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Intraamniotic Triiodothyronine instillation for prevention of respiratory distress syndrome in pregnancies complicated by hypertension

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1 Introduction

Respiratory distress syndrome (RDS) is the main cause of death among premature newborn infants [21]. Despite recent improvements in treatment by neonatal intensive care and respiratory assistance, mortality from RDS remains high [20]. Inadequate pulmonary surfactant is thought to be a primary factor leading to the development of RDS [2].

LIGGINS [12] was the first to observe an accelerated lung maturity of fetal lambs treated *in utero* with glucocorticoids. LIGGINS and HOWIE [14] first reported the beneficial effect of the maternal administration of antepartum glucocorticoid on the incidence of RDS in premature infants. This has since been confirmed by others [3, 5, 8, 18]. However, attention must be drawn to the possibility of an adverse effect of corticosteroid treatment in cases with hypertension-edema-proteinuria syndromes. In this group a significantly higher fetal death rate was observed under betamethasone therapy [13].

Studies indicating a high incidence of RDS in neonatal hypothyroidism [25] suggest the possibility that thyroid hormones may play an important role on fetal lung maturation. Several animal studies have suggested an important influence of thyroid hormones on acceleration of lung maturation and enhancement of surfactant production [22, 27].

Curriculum vitae

PETER SCHREYER, born in Roumania 1936, emigrated to Israel in 1965. Bachelor of Medicine from Hebrew University Hadassah Medical School in 1969. Internship and residency in Asaf Harofe Hospital, 1969–1976. Lecturer, Tel-Aviv University. Publications directed toward amniotic fluid biochemistry, particularly phospholipids as related to RDS and steroid induced fetal lung maturation enhancement. Recently exploring metabolic and endocrine effects of beta mimetic drugs.

Since maternal thyroid hormones cross the placenta in low concentration, the fetus depends primarily upon endogenous production. SACK et al. [23] showed that in sheep fetus, thyroxine injected into the amniotic sac was absorbed and distributed through the fetal body as if it were injected directly into the fetus.

MASHIAH et al. [17] reported good results in the 16 prematures treated by intraamniotic injection of 250 mg of levothyroxine. Triiodothyronine (T_3) is similar to thyroxine (T_4) in its biological action but is more potent on a molar basis [11]. Approximately 20 per cent of T_4 is converted to T_3 [19]. In this study, we investigated the influence of intraamniotic T_3 administration upon fetal plasma

levels of T_3 , TSH, and upon the fetal outcome in patients with impending premature delivery and hypertensive disorders in pregnancy.

2 Patients and methods

Fifteen patients with severe hypertensive disease in pregnancy with threatened spontaneous or elective pre-term deliveries were investigated. The characteristics of the patient population is shown in Tab. I.

Amniocentesis and intraamniotic T_3 injection was performed following ultrasonic localization of the placenta in all cases.

Following amniocentesis, 40 micrograms of T_3 (Triiodothyronine-Glaxo) were injected into the amniotic sac. All patients underwent continuous monitoring till labor and during delivery. Scalp pH values were evaluated in those patients with monitor evidence of fetal distress. Fetal arterial blood samples were collected in a heparinized syringe after delivery and cord clamping. Additional venous blood samples were collected 24, 48 and 72 hours after delivery.

In a control group of eight spontaneous pre-term deliveries of unknown cause without T_3 treatment, cord and venous blood samples from the newborns were collected at identical intervals. Gestational age in this control group was 33.6 ± 1.9 weeks. All patients were free of hypertensive disorders or diabetes mellitus. The modes of delivery were vaginal in six and cesarean section in two cases (Tab. I).

Blood samples were centrifuged at 2000 r.p.m. for 10 minutes, the serum separated and stored at -20°C until analyzed.

Triiodothyronine was analyzed by radioimmunoassay utilizing serulate kits, manufactured by AMES-YISSUM, Jerusalem. The intra-assay coefficient of variance was found to be less than 6%. The cross reactivity of the T_3 anti-serum to thyroxine was found to be less than 0.19%.

The TSH was analyzed by radioimmunoassay utilizing Phadebas kits, PHARMACIA DIAGNOSTICS, Uppsala, Sweden. The test is highly specific, cross reactivity with LH being less than 0.1%, with FSH less than 0.01% and with hCG less than 0.002% by weight.

Tab. I. Characteristics of the patient populations.

	Diagnosis					Labor		Delivery				
	Severe PET	Chronic hypertension & PET	PET & diabetes mellitus	Age/years mean $\pm$ SD	Gest. age mean $\pm$ SD	Elective	Spont.	Cesarean section	Vacuum extraction	Forceps	Assisted breech	Spont. delivery
Treated group	7	6	2	26.8 $\pm$ 2.4	32.4 $\pm$ 2.2	8	7	9	2	2	2	—
	Diagnosis											
	PROM	Plac. previa	Idiopathic prem. delivery									
Control group	2	1	5	24.6 $\pm$ 3.1	33.6 $\pm$ 1.9	3	5	2	—	1	—	5

PET = preeclamptic toxemia PROM = premature rupture of membranes

3 Results

Tab. II shows the interval between T_3 administration and delivery. The shortest interval was six hours and the longest 72 hours.

Tab. II. Interval (hours) between intraamniotic triiodothyronine administration and delivery.

Interval (hours)	No. of patients	Per cent
6-12	3	20
13-24	3	20
25-36	5	33.3
37-48	2	13.3
49-72	2	13.3

Triiodothyronine values in the umbilical cord blood and concurrent venous blood samples in the treated and untreated groups are shown in Tab. III. No significant differences were noted between the two groups.

TSH values of cord blood in the treated group ranged between 2.0 and 8.2 $\mu\text{U/ml}$ ($4.6 \pm 1.8 \mu\text{U/ml}$), while the control group TSH was between 3.0 and 11.2 $\mu\text{U/ml}$ ($5.1 \pm 2.2 \mu\text{U/ml}$), the differences being statistically non-significant.

In seven cases amniotic fluid T_3 levels were evaluated following intraamniotic triiodothyronine injection. The interval between administration of T_3 and sampling ranged from 6 to 51 hours, and amniotic T_3 values ranged from 275 to more than 600 ng/dl. These values are excessively high.

In one patient with a twin pregnancy and pre-eclamptic toxemia, repeat caesarean section was performed at 33 weeks because of fetal acidosis (pH = 7.21) appearing 7½ hours after T_3 instillation into one of the amniotic sacs. No significant

differences between the cord blood T_3 and TSH levels were registered. Twenty four hours after delivery, both twins showed a similar rise of serum T_3 and TSH levels (Fig. 1).

Fig. 1. Plasma T_3 and TSH levels in treated versus untreated twin.

Low APGAR scores (0-6) occurred in ten out of the 15 neonates (67%). In seven cases (43.8%), the newborns suffered from respiratory distress syndrome (RDS) and three of them died. Five out of the seven infants with RDS were born depressed (APGAR 1-6). The characteristics of the group with RDS is presented in Tab. IV.

In the control group, no cases of RDS occurred.

Tab. III. Triiodothyronine levels (ng/dl) in cord blood and consequent blood samples in the two study groups.

Time (hours)	Cord blood	24	48	72
Treated group				
Mean $\pm$ SD	70.2 $\pm$ 10.4	150.5 $\pm$ 38.8	160.6 $\pm$ 32.0	144.7 $\pm$ 34.8
Range	45-85	82-210	98-200	60-208
Untreated group				
Mean $\pm$ SD	71.2 $\pm$ 9.7	167.3 $\pm$ 46.9	190.2 $\pm$ 34.3	153.0 $\pm$ 31.7
Range	60-89	126-260	146-260	102-176

Tab. IV. Characteristics of the RDS group.

Patient	Gest. age weeks	T ₃ inject. delivery interval (hours)	Monitored fetal distress	Scalp pH* or umbilical cord pH	Mode of delivery	Weight (GMS.)	APGAR score	Outcome
KL	29	14	Late decel.	Cord: 7.12	Cesarean section	990	3	Severe RDS
MJ	34	25	Severe variable decel.	Scalp: 7.24	Cesarean section	2650	2	Mild RDS
HS	33	72	Late decel.	Cord: 7.08	Cesarean section	1600	6	Severe RDS, died
GH	28	51	Late decel.	Cord: 7.02	Cesarean section	700	4	Severe RDS, died
ZH	30	40	Severe variable decel.	—	Cesarean section	1200	6	Severe RDS
HR	28	16	Variable decel.	—	Outlet forceps	1200	7	Severe RDS, died
AN	31	8	None	Scalp: 7.31	Outlet forceps	1450	9	Severe RDS

* Scalp pH less than 20 minutes before delivery.

4 Discussion

While glucocorticoids are widely used for enhancing pulmonary maturation in threatened premature labors, their use in pregnancies complicated by a severe hypertensive state is probably contraindicated [13]. In these high risk pregnancies, with a high rate of planned and spontaneous premature labors, other agents which can effect formation of cyclic AMP, increasing the rate of surfactant production may be considered.

Catecholamines, ACTH, glucagon, glucocorticoids, thyroxine and triiodothyronine augment the concentrations of AMP levels through adenylyl cyclase activation. REDDING and DOUGLAS [22] reported an increased number and size of lamellar bodies and amount of surfactant recovered by alveolar washing in adult rats injected with L-thyroxine. WU et al. [27] found that thyroxine injected into rabbit fetuses at 24 days of gestation resulted in accelerated maturation of surfactant system.

Intraamniotic injection of thyroxine in an amount of 200 mcg, enhanced surfactant production as manifested by a decrease in the level of fluorescence polarization (P value) of the amniotic fluid [15]. The same authors found a low incidence of

RDS in a group of patients delivered between 29 and 34 weeks after intraamniotic injection of T₄ [16].

In the present small series of very high risk pregnancies and premature deliveries, intraamniotic injection of T₃ in the amount of 40 mcg had no apparent beneficial effect upon the development of severe RDS. The frequency of RDS was 46.6% (7 out of 15 cases), since it was a selected group with a high incidence of fetal depression and acidosis. The incidence of RDS in such cases is high in spite of mature L/S ratio [26] or following dexamethasone therapy [27]. Further, the injection-delivery interval was wide, ranging from 6 to 72 hours. An animal study showed that an interval of 48 hours was needed to enhance lung maturation after T₄ treatment [27]. In five out of the seven cases with RDS, the injection-delivery interval was less than 48 hours. Moreover, the incidence of RDS is essentially a function of gestational age [7]. The mean gestational age of the seven infants with RDS was 30.4 weeks as compared with 33.1 weeks (excluding the two infants born after 37 weeks) of those without RDS. Finally, fetal blood analysis of T₃ and TSH levels following delivery

showed no evidence of T_3 reaching the fetal compartment.

FISHER et al. [10] have demonstrated a suppression of TSH in human neonates 12–24 hours after intraamniotic injection of T_4 . Those cases were not stressed pregnancies with depressed infants. Since amniotic fluid values of T_3 following injection

in seven cases of our study were found to be very high (275–600 ng/100 ml) as compared to normal levels of 5–30 ng/100 ml reported respectively by ETLING [9] and BURMAN et al. [6], the possibility of malabsorption of amniotic fluid by fetuses in distress cannot be ruled out.

Summary

Intraamniotic thyroxine administration has been reported as beneficial in cases of pregnancy hypertension for fetal pulmonary maturity enhancement.

Triiodothyronine (T_3) similar to thyroxine (T_4) except for its increased potency per mole was administered intraamniotically to 15 hypertensive patients with preterm deliveries. The hypertensive disorder was severe preeclamptic toxemia (7 cases) superimposed preeclampsia upon chronic hypertension (6 patients) and underlying diabetes mellitus (2 patients). Premature labor was elective in 8 and spontaneous in 7 cases. The mean gestational age was 32.4 weeks. The administration-delivery interval following 40 mg intraamniotic T_3 ranged from 6 to 72 hours. Eight untreated spontaneous preterm deliveries (gestational age 33.6 weeks) served as a control group.

Blood samples were collected from the umbilical cord and from the newborn at intervals of 24, 48 and 72 hours following delivery. Triiodothyronine and TSH levels were investigated by radioimmunoassay methods. Cord blood T_3 levels were similar in the treated (70.2 ± 10.4 ng/dl)

and the control groups (71.2 ± 9.7 ng/dl). There were no significant differences in T_3 concentration between the two groups 24, 48 and 72 hours after delivery. TSH values of cord blood in the study group ranged between 2.0 and 8.2 μ U/ml (mean 4.6 μ U/ml) and in the control group between 3.0 and 11.2 μ U/ml (mean 5.1 μ U/ml). These differences are not statistically significant. In the seven cases where amniotic fluid T_3 were determined at delivery, levels were excessively high (275–600 ng/dl). Low

APGAR scores were noted in 10 of the 15 neonates. Respiratory distress syndrome occurred in seven cases (43.8%) with three deaths.

The present study of 15 very high-risk, hypertensive patients with preterm deliveries does not seem to reveal any positive effect of 40 mcg intraamniotic T_3 administration upon the incidence and severity of respiratory distress syndrome.

Fetal blood analysis of T_3 and TSH levels following delivery showed no evidence of triiodothyronine reaching the fetal compartment in these highly stressed pregnancies.

Keywords: Cord blood T_3 , prematurity, Respiratory Distress Syndrome, Triiodothyronine, TSH.

Zusammenfassung

Intraamniotische Instillation von Triiodthyronin zur Prävention eines RDS bei Hypertonus in der Schwangerschaft

Es wurde berichtet, daß die intraamniotische Gabe von Thyroxin bei hypertonen Schwangeren einen günstigen Effekt auf die fetale Lungenreifung hat. Wir verabreichten ebenfalls intraamniotisch Triiodthyronin (T_3), welches eine im Vergleich zu T_4 stärkere Wirkung hat, an 15 hypertone Patientinnen mit vorzeitiger Entbindung. Bei 7 Patientinnen trat der Hypertonus im Zusammenhang mit einer schweren Präeklampsie auf, 6 Patientinnen hatten einen chronischen Hypertonus mit aufgesetzter präeklampsischer Komponente und 2 Patientinnen litten an einem Diabetes mellitus. Die vorzeitige Entbindung war in 8 Fällen geplant, in 7 spontan. Das mittlere Gestationsalter betrug 32.4 Wochen; die Dauer der Geburt nach Applikation von 40 mg T_3 lag zwischen 6 und 72 Stunden.

In der Kontrollgruppe waren 8 spontane vorzeitige Entbindungen mit einem mittleren Gestationsalter von 33.6 Wochen zusammengefaßt.

Wir haben einmal aus der Nabelschnur und auch beim Neugeborenen 24, 48 und 72 Stunden post partum Blut entnommen und radioimmunologisch T_3 und TSH bestimmt. Der T_3 -Spiegel im Nabelblut der behandelten Gruppe (70.2 ± 10.4 ng/dl) war vergleichbar mit dem Wert der Kontrollgruppe (71.2 ± 9.7 ng/dl). Auch 24, 48 und 72 Stunden post partum zeigten sich keine signifikanten Unterschiede zwischen behandelter und unbehandelter Gruppe. Die TSH-Werte im Nabelschnurblut lagen zwischen 2.0 und 8.2 μ U/ml (im Mittel 4.6 μ U/ml) im behandelten Kollektiv und zwischen 3.0 und 11.2 μ U/ml (im Mittel 5.1 μ U/ml) in der Kontrollgruppe. Diese Unterschiede waren nicht statistisch signifikant. In den 7 Fällen, wo wir T_3 im Fruchtwasser unter der Geburt bestimmten, erhielten wir extrem hohe Werte (275 bis 600 ng/dl). Bei 10 der 15 Neugeborenen wurde ein niedriger APGAR-Score gefunden. Ein RDS trat in 7 Fällen auf (43.8%), 3 Kinder starben.

Die vorliegende Untersuchung an 15 Risikopatientinnen mit Hypertonie und vorzeitiger Entbindung zeigt, daß die

intraamniotische Gabe von 40 mg T₃ keinen Einfluß auf die Inzidenz und den Ausprägungsgrad eines RDS hat. Wie die Fetalblutanalyse auf T₃ und TSH ergibt, scheint

das Trijodthyronin erst gar nicht in die fetalen Kompartimente zu gelangen, zumindest nicht bei diesen Risikoschwangerschaften.

Schlüsselwörter: Frühgeborene, RDS, T₃ im Nabelschnurblut, Trijodthyronin, TSH.

Résumé

Injection intra-amniotique de triiodothyronine pour prévenir le syndrome de détresse respiratoire au cours des grossesses compliquées d'hypertension

On a rapporté l'intérêt de l'injection intra-amniotique de thyroxine dans le cas d'hypertension gravidique afin d'améliorer la maturité pulmonaire foetale.

Les auteurs ont injecté dans la cavité amniotique, chez 15 patientes hypertendues ayant accouché prématurément, de la triiodothyronine (T₃) analogue à la Thyroxine (T₄) à l'exception d'une plus grande efficacité par mole.

Il s'agit de patientes avec une pathologie hypertensive sévère: prééclampsie (7 cas), prééclampsie surajoutée à une hypertension (chronique (6 patientes) et hypertension) avec diabète sucré sous-jacent (2 patientes) — l'âge gestationnel moyen est de 32,4 semaines. Le délai entre l'injection intra-amniotique de 40 mg de T₃ et l'accouchement a été de 6 à 72 heures.

Un groupe témoin a été constitué par 8 patientes non traitées ayant accouché prématurément de façon spontanée (âge gestationnel moyen: 33,6 semaines).

Des prélèvements de sang ont été effectués sur le cordon ombilical et chez le nouveau-né 24, 48 et 72 heures après l'accouchement. Les concentrations de Triiodothyronine et de TSH ont été déterminées par radioimmunologie.

Les concentrations de T₃ au sang du cordon sont semblables dans le groupe traité (70,2 ± 10,4 ng/dl) et dans le groupe témoin (71,2 ± 9,7 ng/dl). On n'a pas trouvé de différence significative dans les concentrations de T₃ dans les 2 groupes, 24, 48 et 72 heures après l'accouchement.

Dans le groupe traité les concentrations de TSH au sang du cordon sont comprises entre 2 et 8,2 µU/ml (moyenne: 4,6 µU/ml) et entre 3 et 11,2 µU/ml (moyenne: 5,1 µU/ml) dans le groupe témoin. Ces différences ne sont pas statistiquement significatives. Dans les 7 cas où l'on a déterminé la concentration amniotique en T₃, les taux ont été trouvés élevés de façon très importante (275–600 ng/dl). Un score d'APGAR bas a été noté chez 10 des 15 nouveau-nés. Un syndrome de détresse respiratoire est survenu dans 7 cas (43,8%) avec 3 décès.

Cette étude chez 15 patientes à très haut risque, hypertendues, ayant accouché prématurément ne semble pas mettre en évidence une action positive de l'administration intra-amniotique de 40 mcg de T₃ sur l'incidence et la sévérité du syndrome de détresse respiratoire.

Les dosages de T₃ et de TSH dans le sang du nouveau-né ne mettent pas en évidence de passage de la Triiodothyronine dans le compartiment foetal au cours de ces grossesses à hauts facteurs de stress.

Mots clés: Triiodothyronine, syndrome de détresse respiratoire T₃ au sang du cordon, TSH prématurité.

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