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Fetus thyroid
iodothyronine uterus

The Effect of Fetal Thyroidectomy on Thyroid Hormone Metabolism in Maternal and Fetal Sheep

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Extract

Experiments were conducted to assess the changes in fetal and maternal iodothyronine kinetics in sheep after removal of the fetal thyroid gland early in the 3rd trimester. Uterotomy was performed at 90–125 days of gestational age; the fetal neck was isolated and a thyroidectomy performed. Indwelling exteriorized fetal carotid artery and maternal jugular vein catheters were inserted and dual ^{131}I- and ^{125}I-labeled iodothyronine kinetic studies were conducted in the mother and fetus, respectively, at 4–37 days post-thyroidectomy. Serum thyroxine (T4), triodothyronine (T3), and thyroid-stimulating hormone (TSH) concentrations were measured by radioimmunoassay (RIA). Before thyroidectomy the mean fetal serum T4 level was 12.2 μg/100 ml (nine animals); this value fell to a mean of 1.7 μg/100 ml 3 days postoperatively and to a mean of <0.7 μg/100 ml 5–6 days post-thyroidectomy. The mean fetal serum T3 level was <18 ng/100 ml before thyroidectomy and remained unmeasurable throughout the study. The mean maternal serum T4 and T3 concentrations were 8.9 μg/100 ml and 94 ng/100 ml before thyroidectomy and did not change significantly during the study period. Maternal T4 turnover ($T4_S$) averaged 533 μg/24 hr (11.9 μg/kg/24 hr) after fetal thyroidectomy, whereas the fetal value was <4.9 μg/24 hr (<3.2 μg/kg/24 hr). Maternal T3 turnover ($T3_S$) averaged 62 μg/24 hr (1.27 μg/kg/24 hr) after fetal thyroidectomy; the fetal value was <2.26 μg/24 hr (<1.05 μg/kg/24 hr). These fetal values, and particularly the the T4 results, are much less than those in the euthyroid fetus (<1.45 and 41 μg/kg/24 hr for T3 and T4).

Placental transfer of butanol-extractable T4 and T3 radioactivity occurred in both the fetal-maternal (F-M) and maternal-fetal (M-F) directions; chromatographic studies revealed that the transferred radioactivity represented T4 or T3. The mean fractional rate constants for T4 transfer were 0.0009/hr^{-1} and 0.00003/hr^{-1} and for T3 transfer, 0.007/hr^{-1} and 0.002/hr^{-1} in the F-M and M-F directions. Estimated net transfer of T4 was 0.6 μg and of T3, 0.7 μg/24 hr in the M-F direction. These amounts represent only about 7% of total T4 equivalent turnover (T4s + 4 × T3s) in euthyroid fetuses, and the high fetal serum TSH concentrations (300–1,500 μU/ml) indicated that the thyroidectomized fetuses were, in fact, hypothyroid. The present data indicate that fetal thyroidectomy in the sheep results in fetal hypothyroidism which persists in spite of large M-F gradients of T4 and T3 and a large F-M gradient of TSH. The results further substantiate the autonomy of the fetal pituitary-thyroid sys-

tem; TSH and thyroid hormones do not cross the placenta in significant quantities even after fetal thyroidectomy.

Speculation

The present results suggest that the athyroid fetus probably develops *in utero* in the absence of significant quanities of thyroid hormones. The fact that growth retardation is not observed at birth in the athyroid human fetus suggests that fetal somatic growth may not be thyroid hormone dependent. The high rate of $T4_s$ in the euthyroid fetus may be important to development of fetal brain and of bone near term.

Introduction

We reported studies previously of thyroid hormone kinetics and placental iodothyronine transfer in maternal and euthyroid fetal sheep during the 3rd trimester of pregnancy [3–5]. The results of these studies indicated that the ovine fetal pituitary-thyroid axis is autonomous and that ovine fetal T4 turnover exceeds maternal turnover by a factor of 6–8. The experiments in the present report were conducted to assess the changes in fetal and maternal iodothyronine kinetics in the sheep when the fetal thyroid gland is removed early in the 3rd trimester.

Methods and Materials

Seven 1–4-year-old Columbia and/or Columbia Suffolk date-bred ewes were obtained from a local source, maintained at environmental temperatures of 50–82° F, and given free access to alfalfa and water. Under spinal anesthesia, a uterotomy was performed at 90–125 days gestation. The fetal neck was isolated, exposed, and a thyroidectomy performed. In four animals (*sheep 2, 4, 21,* and *22*), indwelling, exteriorized fetal carotid artery and maternal jugular vein catheters were placed at the time of thyroidectomy. In three animals (*sheep 14, 19,* and *20*), a repeat uterotomy was performed 25–27 days post-thyroidectomy, at which time catheters were inserted. Kinetic studies were begun 4–37 days post-thyroidectomy. Five studies were conducted in which tracer doses of ^{125}I-labeled T4 (200 μCi, spec act 100 mCi/mg) and ^{131}I-labeled T4 (200–450 μCi, spec act 90 mCi/mg) were injected into the fetus and mother, respectively (Table I). In four studies, ^{125}I-labeled T3 (100 μCi, spec act 100 mCi/mg) and ^{131}I-labeled T3 (200–400 μCi, spec act 84 mCi/mg) were injected into the fetus and mother, respectively

Table I. Age and weight of animals used in the thyroxine kinetic studies

Sheep	Estimated gestational age at thyroidectomy, days	Estimated gestational age when study performed, days	Weight, kg	
			Maternal	Fetal
2	105	109	39.5	1.010
4	100	104	39.1	1.475
14	97	124	53.2	1.530
19	90	120	47.7	1.360
20	95	125	54.5	2.580
Mean			46.8	1.711
SEM			3.3	0.26

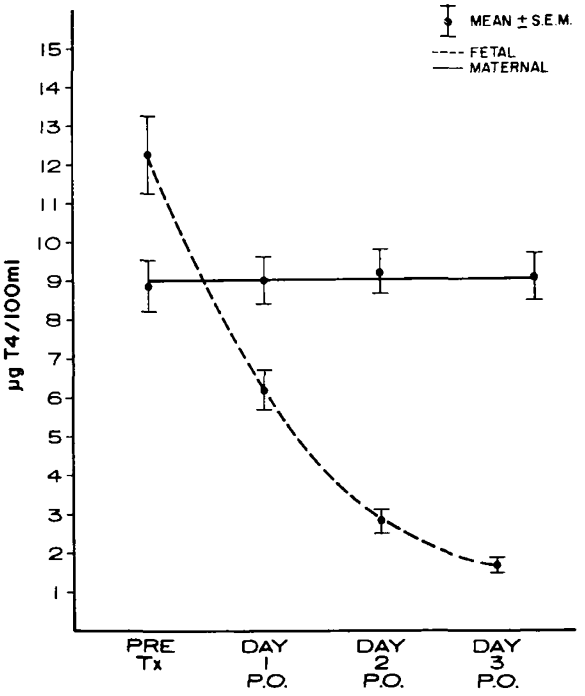

Fig. 1. Disappearance of endogenous plasma serum thyroxine (*T4*) concentrations after fetal thyroidectomy. Fetal serum thyroxine values fall from a mean of 12.2 to a mean of 1.7 μg/100 ml within 3 days. *P.O.*: postoperative.

(Table III). Two of the T3 kinetic studies were conducted in preparations in which T4 kinetics had been studied 7 days previously (*sheep 90* and *95*). During each study serial blood samples were drawn from fetus and mother for a period of up to 72 hr. Potassium perchlorate (400 mg) was administered orally to the mother twice daily throughout the study.

Aliquots of the injected radioiodinated iodothyronine were kept in a 1% albumin solution as reference standards. Alkali-washed butanol extracts of 250-μl aliquots of each serum were prepared in duplicate as described by Fisher *et al.* [8]; 94–99% of the T3 or T4 radioactivity and 0.2–0.5% of the inorganic iodine were recovered in the washed butanol extracts. Butanol extracts and standards were counted for ^{125}I and ^{131}I activities and butanol-extractable serum radioactivity recorded as a percentage of the injected dose per liter of plasma. Serum butanol-extractable radioactivity was plotted semilogarithmically against time and the final, single exponential disappearance curves were determined by least-squares regression analysis. From these curves, the half-time ($t_{1/2}$) of plasma disappear-

Table II. Thyroxine (T4) kinetic data in maternal and thyroidectomized fetal sheep[1]

Sheep	Maternal					Fetal				
				$T4_S$					$T4_S$	
	T4 V_D, liters	T4 $t_{1/2}$, days	Serum T4 conc., μg/100 ml	μg/24 hr	μg/kg/24 hr	T4 V_D, liters	T4 $t_{1/2}$, days	Serum T4 conc., μg/100 ml	μg/24 hr	μg/kg/24 hr
2	11.0	1.12	8.8	600	15.2	0.74	0.83	<0.7	<4.87	<4.82
4	14.3	1.38	10.0	715	18.3	0.67	0.71	<0.7	<4.83	<3.28
14	11.1	1.54	8.0	400	7.5	1.22	0.92	<0.7	<6.40	<4.19
19	14.7	1.71	7.5	452	9.5	1.09	1.33	<0.7	<3.97	<2.02
20	12.0	1.33	8.0	499	9.2	1.14	1.17	<0.7	<4.71	<1.82
Mean	12.6	1.42	8.5	533	11.9	0.97	0.99	<0.7	<4.95	<3.23
SEM	0.8	0.10	0.4	56	2.1	0.11	0.11		<0.40	<0.60

[1] V_D: T4 volume of distribution; $t_{1/2}$: plasma half-time of labeled T4 disappearance; $T4_S$: daily T4 turnover.

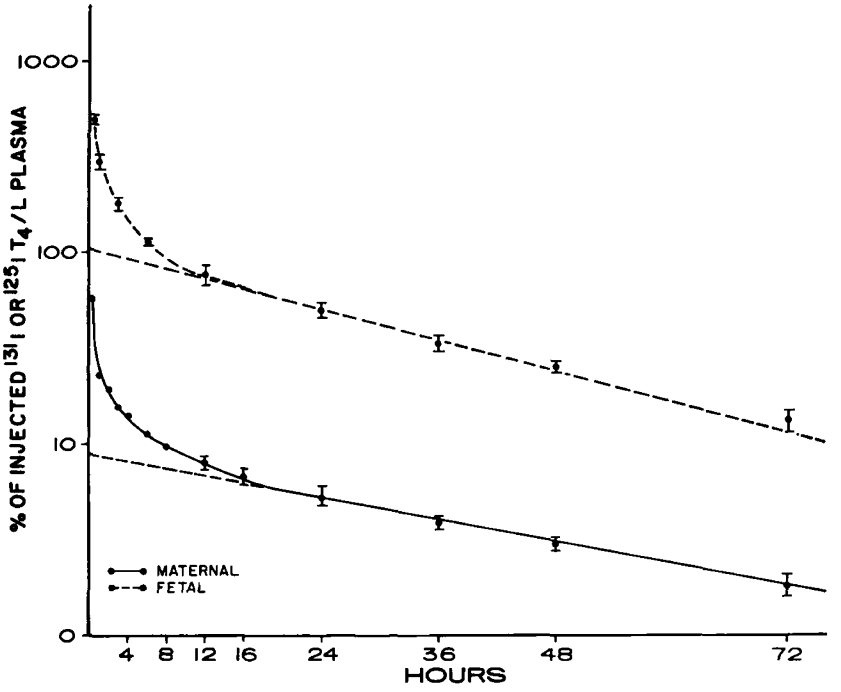

Fig. 2. Labeled thyroxine (^{131}I *or* ^{125}I T_4) disappearance in intact maternal and thyroidectomized fetal sheep after separate injections of ^{131}I and ^{125}I, respectively. Each point and deviation represents the mean ± SEM of five animals.

ance of T3 and T4 were determined. T3 and T4 distribution volumes (V_D) were estimated by extrapolation of the final single exponential disappearance curves to zero time and calculation of the apparent volume of hormone distribution by a simple dilution formula. Fractional T3 and T4 degradation rates (k) were computed as: $k = 0.693/(t_{1/2})$.

The turnover rates of T3 and T4 were calculated as: $T3_S$ or $T4_S$ (μg/24 hr) = serum T3 or T4 (μg/liter) $\times$ V (liter) $\times$ k. Serum T4 and T3 concentrations were measured by radioimmunoassay methods developed in our laboratories [1, 2]. Serum TSH was measured using a double antibody, heterologous (bovine) radioimmunoassay system developed in our laboratories. This system is sensitive to about 10 μU ovine TSH standard [14]. Student's *t* test was used to assess significance of the differences between euthyroid and hypothyroid data.

Fetal-maternal and maternal-fetal clearances of labeled T3 and T4 were estimated by assuming exchange between two compartments (maternal and fetal) from which irreversible clearance is ongoing simultaneously; these methods have been described previously [4]. To identify the form of radioactivity crossing the placenta, unwashed butanol extracts of serum, supernatant solutions from protein-bound iodine (PBI) precipitates, and dialysates from maternal and fetal sera were chromatographed on Whatman no. 3 paper using butanol-acetic acid (BAA) and tertiary amyl alcohol-ammonia (TAA) solvent systems as described previously [4].

Results

T4

Maternal and fetal weights and fetal gestational ages at the time of thyroidectomy and at the time of the T4 kinetic studies are listed in Table I. Before thyroidectomy the mean fetal serum T4 level was 12.2 μg/100 ml (nine animals); this value fell to a mean of 1.7 μg/100 ml 3 days postoperatively (Fig. 1) and to a mean of <0.7 μg/100 ml 5–6 days post-thyroidectomy. The mean maternal serum T4 concentration was 8.9 μg/100 ml before thyroidectomy and did not change significantly during the study period. Table II summarizes the T4 V_D and T4 $t_{1/2}$ values, serum T4 concentrations, and calculated T4 turnover rates for the five maternal-fetal pairs. Composite maternal and fetal T4 disappearance curves are depicted in Figure 2. Mean maternal and fetal T4 distribution volumes were 12.6 and 0.97 liters. Mean ± SEM extrathyroidal T4 pool sizes in the mothers and their fetuses (not shown) were 1070 μg ± 97 μg and <6.8 μg ± <0.8 μg; mean $t_{1/2}$ values were 1.42 and 0.99 days. Mean ± SEM fractional degradation rates [1] for T4 (not shown) were 0.50 ± 0.03 and 0.77 ± 0.10 in the mothers and fetuses. Calculated mean maternal and fetal T4 turnover rates were 11.9 and <3.2 μg/kg/24 hr.

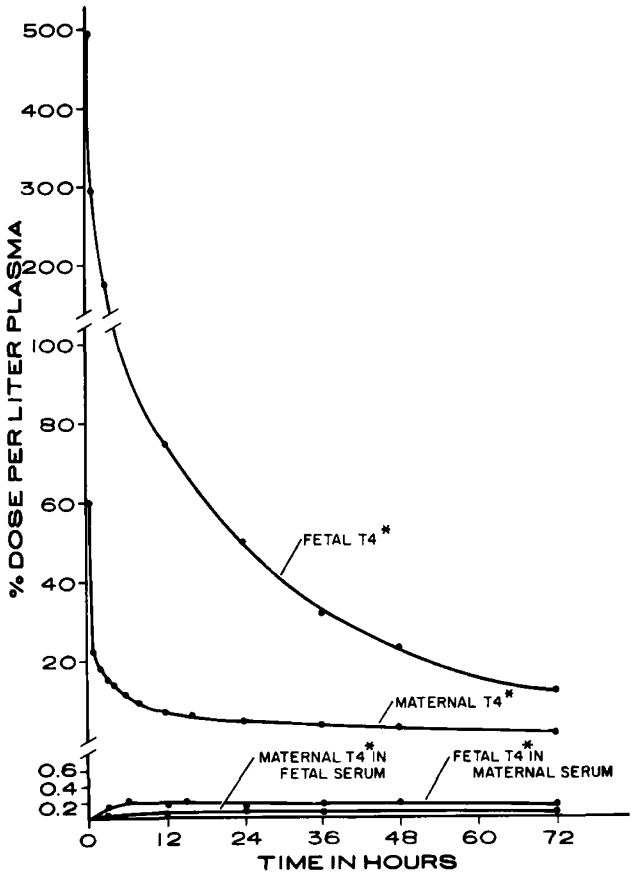

Fig. 3. Arithmetic plots of the disappearance of labeled thyroxine (*T4**) from fetal and maternal sera and the appearance of fetal-labeled T4* in maternal serum and maternal-labeled T4* in fetal serum. The data represent mean values of all experiments.

Placental transfer of butanol-extractable radioactivity occurred in both directions (Fig. 3). The mean fractional rate of T4 transfer was greater in the fetal to maternal direction ($0.00088/hr^{-1}$ *versus* $0.00003/hr^{-1}$); the maximum concentration of fetal T4 label in maternal serum at 24–36 hr was twice the maximum concentrations of maternal T4 label in fetal serum. Chromatography of the dialysates of maternal and fetal sera and of PBI supernatants revealed predominantly inorganic iodide, as expected. However, some T4 was identified. By contrast, chromatography of al-

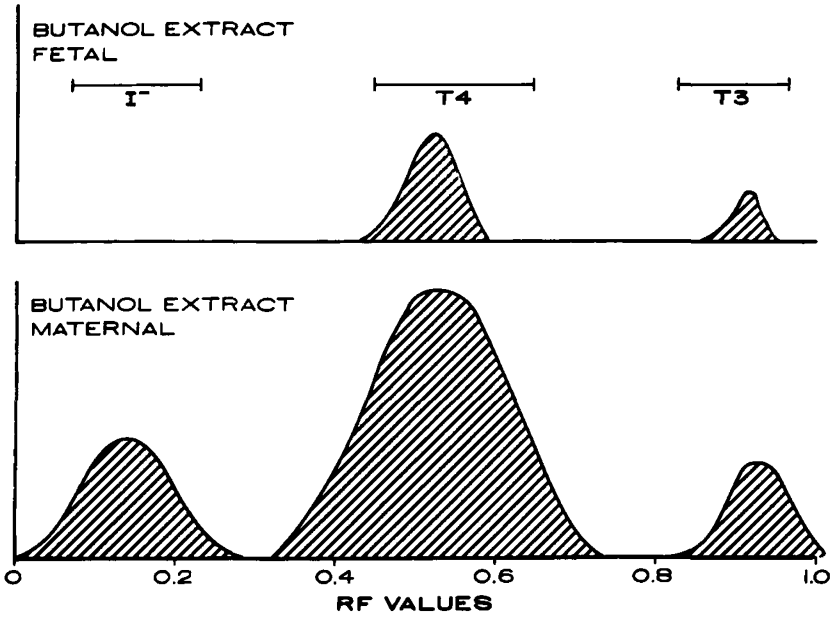

Fig. 4. Drawings of paper chromatographs of unwashed butanol extracts of fetal and maternal sera developed in a tertiary amyl alcohol-2 N ammonia solvent system. The extracts show predominantly thyroxine (*T4*) with small amounts of triiodothyronine (*T3*). Iodide is present in the extracts of maternal sera since these extracts were not washed with alkali.

kali-washed butanol extracts of sera showed predominantly T4, although a small amount of T3 (<1%) was separated using the TAA solvent systems. Representative chromatographs are shown in Figure 4.

T3

Table III lists maternal and fetal weights and fetal gestational ages at the time of thyroidectomy and at the time of isotope study. Table IV summarizes T3 V_D and T3 $t_{1/2}$ values, serum T3 concentrations, and calculated T3 turnover rates for the four maternal-fetal pairs. Composite maternal and fetal T3 disappearance curves are depicted in Figure 5. The mean and SEM maternal serum T3 concentration was 94 ± 5.3 ng/100 ml before thyroidectomy and did not change significantly during the study period. Before thyroidectomy the mean fetal serum T3 level was <18 ng/100 ml, the lower limit of the assay, and remained unmeasurable throughout the study. Mean maternal and fetal T3 V_D values were 36.7 and 7.5 liters. The mean ± SEM extrathyroidal T3 pool sizes in the mothers and fetuses (not shown) were 25.4 μg ± 5 μg and <1.50 μg ± 0.22 μg; mean maternal and fetal T3 $t_{1/2}$ values were 6.7 and 10.0 hr. Mean ± SEM fractional degradation rates (k) of T3 were 2.52 ± 0.16 and 1.67 ± 0.05 in the mothers and fetuses (not shown). Calculated mean T3 turnover rates were 1.27 and <1.05 μg/kg/24 hr in the mothers and fetuses.

Table III. Age and weight of animals used in the triiodothyronine kinetic studies

Sheep	Estimated gestational age at thyroidectomy, days	Estimated gestational age when study performed, days	Weight, kg	
			Maternal	Fetal
19	90	127	47.7	1.360
20	95	132	54.5	2.580
21	110	114	50.0	1.700
22	125	129	51.8	2.570
Mean			51.0	2.202
SEM			1.4	0.22

Placental transfer of butanol-extractable T3 radioactivity occurred in both directions (Fig. 6). The mean fractional rate of T3 transfer was greater in the fetal to maternal direction ($0.0068/hr^{-1}$ *versus* $0.0018/hr^{-1}$); the maximum concentration of fetal T3 label in maternal serum at 1–2-hr was between 2 and 5 times the maximal concentration of maternal T3 label in fetal serum (at 12 hr).

Chromatography of butanol extracts revealed that the radioactivity migrated as T3 in both the BAA and TAA solvent systems. The dialysates of maternal and fetal sera and the PBI supernatants contained predominantly iodide, as in the T4 studies. However, there was also a substance which appeared in the aqueous

Table IV. Triiodothyronine (T3) kinetic data in maternal and thyroidectomized fetal sheep[1]

Sheep	Maternal					Fetal				
				$T3_S$					$T3_S$	
	T3 V_D, liters	T3 $t_{1/2}$, days	Serum T3 conc., ng/100 ml	μg/24 hr	μg/kg/24 hr	T3 V_D, liters	T3 $t_{1/2}$, days	Serum T3 conc., ng/100 ml	μg/24 hr	μg/kg/24 hr
19	19.2	5.7	100	55.4	1.16	4.8	10.5	<18	<1.36	<0.70
20	18.5	7.8	80	31.3	0.57	7.0	10.6	<18	<1.99	<0.77
21	34.5	7.0	104	85.8	1.72	8.1	9.4	<18	<2.60	<1.53
22	34.5	6.3	92	84.4	1.63	10.0	9.6	<18	<3.11	<1.21
Mean	26.7	6.7	94	62.2	1.27	7.5	10.0	<18	<2.26	<1.05
SEM	4.5	0.5	5.3	13.0	0.26	1.1	0.3		<0.39	<0.19

[1] V_D: T3 volume of distribution; $t_{1/2}$: plasma half-life of labeled T3 disappearance; $T3_S$: daily T3 turnover.

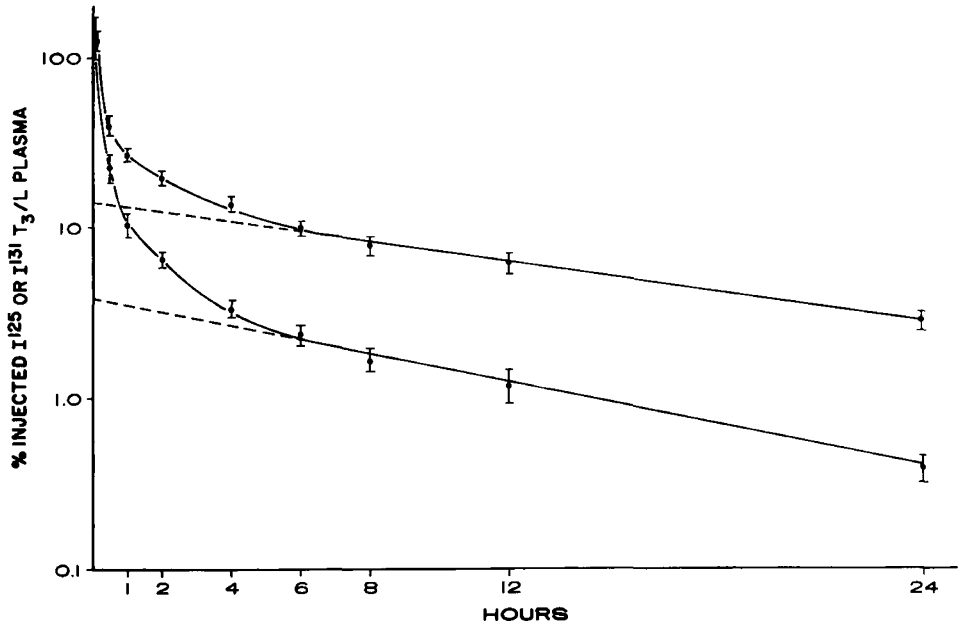

Fig. 5. Labeled triiodothyronine (I^{125} *or* I^{131} T_3) disappearance in intact maternal and thyroidectomized fetal sheep. The upper line represents the disappearance of ^{125}I- labeled triiodothyronine (T3) from fetal serum, the lower line the disappearance of ^{131}I-T3 from maternal serum after separate injections. Each point and deviation represents the mean ± SEM for four animals.

dialysates of fetal and maternal sera moving just ahead of iodide and not present in the washed butanol extracts. This compound may represent the T3 sulfate conjugate previously identified in fetal and maternal blood of monkeys by Schultz *et al.* [13] (Fig. 6).

Serum TSH concentrations were measured in three of the five thyroidectomized fetuses in the T4 studies (*14, 19,* and *20,* Table I); the values were 350, 720, and 1,500 μU/ml, respectively, at the time of study 27–30 days after thyroidectomy.

Discussion

The present data show that after thyroidectomy the near term ovine fetus rapidly becomes hypothyroid; the serum T4 concentration falls to <0.7 μg/100 ml; serum T3 levels are unmeasurable (<18 ng/100 ml), and serum TSH concentrations increase to 300–1500 μU/ml. Moreover, these low fetal serum iodothyronine values persist in spite of large maternal to fetal gradients of T4 and T3 and a large fetal to maternal gradient of TSH across the placenta. These results are in agreement with data of Hopkins and Thorburn [11], who also reported a rapid fall of fetal serum T4 (from a mean of 11 μg/100 ml to undetectable levels) after fetal thyroidectomy.

The maternal serum T4, T4 V_D, and $T4_S$ values in the present report (Table II) are significantly greater than those previously reported in our euthyroid ovine

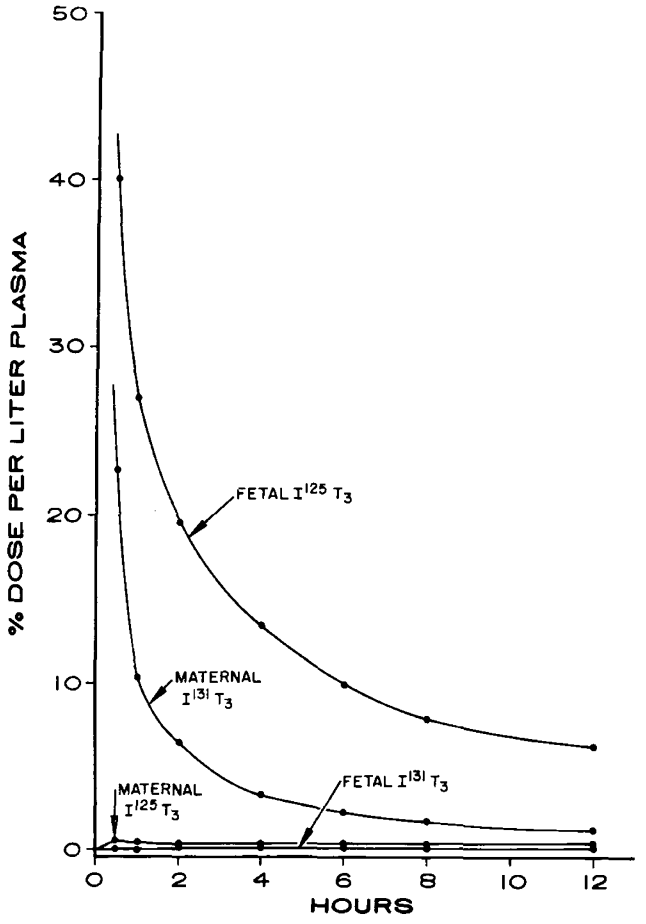

Fig. 6. Arithmetic plots of the disappearance of labeled triiodothyronine ($I^{131}T_3$) from fetal and maternal sera and the appearance of fetal ^{125}I-labeled triiodothyronine (T3) in maternal serum and maternal ^{131}I-labeled T3 in fetal serum. The data represent mean values for all experiments.

studies [3]. Several factors might account for this. Serum T4 was measured by RIA in the present study rather than the Murphy-Pattee method as in the previous report; T4 RIA results are 15–20% higher than results using the Murphy-Pattee method, inasmuch as the latter are not corrected for extraction losses. A lower mean environmental temperature and the fact that most of the present sheep had been shorn might be of significance; both factors would tend to increase T4 turnover [9]. In addition, wound infections associated with T4 sequestration might have contributed [10].

In the thyroidectomized fetuses, the T4 V_D and T4 $t_{1/2}$ values were similar to results reported previously in euthyroid fetuses [3], although the serum T4 values and $T4_S$ were much lower due to fetal thyroidectomy. The mean fetal serum T3 concentrations were <18 ng/100 ml in both euthyroid and hypothyroid animals, and the mean T3 V_D values were similar (Reference 4 and Table IV). The mean T3 $t_{1/2}$ value, however, was significantly longer in the hypothyroid fetuses (10.0 ± 0.3 hr *versus* 5.5 ± 0.6 hr, $P < 0.001$) and the mean fractional T3 degradation rate (k) was therefore less (1.67 *versus* 3.9, $P < 0.01$). This may be accountable on the basis of relatively unsaturated iodothyronine-binding proteins.

Placental transfer of T3 and T4 were estimated as previously described [4]. Mean net T4 transfer approximated 0.6 μg/24 hr in the maternal to fetal direction, and mean net T3 transfer approximated 0.7 μg/24 hr in the maternal to fetal direction. These amounts represent less than 0.2% and about 50%, respectively, of the mean daily T4 and T3 turnover rates measured in the euthyroid fetus [3–5]. If a T3/T4 potency ratio of 4/1 is assumed, these values represent only about 7% of the total T4 equivalent turnover ($T4_S + 4 \times T3_S$) in the euthyroid fetuses. The high fetal serum TSH

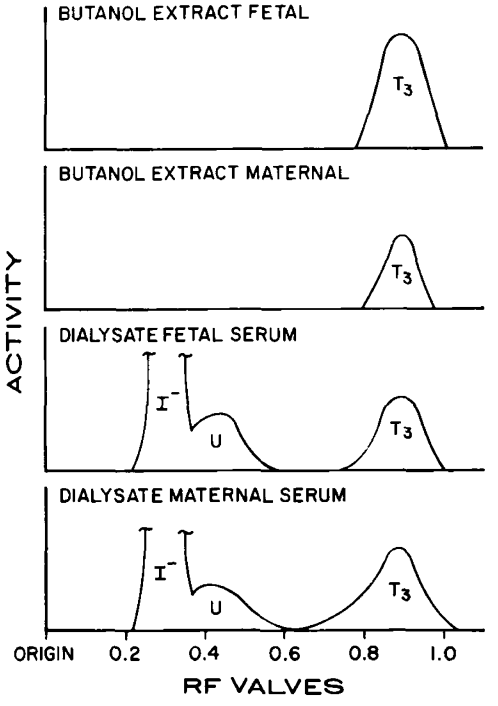

Fig. 7. Drawings of paper chromatograms of fetal and maternal sera 2–4 hr after administration of ^{125}I-labeled triiodothyronine (T_3) to the thyroidectomized fetus. The chromatograms were developed in a butanol-acetic acid solvent system. The two upper panels show the triiodothyronine peaks in washed butanol extracts of fetal and maternal sera; the two lower panels show the iodide and unidentified peaks of activity in dialysates of fetal and maternal sera. The vertical axis represents radioactivity and the horizontal axis, R_F values.

values (300–1500 μU/ml) indicate that the thyroidectomized fetuses were, in fact, hypothyroid.

The present data regarding placental transfer of iodothyronines are in general agreement with earlier reports. Dussault *et al.* [3] found essentially no transfer of labeled T4 across the ovine placenta. Hopkins *et al.* [11], after injecting 500 μg of T4 into pregnant ewes at 123–146 days of gestational age and approximately 13–36 days after fetal thyroidectomy, found no rise in fetal serum T4 concentrations even though there was a 4–6 μg/100 ml T4 gradient across the placenta. Robin *et al.* [12] found a small net bidirectional exchange of labeled T4 in the last trimester in pregnant sheep, but this was not quantified in terms of unlabeled hormone.

Finally, in maternal and fetal blood after administration of labeled T3, we observed a peak of radioactivity with chromatographic characteristics similar to the T3 sulfate reported in fetal and maternal blood of monkeys by Schultz *et al.* [13]. We did not, however, conduct sulfatase hydrolysis of this compound. Because this substance seemed highly polar and did not appear in the aqueous alkali-washed butanol extracts, it did not complicate the kinetic data of this study. The T3 observed during chromatography of fetal serum after injection of radioiodine-labeled T4 may represent T3 derived either from artifactual deiodination of thyroxine during TAA paper chromatography or *in vivo* conversion of T4 to T3 [6, 7].

Summary

Fetal thyroidectomy has been performed on fetal sheep in utero between 90 and 125 days of gestational age. After this procedure, the fetus rapidly becomes hypothyroid, as indicated by unmeasurable serum levels of T4 and T3 and very high serum TSH concentrations. Daily fetal $T4_S$ and $T3_S$ average less than 3.23 and 1.05 μg/kg/24 hr as contrasted with values of 41 and <1.45 μg/kg/24 hr in euthyroid fetuses (reported previously). Maternal serum T4 and T3 concentrations remain unchanged so that large maternal to fetal gradients of T4 and T3 exist across the placenta. In spite of this, there is little net transfer of maternal T4 or T3 to the fetus. These results further substantiate the autonomy of the fetal pituitary-thyroid system.

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