See p 400 for more data on fetal gland size.

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SE[illegible] AND THYROID GLAND TRIIODOTHYRONINE IN THE HUMAN FETUS

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ABST[illegible]CT

Se[illegible]n T3 concentrations are [illegible]ow (<15 ng/100 ml) before 24 weeks and increase progressively thereafter to term, but both T3 and free T3 (FT3) levels are lower than paired maternal concentrations. Moreover, throughout gestation T4/T3 and FT4/FT3 ratios consistently exceed paired maternal ratios. The mean T4/T3 content ratio of fetal thyroid glands (14.3) is simi[illegible]r to that (19.5) of adul[illegible] glands. These data indica[illegible] that a state of relative feta[illegible] T3 deficiency exists in the [illegible]man as in the sheep. This [illegible]eficiency probably is not due [illegible] decreased T3 secretion.

INT[illegible]DUCTION

We have reported that serum T3 concentrations in fetal sheep are lower than paired maternal levels and that fetal serum T4/T3 concentration ratios are higher than maternal ratios (1). T3 turnover also is relatively low, and the ratio of T4 to T3 turnover is greater in fetal than maternal sheep (1). To determine whether a similar state of relative T3 deficiency exists in the human fetus, we measured T3, FT3, T4, and FT4 in cord blood of 8 fetuses aborted by elective uterotomy between 13 and 24 weeks gestation and in 16 newborn infants delivered vaginally between 25 and 40 weeks. In addition, the T3 and T4 content of 14 human fetal thyroid glands was measured to determine whether the T3 available for secretion might be relatively deficient. These glands were obtained from aborted or stillborn fetuses between 13 and 31 weeks gestation.

METHODS

T3 and T4 were measured in whole serum using double antibody radioimmunoassay (RIA) procedures employing 8-anilino, 1-napthalene sulfonic acid (ANS) to block thyroxine-binding globulin (TBG) (2,3,4).

FT3 and FT4 were measured by modification of the dialysis and magnesium precipitation technique of Sterling and Brenner (5). Fetal thyroid glands were obtained at autopsy, weighed, and immediately frozen. For analysis, the glands were thawed and dried and the dried glands reweighed, homogenized, and hydrolyzed with pronase under nitrogen as described by Inoue and Taurog (6). T3 and T4 concentrations in the homogenate hydrolyzates were measured by RIA as described recently for adult glands (7).

RESULTS

The serum T3 and T4 data are shown in Table I. T3 was not detected in fetal blood before 24 weeks gestation at a resolution limit of the T3 RIA of 15 ng/100 ml. T3 was detected in 13 of the 16 fetal specimens between 25 and 40 weeks, and the concentrations of T3 and FT3 seemed to increase progressively during this period. However, even at term, fetal concentrations were lower than paired maternal values. Fetal serum T4 and FT4 concentrations also increased progressively between 13 and 40 weeks.

However, the rate of increase of T3 exceeded that of T4 so that T4/T3 and FT4/FT3 ratios in fetal sera decreased progressively with increasing gestational age; mean values between 35 and 40 weeks were 188/1 and 192/1, respectively, whereas the mean ratios in maternal sera were 102/1 and 87/1, respectively.

The fetal thyroid gland T3 and T4 content data are shown in Table II. Both T3 and T4 content tended to increase progressively between 13 and 31 weeks, but the T4/T3 ratio remained relatively constant; the mean (and SEM) ratio was 14.3 ± 4.5.

DISCUSSION

We have shown in man that there is no correlation between maternal and fetal serum T4 or FT4 concentrations at any time during gestation (8,9); the present results confirm these earlier observations and indicate that maternal and fetal serum T3 and FT3 concentrations also are dissimilar. Larsen, too, has reported low total T3 concentrations in human cord blood (10).

The low T3 and FT3 levels in fetal blood near term occur in association with serum T4 and FT4 levels comparable to or even exceeding maternal values (Table I). Thus, the mean fetal serum T4/T3 and FT4/FT3 concentration ratios between 35 and 40 weeks are much higher than those in paired maternal blood. These data indicate that a state of relative fetal T3 deficiency exists in the human as in sheep (1, 11). Possible explanations include: a) a relatively high T4/T3 secretion ratio from the fetal thyroid gland; b) a relatively low rate of T4 to T3 conversion by extrathyroidal tissue of the fetus; or c) a relatively high rate of T4 conjugation and biliary excretion so that T4 is relatively unavailable for conversion to T3. The first possibility is excluded by the present results. The mean T4/T3 ratio in the fetal thyroid (14.3/1, Table II) is similar to that (19.5/1) which we have reported recently in the euthyroid adult (7). Thus, the fetus either cannot convert T4 to T3 at a rate comparable to the adult or T4 is unavailable for such conversion.

This T3 deficiency might represent a state of relative hypothyroidism, since fetal serum TSH concentrations during the last half of gestation are higher than maternal levels (8, 9, 12,13). Although this possibility cannot be excluded, it seems unlikely. First, the concentrations of anterior and posterior pituitary hormones in fetal blood between 20 and 40 weeks gestation generally are elevated, including GH, FSH, LH, and ADH (14-16), and the elevated serum TSH level probably reflects this general hypothalamic-pituitary overactivity; Grumbach suggests that this hypothalamic overactivity is due to a lack of higher central nervous system inhibitory input (15). Second, the fetus is capable of responding to hypothyroidism with marked hyperthyrotropinemia (17). Moreover, fetal serum T3 levels increase markedly in response to the TSH surge during the early hours of extrauterine life (18,19). Thus, the fetus is capable of augmenting TSH and T3 secretion, and increased levels of both hormones might be expected as a manifestation of hypothyroidism in the presence of residual functional thyroid tissue.

. Serum thyroxine and triiodothyronine concentrations in maternal and fetal sera between 13 and 40 weeks gestation

	Age (wks)	Maternal T4 µg%	Maternal FT4 ng%	Maternal T3 ng%	Maternal FT3 pg%	Fetal T4 µg%	Fetal FT4 ng%	Fetal T3 ng%	Fetal FT3 pg%
	13	14	3.4	168	453	2.0	1.6	<15	---
	13	18	3.8	174	331	2.4	1.9	<15	<102
	16	12	2.3	160	384	2.6	2.3	<15	<114
	17	11	2.5	204	673	2.2	2.0	<15	<122
	18	18	4.1	152	395	3.1	2.0	<15	<111
	19	17	3.2	224	560	1.9	1.0	<15	<95
	19	18	4.3	168	487	2.5	1.6	<15	---
	24	12	3.0	184	423	4.2	2.7	<15	<105
	25	22	3.5	180	288	5.6	3.1	<15	<75
	28	19	10.5	200	1040	14	2.2	20	32
	29	32	4.8	288	518	11	4.4	26	112
	29	30	4.2	280	532	13	5.2	<15	<71
	30	15	3.0	180	378	10	4.2	33	162
	32	19	3.0	160	352	14	3.9	44	141
	33	16	3.4	200	340	9	3.8	66	224
	34	19	4.4	200	560	7.2	3.6	<15	<69
	34	19	2.9	208	395	5.6	2.0	26	94
	35	28	4.2	208	374	17	3.6	126	315
	36	21	3.6	180	378	17	4.8	80	256
	36	26	5.2	256	563	16	4.2	72	216
	37	19	3.0	160	336	16	4.2	70	210
	37	32	5.1	168	268	11	4.1	72	187
	38	16	2.2	144	302	14	4.8	52	203
	40	18	2.8	184	386	13	6.1	68	252
ean		19.6	3.9	193	447				
EM		1.2	0.3	7.7	33				
		Mean 13-24 wks				2.6	1.9	<15	<108
		SEM				0.3	0.2	--	<4
		Mean 25-34 wks				9.9	3.6	30	109
		SEM				1.1	0.3	5.9	20
		Mean 35-40 wks				14.5	4.5	77	234
		SEM				0.9	0.3	8.7	16

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Table II. Fetal thyroid gland weight and T4 and T3 content

Fet No.	Age (wks)	Wet wt. mg	Dry wt. mg	T4 µg/gland	T3 µg/gland	T4/T3
1	13	22	1.1	0.06	0.010	6.0
2	15	30	6.4	0.40	0.025	16
3	16	11	1.8	0.05	0.010	5.0
4	16	24	7.7	0.12	0.011	11
5	16	34	6.0	0.52	0.044	12
6	17	51	10.0	0.83	0.025	2.5
7	17	23	3.7	0.12	0.020	6.0
8	17	48	5.4	0.22	0.020	11
9	18	107	44.6	0.76	0.052	14
10	19	109	37.5	0.96	0.060	1.6
11	20	87	34.5	3.20	0.044	70
12	20	67	19.0	1.52	0.120	13
13	26	315	134	2.80	0.220	12
14	31	565	206	3.00	0.150	20

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