homogenates. J Clin Invest 61:459
31. Silva JE, Larsen PR 1978 Contributions of plasma triiodothyronine and local thyroxine monodeiodination to triiodothyronine to nuclear triiodothyronine receptor saturation in pituitary, liver and kidney of hypothyroid rats. Further evidence relating saturation of pituitary nuclear triiodothyronine receptors and the acute inhibition of thyroid-stimulating hormone release. J Clin Invest 61:1247
32. Silva JE, Dick TE, Larsen PR 1978 The contribution of local tissue thyroxine monodeiodination to the nuclear 3,5,3′-triiodothyronine in pituitary, liver and kidney of euthyroid rats. Endocrinology 103: 1196
33. Crantz FR, Larsen PR 1980 Rapid thyroxine to 3,5,3′-triiodothyronine conversion and nuclear 3,5,3′-triiodothyronine binding in rat cerebral cortex and cerebellum. J Clin Invest 65:935