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Plasma iodothyronine levels in lambs during the perinatal period : influence of thyrotropin injection

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Summary. Plasma thyroxine (T_4) and triiodothyronine (T_3) levels were measured in 7 pregnant ewes and their 9 chronically cannulated foetuses during the last 37 days of gestation and the first 5 days after parturition. The highest plasma T_4 and T_3 levels were measured in lambs during the hours following parturition.

In 7 chronically cannulated 139-day old foetal lambs, the intravenous injection of ovine thyrotropin (oTSH ; 7 mU per foetus) induced a significantly more intense increase in plasma T_4 and T_3 levels than that observed after the same dose of oTSH in seven 130-day old foetuses.

In newborn lambs, the increase in plasma T_4 levels after oTSH injection (3.5 mU per kg body weight) was not different in 8-hour old and 36-hour old animals, but was more intense at 120 h after birth than at 8 or 36 h after birth. The rise in plasma T_3 levels after oTSH increased with age at 8, 36 and 120 h following birth.

Plasma T_4 and T_3 measurements made in the same lambs before and after birth confirmed the fragmentary values obtained in foetal and newborn lambs in other previous studies. The rise in plasma iodothyronine levels after TSH injection in lambs increased at the end of gestation and the beginning of neonatal life, except during the first hours after delivery when these levels were high.

Introduction.

Studies performed in lambs during the perinatal period suggest that the high plasma iodothyronine levels measured in newborn ovines (Nathanielsz, 1969 ; Davicco, Vigouroux and Barlet, 1980) can be related to several causes : (i) increased thyroid gland secretion of thyroxine (T_4) and triiodothyronine (T_3) (Slebodzinski, 1972 ; Klein, Oddie and Fisher, 1980), (ii) increased hepatic conversion of T_4 to T_3 in the newborn compared to the foetus (Wu *et al.*, 1978). The increased T_4 secretion observed in the early hours after birth was initially attributed to a thyrotropin (TSH) surge (Fisher *et al.*, 1977) ; however, serum TSH concentrations are similar before and after birth in lambs (Klein and Fisher, 1980), and the T_4 response to thyroliberin-stimulated TSH release is greater in newborn lambs than in foetuses (Klein and Fisher, 1980). Thus, these latter experiments suggest increased thyroid gland sensitivity to TSH in the newborn (Klein, Oddie and Fisher, 1980). The purpose of the present work was (i) to

measure simultaneously plasma T_4 and T_3 levels in lambs and their dams during the perinatal period and (ii) to compare the response of lambs to TSH given before and after birth.

Material and methods.

Animals. — We used 21 primiparous Limousine × Romanov ewes of known gestational age mated with an Ile-de-France ram after oestrus synchronization. They were housed on straw in individual pens. Each animal was fed hay (3 kg per day) and grain concentrate (300 g per day) and had free access to tap water. The length of gestation for ewes of this genotype in our flock is 145 ± 2 days.

Using 14 ewes under halothane anesthesia, between days 100 and 110 of gestation, we chronically implanted into their twin foetuses one catheter in the left carotid artery for blood sampling and one in the right jugular vein for hormone injections. The foetuses of the other 7 ewes (5 with singletons and 2 with twins) only had a catheter implanted in the left carotid artery. The technique, derived from that used by Mellor and Matheson (1975) for chronic catheterization of the umbilical vessels of foetal sheep, has already been described in detail (Barlet *et al.*, 1978). Each ewe delivered a live lamb on days 144 to 147 of gestation. The birth weight of single (3.6 ± 0.2 kg ; mean ± SEM) and twin (3.1 ± 0.3 kg) lambs was not different from that of the control lambs from unoperated primiparous ewes of the same flock. After birth, the lambs were left with their dams and suckled *ad libitum.*

To measure plasma T_4 and T_3 levels, serial blood samples (1 ml each) were simultaneously collected from the last 7 ewes (by puncture of the external jugular vein) and from their 9 foetuses during the last 37 days of gestation and the first 5 days after parturition. The other ewes were divided into two groups : 7 were used on day 130 and 7 on day 139 of gestation. Each time, one foetus of each ewe was intravenously injected (7 mU per foetus) with purified ovine thyrotropin (oTSH ; NIAMDD - oTSH-9 ; 7.5 IU/mg) ; the body weight of 130 to 140-day old foetuses of this genotype is approximately 2 kg. Twin foetuses, used as controls, simultaneously received the same volume of vehicle (1 ml of sterile 0.9 p. 100 NaCl).

Three groups of 7 to 8 lambs each were intravenously injected with oTSH (3.5 mU per kg body weight) at 8, 36 or 120 h after birth. The lambs were chosen according to their birth time, so that each injection could be given at 9 a.m. Control lambs of the same age received the same volume (0.5 ml per kg body weight) of vehicle.

The blood of newborn lambs was collected by puncture of the jugular vein opposite to the one in which the oTSH was injected. The plasma was centrifuged and frozen until assay.

Analysis. — Plasma total T_4 and T_3 concentrations were measured by radioimmunoassay using T_3 (Trik) and total T_4 (Tetrak) radioimmunoassay kits from the « Commissariat à l'Energie atomique » (Gif-sur-Yvette, France). Plasma samples of 100 µl and 10 µl were used for T_4 and T_3 determinations, respectively.

In our experimental conditions, reproducibility was 2 p. 100 for the T_4 assay and sensitivity was 2 ng/ml of plasma. For the T_3 assay, reproducibility was 3 p. 100 and sensitivity was 15 pg/ml of plasma. No significant interaction with other iodothyronines or iodotyrosines was observed in any assay.

The results were expressed as the mean ± SEM. Student's t-test or variance analysis was used for statistical comparison.

Results.

During the last 36 days of gestation, the mean plasma T_4 level was higher in foetuses (8.3 ± 0.4 µg/dl) than in ewes (5.0 ± 0.3 µg/dl ; $P < 0.01$). In lambs, plasma T_4 levels increased from 5.4 ± 2.5 µg/dl 4 days before term to 11.1 ± 0.6 µg/dl ($P < 0.05$) 2 days later, decreased to 8.0 ± 0.6 µg/dl ($P < 0.05$) 1 day before parturition, rose to 14.4 ± 0.4 µg/dl ($P < 0.01$) 6 h after birth, decreased to 7.8 ± 0.8 µg/dl ($P < 0.01$) 48 h after birth and then remained stable until 120 h (8.1 ± 1.3 µg/dl). In ewes, the plasma T_4 levels were unchanged between day 37 before parturition (7.0 ± 1.0 µg/dl) and day 5 after parturition (8.1 ± 1.3 µg/dl). Thus, during the first 5 days after birth, the mean plasma T_4 level was still higher in newborn lambs (10.3 ± 0.8 µg/dl) than in their dams (5.7 ± 0.5 µg/dl ; $P < 0.01$) (fig. 1).

Between days -37 and -1 before parturition, the mean plasma T_3 level was higher in ewes (150 ± 8 ng/dl) than in foetuses (95 ± 9 ng/dl) ; $P < 0.01$), but during the first 5 days after delivery the mean plasma T_3 level was higher in lambs (328 ± 16 ng/dl) than in dams (185 ± 12 ng/dl ; $P < 0.01$). Plasma T_3

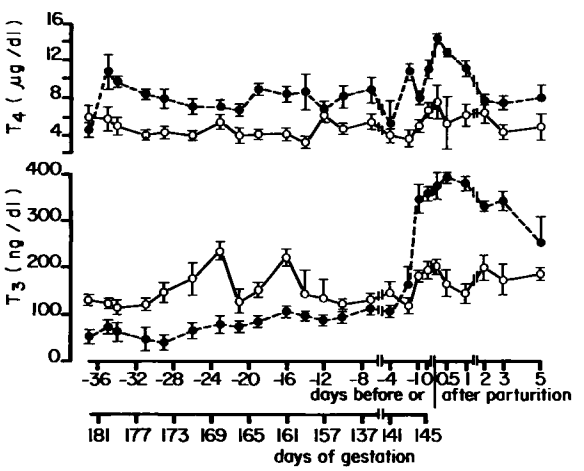

FIG. 1. — *Plasma total thyroxine* (T_4) *and triiodothyronine* (T_3) *levels in 7 ewes* (solid lines) *and their 9 chronically cannulated foetuses (dashed lines) during the last 37 days of gestation and the 5 days following parturition* (mean ± SEM)

TABLE 1

Variance analysis comparing 130-day-old and 139-day-old foetuses injected with oTSH

	Age	Treated and control foetuses	Time of sampling	Age, treated and control foetuses	Age, time of sampling	Treated and control foetuses, time of sampling	Age, treated and control foetuses, time of sampling
$\overline{T_4}$							
Residual error : 1.897							
Significance	$P < 0.01$	$P < 0.01$	$P < 0.05$	$P < 0.05$	N.S.	N.S.	N.S.
Degrees of freedom	1-35	1-35	8-35	1-35	8-35	8-35	8-35
$\overline{T_3}$							
Residual error : 17.980							
Significance	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.05$	$P < 0.05$	N.S.
Degrees of freedom	1-35	1-35	8-35	1-35	8-35	8-35	8-35

levels increased progressively in lambs between days -37 (53 ± 8 ng/dl) and -6 (106 ± 13 ng/dl) before parturition. A marked rise occurred before birth (from -4 to -1 days) with levels around 360 ng/dl. Plasma T_3 levels then decreased to 249 ± 61 ng/dl on day 5 after parturition (fig. 1). In pregnant ewes, the highest plasma T_3 levels were measured on days -23 and -16 before parturition (237 ± 21 ng/dl and 223 ± 18 ng/dl, respectively). In these ewes plasma T_3 levels increased from 119 ± 3 ng/dl 48 h before lambing to 205 ± 8 ng/dl 6 h after lambing ($P < 0.01$) and remained stable until day 5 after parturition (186 ± 12 ng/dl) (fig. 1).

During the 48 h following injection, no significant variation in plasma T_4 and T_3 levels was observed in the 7 foetuses injected with oTSH (7 mU per foetus) on day 130 of gestation. In the 7 foetuses injected with the same dose of oTSH on day 139 of gestation, a 3.5-fold increase in plasma T_4 levels was observed 3 h after the injection. Significantly elevated T_4 levels were found in these treated 139-day old foetuses from 45 min to 48 h after the injection ; a 2-fold increase in plasma T_3 levels, which persisted for 6 h, occurred 2 h after oTSH injection. The injection of the same volume of vehicle (1 ml per foetus) in control foetuses was without any effect on foetal plasma iodothyronine levels (table 1 ; figs. 2a, b).

The increase in plasma T_4 levels after TSH injection was not different in 8-hour old and 36-hour old newborn lambs. However, the increase in plasma T_3 levels following TSH injection was greater in 36-hour old lambs than in 8-hour

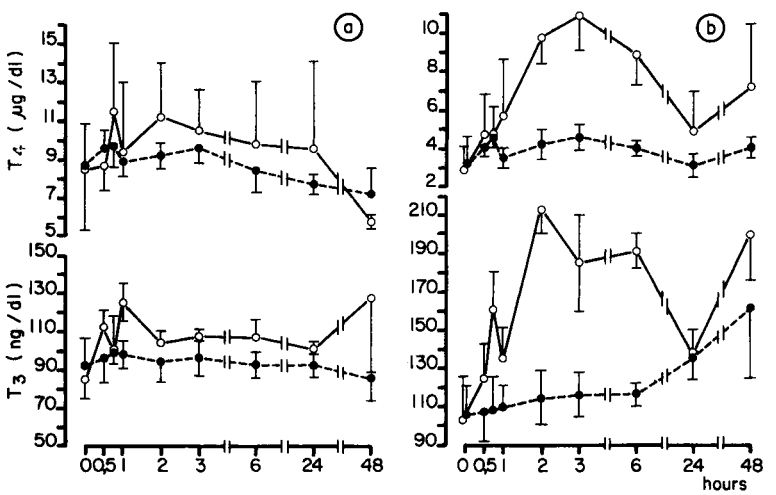

FIG. 2. — *Influence of an intravenous injection of oTSH* (7 mU per foetus) *in foetal lambs at 130 days* (a) *and 139 days* (b) *of gestation.* Solid line : treated animals ; n = 7 for each group ; dashed line : twin control lambs ; mean ± SEM. For statistical evaluation see table 1.

old lambs (table 2 ; figs. 3a, b). Similarly, the rise in plasma T_4 and T_3 levels following TSH injection in 120-hour old lambs was more intense than in 8-hour old lambs or 36-hour old lambs (table 2 ; figs. 3a, b, c).

Discussion.

Developmental patterns for plasma total T_4 and T_3 levels in the ovine species during the perinatal period have already been reported. However, the present study measured, for the first time, changes in both plasma T_4 and plasma T_3 levels in the same animals (lambs and ewes) over a long period before and after birth.

Using 2 Merino ewes which lambed after 150 days of gestation, Thorburn and Hopkins (1973) found a significant decrease in foetal plasma T_4 concentration during the last 10 days before delivery, while Nathanielsz *et al.* (1973), did not find such changes in foetuses from Welsh Mountain ewes which lambed between 141 and 146 days of gestation. Similarly, Klein, Oddie and Fisher (1978) did not observe a decrease in foetal plasma T_4 levels during the last 13 days of gestation. Mellor *et al.* (1976) demonstrated a decrease in the plasma T_4 concentration of only 11 out of 21 Scottish Blackface and Welsh Mountain foetuses which had been chronically cannulated. Between days 105 and 129 of gestation, there was no correlation between plasma T_4 concentration and gestational age in 11 ovine foetuses (Klein and Fisher, 1980). In the 9 foetuses used in the present experiment, born at term on days 144 to 147 of gestation, plasma T_4 concentration did not vary significantly between day 36 before parturition and the time of parturition (fig. 1).

The low serum T_3 in the sheep foetus during days 85 to 140 of gestation is due to a high metabolic clearance rate and decreased production of T_4 by monodeiodination (Chopra, Sack and Fisher, 1975). Studies in ovine euthyroid maternel-foetal pairs have shown nearly total placental impermeability to labelled T_4 or labelled T_3 in both directions ; absolute placental T_3 transfer was 2 μg per day and less than 1.2 μg per day in the maternal to foetal and foetal to maternal directions, respectively (Dussault *et al.*, 1972). The rise in plasma T_3 levels occurring in foetal plasma during the last 4 days of gestation might result from the stimulation of T_4-β deiodination induced by the cortisol rise which precedes delivery (Mathur *et al.*, 1980).

In newborn lambs delivered at a low temperature, plasma T_3 levels increased sharply after birth ; this increase does not appear in lambs delivered in a water-bath at 38 °C (Fisher *et al.*, 1977). The relatively high external temperature (20 °C) at which the lambs used in this experiment were born and kept during the first week of postnatal life, might explain why there was only a slight increase in foetal plasma T_3 levels during the hours following delivery (fig. 1).

The plasma TSH level measured in foetal lambs during the last 20 days of gestation was 3.2 ng/ml), *i.e.* 6.4 mU/dl (Hopkins, Wallace and Thorburn, 1975). We can thus assume that our treated foetuses were injected with a

physiological dose of oTSH (7 mU per foetus). Such a dose of oTSH injected into foetuses had no effect on maternal thyroxinemia or triiodothyroninemia. As already demonstrated (Fisher *et al.*, 1977), iodinated bovine TSH does not cross the ovine placenta. When TSH-releasing hormone (TSH-RH) (50 µg) was injected into chronically catheterized sheep foetuses between days 113 and 144 of gestation, no effect was observed on plasma T_3 and T_4 levels in 113 to 130-day old foetuses, while in 144-day old foetuses, plasma T_3 increased from 37 ng/dl to 90 ng/dl in 120 min (Wallace *et al.*, 1979).

In three 1 to 6-day old lambs, plasma T_4 concentration increased between 60 and 120 min after TSH-RH injection ; the 6-day old lamb, but not the 1 or 2-day old animal, showed a consistent increase in plasma T_3 concentration in response to TSH-RH injection (Wallace *et al.*, 1979). In our experiment, oTSH injection significantly increased plasma T_4 and T_3 levels in each group of newborn lambs (fig. 3 ; table 2).

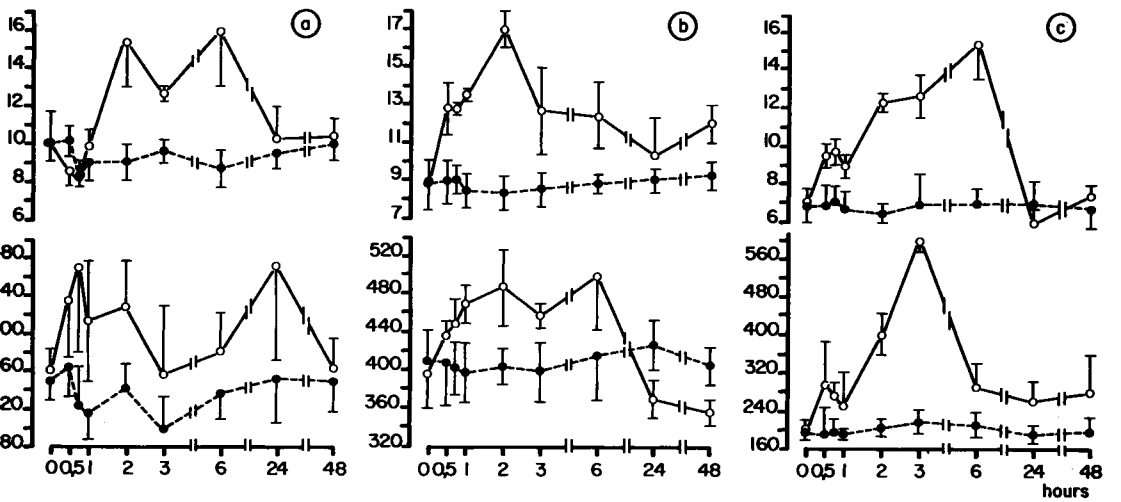

FIG. 3. — *Influence of an intravenous injection of oTSH* (3.5 mU per kg body weight) *on plasma thyroxine* (T_4) *and triiodothyronine* (T_3) *levels in newborn lambs at 8 h* (a), *36 h* (b) *and 120 h* (c) *after birth.* Solid line : 7 treated animals in each group ; dashed line : 7 control lambs in each group ; mean ± SEM. For statistical evaluation see table 2.

The iodothyronine level in the blood represents the ratio of iodothyronine secretion to its metabolic clearance rate. In foetal lambs, T_4 utilization increased from 0.33 µg per hour per kg of body weight to 0.73 µg per hour per kg of body weight between days 111 and 139 of gestation (Nathanielsz *et al.*, 1973), while in newborn lambs it decreased from 0.6 ± 0.08 µg per hour per kg of body weight to 0.2 ± 0.04 µg per hour per kg of body weight between days 3 to 4 and 10 to 11 of postnatal life (Nathanielsz, 1970). Thus, the increasing effect of TSH on plasma T_4 levels between days 130 and 139 of gestation would result from

TABLE 2

Variance analysis comparing 8-hour-old, 36-hour-old and 120-hour-old newborn lambs injected with oTSH

	Age		Treated and control lambs		Time of sampling		Age, treated and control lambs		Age, time of sampling		Treated and control lambs, time of sampling		Age, treated and control lambs, time of sampling	
	T_4	T_3	T_4	T_3	T_4	T_3	T_4	T_3	T_4	T_3	T_4	T_3	T_4	T_3
8 h-36 h														
Residual error	1.691	37.124												
Significance	N.S.	P < 0.01	P < 0.01	P < 0.01	P < 0.01	N.S.	P < 0.01	P < 0.05	N.S.	N.S.	P < 0.01	P < 0.01	N.S.	N.S.
Degrees of freedom	1-70	1-35	1-70	1-35	8-70	8-35	1-70	1-35	8-70	8-35	8-70	8-35	8-70	8-35
8 h-120 h														
Residual error	1.083	38.606												
Significance	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	N.S.	P < 0.01
Degrees of freedom	1-70	1-35	1-70	1-35	8-70	8-35	1-70	1-35	8-70	8-35	8-70	8-35	8-70	8-35
36 h-120 h														
Residual error	1.919	40.754												
Significance	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	N.S.	P < 0.01	N.S.	P < 0.01	P < 0.01	P < 0.01	N.S.	P < 0.01
Degrees of freedom	1-70	1-35	1-70	1-35	8-70	8-35	1-70	1-35	8-70	8-35	8-70	8-35	8-70	8-35

increased thyroid T_4 secretion. In newborn lambs, the maximal increase in plasma T_4 levels occurred in 5-day old animals (fig. 3). This could also partly result from decreased T_4 utilization in these animals. The metabolic clearance rate for T_3 was 40 $\pm$ 5 l per m^2 per day in 7-day old lambs (Klein, Oddie and Fisher, 1980), significantly less than in 95 to 140-day old foetuses where it was 80.2 $\pm$ 8.9 l per m^2 per day (Chopra, Sack and Fisher, 1975). However, to our knowledge, nobody has measured the changes in the metabolic clearance rate of T_3 throughout foetal and neonatal life in the ovine species. Thus, we cannot decide whether the increasing effect of oTSH with age in foetal and neonatal lambs mainly results from increasing sensitivity of follicular cells to TSH throughout foetal and neonatal life, and/or from a simultaneous decreasing metabolic clearance rate of T_3.

It is also interesting to note that the effect of TSH on plasma T_4 and T_3 levels was more intense in 139-days old foetuses than in 130-day old ones ; basal plasma T_4 and T_3 levels were 2.9 $\pm$ 1.3 µg/dl and 103 $\pm$ 23 ng/dl, respectively, in the former ; they were 8.5 $\pm$ 3.3 µg/dl and 85 $\pm$ 11 ng/dl, respectively, in the latter. Similarly, basal plasma T_4 and T_3 levels were lower in 120-hour old lambs than in 8-hour old newborn lambs. Therefore, in foetuses as in newborn lambs, the lowest basal iodothyronine levels were associated with an increasing TSH effect on plasma T_3 and T_4 levels. Studies from several laboratories suggest that circulating T_4 and T_3 regulate thyroid function by a feed-back mechanism wherein the iodothyronines act directly on the gland to inhibit its responses to TSH stimulation (Cortell and Rawson, 1944 ; Yu *et al.,* 1976 ; Goldenheim *et al.,* 1979). Thus, the high levels of circulating T_4 and T_3, measured in lambs during the hours after birth (fig. 1), might partly explain the decreased response to the oTSH measurement in 8-hour old and 36-hour old lambs. Secondly, in rats thyroidal TSH receptors are regulated by endogenous TSH ; after exposure to TSH, the thyroid lobes show decreased responsiveness to the hormone (Witte and McKenzie, 1981). Therefore, the neonatal TSH surge described in lambs (Fisher *et al.,* 1977) would also decrease the response of 8-hour old and 36-hour old lambs to exogenous TSH. Since the development of the foetal hypothalamic-pituitary-thyroid axis takes place between 120 days of gestation and 1 to 2 postpartum weeks (Fisher *et al.,* 1977), it is not complete at 130 days of gestation. This could also explain the decreased response to oTSH in 130-day old foetuses.

In conclusion, our results confirm previous fragmentary results obtained by other groups using few animals. They demonstrate that the injection of a physiological dose of ovine TSH in chronically cannulated ovine foetuses and newborn lambs significantly increased the plasma T_4 and T_3 levels in 139-day old foetuses and 5-day old lambs, while it had less effect in 130-day old foetuses and 8 to 36-hour old lambs. This suggests increased thyroid gland sensitivity to TSH at the end of gestation and the beginning of neonatal life, except during the first postpartum hours, which are characterized by high plasma levels of iodothyronines.

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Résumé. Les taux plasmatiques de thyroxine (T_4) et de triiodothyronine (T_3) ont été mesurés chez 7 brebis gestantes primipares et leurs 9 fœtus (cathétérisés chroniquement *in utero*) durant les derniers 37 jours de gestation et les 5 jours suivant la parturition. Les plus fortes thyroxinémie (14 ng/dl) et triiodothyroninémie (370 ng/dl) ont été mesurées chez les nouveau-nés 6 heures après la naissance.

Chez 7 fœtus de 139 jours, l'injection intraveineuse de TSH ovine (7 mU par fœtus) induisait une élévation de T_4 et T_3 plus intense que celle observée avec une dose analogue de TSH chez 7 fœtus de 130 jours.

Chez les agneaux nouveau-nés, l'élévation de la T_4 plasmatique consécutive à une injection de TSH ovine (3,5 mU par kg de poids vif) n'était pas différente chez 7 agneaux de 8 h et chez 7 agneaux de 36 h, mais elle était plus intense chez 7 agneaux de 120 h. L'élévation de la triiodothyroninémie consécutive à TSH augmentait avec l'âge des animaux entre 8 h et 120 h après la naissance.

En conclusion, les mesures de T_4 et T_3 réalisées sur les mêmes animaux avant et après la naissance confirment des résultats fragmentaires obtenus précédemment par d'autres auteurs. Nos résultats démontrent également que l'élévation des iodothyronines plasmatiques consécutive à une injection de TSH se fait plus intense en fonction de l'âge du fœtus et du nouveau-né, à l'exception des heures suivant la parturition où les taux plasmatiques de T_3 et T_4 sont élevés.

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