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The effect of intraamniotic thyroxine administration on fetal lung maturity in man

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1 Introduction

The best treatment of respiratory distress syndrome (RDS) is preventive. The occurrence of the syndrome can be lessened by the antenatal assessment of fetal lung maturity, thus leading to an improved selection of pregnancies for induction. Parallel to this passive management many efforts have been made to accelerate the physiological synthesis of pulmonary surfactant.

LIGGINS and HOWIE [8] were the first to demonstrate a decrease in RDS in premature infants by the antenatal administration of Betamethasone to the mother. Since then other corticosteroids and other routes of administration have also come into use [2, 17].

Due to the theory that the increase in the phospholipid component of surfactant may be mediated by thyroxine, its use for accelerating fetal lung maturity has been tested.

Experimental studies in rats and rabbits have demonstrated the effect of thyroxine in accelerating fetal lung maturity [11, 18]. In humans thyroxine has been injected into the amniotic sac for other purposes 12–24 hours prior to delivery without any early deleterious effect to mother or newborn [4]. These observations provided the basis for using this hormone in pregnant women in order to accelerate fetal lung maturity.

Curriculum vitae

SHLOMO MASHIACH, born in Tel-Aviv, Israel in 1937. Graduated (M.D.) at the Hebrew University, Hadassah Medical School in Jerusalem in 1961. Training in Obstetrics and Gynecology at Sheba Medical Center, Tel-Hashomer, Israel, 1971. Senior Lecturer in Obstetrics and Gynecology at the School of Medicine in the University of Tel-Aviv. Since

1975 Deputy Director at the Department of Obstetrics and Gynecology at Sheba Medical Center Tel Hashomer. In 1968 was awarded a year prize for the best work published in Hebrew on Combined Treatment of Sterility with Human Menopausal Gonadotropins and Clomiphene Citrate. Member of International Fertility Association. Current studies: Diagnosis of fetal condition by ultrasound and alpha-feto-protein. Evaluation of fetal lung maturity by a new method of measuring the microviscosity of the amniotic fluid. The influence of thyroxine and cortico-steroids on fetal lung maturation.

Reports in the literature have also demonstrated the link between low thyroxine levels and an increased incidence of RDS [3, 15]. Our preliminary report showed promising results using thyroxine to accelerate human fetal lung maturity [9]. The results presented here are those of an extended and controlled study.

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The object of this study was to ascertain the effect of thyroxine administration on the biochemical and clinical maturation of fetal lung.

Thyroid hormone was injected intra-amniotically in 16 high risk pregnancies between 29–34 weeks. The incidence of RDS and the fetal lung maturity were then examined and compared to a control group.

Fetal lung maturity was determined in the following study by a new method based on a fluorescence polarization technique [14].

2 Materials and methods

The physical basis of this new method of assessment of fetal lung maturity stems from the empirical relation between the viscosity and surface tension of fluids. Both of these physical parameters are determined by the intermolecular forces of the fluid and are therefore interrelated. The correlation between these parameters implies that the surface tension of the pulmonary surfactant can be translated into an intrinsic viscosity parameter which may be expressed in terms of microviscosity [13]. The efficient technique for determination of lipid microviscosity is by fluorescence depolarization of a hydrocarbon probe 1,6-diphenyl 1,3,5-hexatriene (DPH) embedded in the core of the system. The detected degree of fluorescence polarization P is directly related to the rotational motion of the probe and therefore to the microviscosity of the hydrocarbon region of the lipid assembly. Measurements are carried out with a highly accurate microviscosimeter now termed FELMA* [14].

3 Determination of P

One ml of amniotic fluid centrifuged at 1000 PRM for 10 minutes is mixed with four ml of DPH dispersion and is incubated at 37°C for 30 minutes. The sample is then allowed to cool to room temperature and is ready for determination of the fluorescent polarization P .

Fluorescence polarization P is not a linear parameter, therefore we have tried in a previous study to translate it into viscosity units ϵ = Poise.

* FELMA – Fetal lung maturity analyzer, Elscint Ltd., Haifa, Israel.

In the present study we are using again the P value for it is already well accepted in several centers and practically, P values obtained from amniotic fluid samples are all within the linear zone of the scale.

In the first publication using that method [14] fetal lung maturity was defined as a P value of 0.310 or below. Since then with some experience of the method $P = 0.315$ (0.312 ± 0.005) is taken as the upper limit of maturity.

All amniotic fluid samples were obtained by trans-abdominal amniocentesis. Any sample contaminated by blood or meconium was discounted.

4 Selection of patients

183 amniotic fluid samples were obtained in order to determine the lung maturity (P) at different stages of pregnancy. This series comprises pathological pregnancies (e.g. premature contractions, pre-eclamptic toxemia, rhesus incompatibility, diabetes, placental insufficiency and placenta praevia) in which premature delivery was inevitable or necessary, and also normal pregnancies examined prior to elective caesarean section. The study was carried out in two stages.

In the first stage the microviscosity (P) of 104 pathological pregnancies was measured in order to evaluate the advisability of early delivery. When the data from this group was found to be reliable by clinical confirmation, thyroxin was administered to 16 other patients who were between 29–34 weeks of pregnancy. The 104 patients of the first stage of this study were therefore regarded as a control group as compared to the second group of 16 patients who received treatment.

4.1 Untreated group – 138 amniotic fluid samples were obtained from 104 untreated cases. The results of these samples were used in order to plot the P value curve as a function of gestational age.

73 out of these samples were obtained once from singleton pregnancies. 25 were obtained twice from singleton pregnancies 3 were obtained three times from singleton pregnancies and 3 samples were obtained once each from multiple pregnancies (one sample per sac).

The untreated group itself is confined to those 50 amniotic fluid samples which were withdrawn

from 38 pregnant women between 29–34 weeks which was the gestational period under study.

The remaining 88 amniotic fluid samples from the untreated group are not included as they do not fall within the range of gestational age of the experimental group.

4.2 Experimental group: The experimental group comprised 16 patients in whom amniocentesis was performed at a gestational age 29–34 weeks. In 8 cases two amniotic fluid samples were taken. In 3 cases, 3 amniotic fluid samples, and in the remaining 5 patients four samples were taken in each case. A total therefore of 45 amniotic fluid samples were taken in this experimental group.

4.3 Group matching: Both the experimental and control groups were divided into three subgroups according to gestational age.

Sub-group I (29–30 weeks) consisted of 18 control cases and 2 treated cases.

Sub-group II (31–32 weeks) consisted of 7 control cases and 6 treated cases.

Sub-group III (33–34 weeks) consisted of 25 control cases and 8 test cases.

The distribution of pathologies in these groups is shown in Tabs. Ia, b, c.

Tab. 1a. The distribution of pathologies in both treated and untreated cases. Sub group I (29–30 weeks).

Pathology	Untreated group	Experimental group
Rhesus incompatibility	2	
Premature contractions	9	1
Preeclamptic toxemia	3	1
Diabetes	3	
Placenta praevia	1	
Total	18	2

Tab. 1b. The distribution of pathologies in both treated and untreated cases. Sub group II (31–32 weeks).

Pathology	Untreated	Experimental
Premat. cont.	3	1
Preeclamptic Toxemia	2	3
Diabetes	2	2
Total	7	6

Tab. 1c. The distribution of pathologies in both treated and untreated cases. Sub group III (33–34 weeks).

Pathology	Untreated	Experimental
Prem. cont.	7	2
Preeclamptic toxemia	6	2
Diabetes	5	2
Placenta praevia	3	1
Rh incompatibility	1	
Placental insufficiency	3	1
Total	25	8

4.4 The criteria and conditions used in the selection of patients were:

1. The thyroxine injection and date of delivery, both occurred between 29–34 weeks when there was no doubt as to gestational age.
2. The P value was determined before and after the administration of T_4 in order to ascertain the effect of T_4 on this parameter.
3. Clinical follow-up was carefully recorded during the neonatal period.
4. A unified approach to treatment of pathological conditions was strived for both the experimental and the untreated groups.
5. No additional treatment (e.g. steroids) was administered to either groups for the acceleration of fetal lung maturity.

4.5 Multiple pregnancies: In the entire series there were 5 cases of multiple pregnancy. 3 sets of twins in the control group 1 set of twins in the experimental group and 1 set of triplets in the experimental groups.

In the cases of multiple pregnancy in order to ensure that we were handling the individual sacs, we used ultrasonography to ascertain the position of the fetuses and dye* was added to differentiate the sacs from one another. The technique in the use of the dye was to inject it into first sac after amniocentesis had been performed in that sac, so that when the amniocentesis was performed in the second sac, the colourless fluid withdrawn was a proof of puncture of a different sac.

* Indigocarmine 0.4%

In the cases of triplets, dye was injected also into the second sac (following the amniocentesis in that sac).

In those cases in which a repeat amniocentesis was performed, the above procedure was carried out, but a radiopaque medium** was used in place of regular dye. The amniotic fluid samples were placed in tubes which were then X-rayed in vitro.

4.6 Thyroxine administration: Prior to each injection of thyroxine, 20 ml of clear fluid were obtained by amniocentesis. 250 µg of Levothyroxine*** were then injected through the same needle. In all cases a recording of the fetal heart beats was made for some hours following the injection in order to diagnose fetal tachycardia or any other kinds of arrhythmia as a possible sign of T₄ overdose.

The only criterion for the administration of a second T₄ injection was the P value of the previous amniocentesis.

4.7 RDS was defined as follows:

1. Grunting
2. Sternal and intercostal retractions
3. An X-ray picture of reticular granularity and an air bronchogram.
4. Tachypnea
5. Cyanosis in room air
6. Alae nasi movements

A diagnosis was not regarded as certain unless at least criteria, 1, 2 and 3 were present.

5 Results

The effect of intra-amniotic T₄ injection on the dynamics of fetal lung ripening in 16 cases is shown in Fig. 1. In 14 cases the fetal lungs matured (P value ≤ 0.315), in 6 bases after one injection and in other cases after two or more injections. One case of the 14 was already mature when the first amniocentesis was performed. In two cases maturity was not achieved, though in one of them

the Fluorescence polarization value "P" was borderline (P = 0.317).

The mean P value after thyroxine administration were compared to the mean P values in the control group where P values of amniotic fluid samples were determined but T₄ was not given. (Fig. 2).

No statistical evaluation was made in experimental sub-group I (29–30 weeks) as there were too few cases.

In subgroup II (31–32 weeks) there was a statistically significant difference (P < 0.005).

The clinical details of the 16 patients are shown in Tab. II. Each of the fetuses was delivered before 34 weeks. Nine were delivered by caesarean section for various indications, and seven vaginally, of which four with pathological presentations. The birth weights of the premature infants were between 900–2900 grams and RDS was seen in only one infant.

21 out of the 38 pregnant women who comprise the control group gave birth beyond the 34th week of pregnancy, in four of these newborns RDS developed.

6 Discussion

One of the methods available to prevent intra-uterine death in high risk pregnancies is to induce labor prematurely. The dilemma faced when deciding upon the management, however, is in exposing the premature infant to RDS (especially under 34 weeks). The use of pharmacological agents for accelerating fetal lung maturity is an important approach demanding further investigation and development.

Corticosteroids have proved to be an acceptable method for accelerating lung maturity. In cases of high risk pregnancy, however, such as toxemia and placental insufficiency, where acceleration of maturity is most needed, there is a relative contraindication to giving steroids [8]. The incidence of intra-ventricular cerebral hemorrhage has been reported to be higher in RDS infants who have received steroids than in a control group [1, 16]. Therefore, the search for other modes of treatment is understandable.

As far as we know thyroxine has never been used to accelerating fetal lung maturity in the human.

** Diatrizoate sod. 50% (Triognost)

*** Synthroid (Flint Laboratories, USA).

Fig. 1. The effect of intra amniotic T_4 administration on the dynamics of fetal lung ripening in 16 cases. The black dots indicate amniocentesis followed by T_4 administration. The clear circles indicate amniocentesis not followed by administration of T_4 . The broken horizontal line at level $P = 0.315$ indicates that value which corresponds with the threshold of fetal lung maturity.

This in spite of encouraging results in animals [11, 18], and the lack of early side effects to mother and infant reported by FISHER et al. [4]. Since thyroxine does not cross the placenta in significant quality [6] it is necessary to inject it directly into the amniotic sac. The

fetus absorbs the hormone from the liquor as if it had been injected intrafetally [12].

Whilst our interest in the human lies in the acceleration of lung maturity following administration of thyroxine to the fetus, note must be taken of the reported effects upon brain development

Fig. 2. Mean P values of 14 cases after T_4 treatment and 138 cases with no such a treatment. The curve indicates the change in mean P value and in the standard deviation with gestational age in 138 samples of the 104 untreated cases. The two marks at level 31-32 weeks and 33-34 weeks respectively indicate the mean P value and the standard deviation of experimental subgroups II & III.

following administration of T_4 to newborn rats [10].

Carefull follow-up on human newborns regarding some possible influence of T_4 on the central nervous system is being carried out. So far no abnormality has been noted.

The dosage of 250 μ g was arrived at in a preliminary study carried out in our department [9]. This dose is thrice the daily production of T_4 and its possible effect on the treated fetus [7].

This study, being a retrospective one, requires careful evaluation to achieve statistical significance. Patients in this study were admitted only according to strict criteria previously described.

In 28 high risk pregnancies or inevitable premature deliveries T_4 was injected into the amniotic sac. Only 16 cases fulfilled these criteria. All the other 12 cases were discounted because of the impossibility to fulfill either one or more of the mentioned above criteria and conditions used in the selection of patients. Eight of them were discounted because of the impossibility of re-examining the P value after treatment (either due to the intervention of labor, or contamination of the sample with blood or meconium). One of these 12 developed RDS.

In all 16 cases the P value fell after injection. 13 of these cases achieved maturity ($P < 0.315$) after one or more injection of T_4 . In one case (K.S.) P value was already mature spontaneously in the first amniocentesis. In another case (L.V.) the value reached the threshold of maturity and in a third case (K.N.) labor occurred one week after the first injection and 6 hours after the second of T_4 , when the P value was still 0.350.

Determination of fetal lung maturity with the Fetal Lung Maturity Analyzer "FELMA" enables us to observe the dynamics of surfactant production.

We intend to publish in the near future, the results of studies performed by us from which we feel confident to conclude that the P value can be used as a reliable indicator of fetal lung maturity. In these studies, over a period of three years, we analyzed several hundreds of samples with the microviscosimeter FELMA and compared these results with the L/S ratio, the "foam test" and the clinical outcome of the newborn.

T_4 in itself does not interfere with the fluorescence polarization of the examined samples as the P value of T_4 solution was measured and was found to be undetectable.

Tab. II. Clinical details of the treated patients.

Indication	Age at delivery (weeks)	Mode of delivery	Weight (grams)	Apgar Score 1 min.	Outcome
1. Z.E. Premature contractions	31,2/7	Vaginal (Breech)	1740	0	No RDS*
2. K.G. Toxemia + Severe placental insufficiency	32,2/7	L.S.C.S.	940	5	No RDS
3. S.E. Premature contractions	30,1/7	Vaginal	900	9	No RDS
4. S.R. Placenta praevia	33	L.S.C.S.	2340	9	No RDS
5. L.D.a Multiple pregnancy	32,4/7	L.S.C.S.	1380	7	No RDS
6. L.D.b Premature contractions	32,4/7	L.S.C.S.	1640	7	No RDS
7. A.A. Juvenile diabetes	33	L.S.C.S.	2600	8	No RDS
8. H.M. Toxemia	30	L.S.C.S.	1070	4	RDS PDA**
9. F.S. Multiple pregnancy premature contractions	31,3/7	L.S.C.S.	1310	6	No RDS
10. K.A. Juvenile Diabetes + Toxemia	33	L.S.C.S.	2200	8	No RDS
11. L.V. Toxemia	31	L.S.C.S.	1010	7	No RDS
12. G.D.a Multiple pregnancy – triplets Premature contractions	32,2/7	Vag. vertex	1870	10	No RDS
13. G.D.b Triplets – Premature contractions	32,2/7	Vaginal (Breech)	1690	9	No RDS
14. G.D.c Triplets – Premature contractions	32,2/7	Internal version	1260	7	No RDS
15. K.N. Premature contractions	29,6/7	(Vag. (face)	1960	6	no RDS
16. K.S. Juvenile diabetes	33,5/7	L.S.C.S.	2900	7	No RDS

* RDS = Respiratory Distress Syndrome

** PDA = Patent Ductus Arteriosus

In order to determine whether the change in P value was an expression of thyroxine treatment and not merely due to gestational age, we compared mean P values after a course of thyroxine treatment and mean P values in an untreated control group. The control group comprised the same pathological spectrum as the test group.

Treatment for the specific pathological state when indicated was identical in both groups of patients.

Because the test group was small it was divided into subgroups of 2 weeks and not into separate weeks.

In the subgroup I (29–30 weeks) there were only 2 cases, therefore, it was impossible to carry out statistical analysis on them and they were not included in Fig. 2.

As can be seen from the results in Fig. 2 there is a statistically significant difference in the mean results of the subgroup II (31–32 weeks) and III (33–34 weeks) and their respective control groups. It seems logical to explain these effects as resulting from the action of T_4 on surfactant synthesis.

Thyroid hormones fundamental actions are not entirely understood.

Although it requires up to several days before a major clinical effect with T_4 is manifest, in adults, it seems that T_4 can act solely without converting to T_3 [4]. Hence it is not impossible to explain the somewhat fast biological effect of T_4 on few cases in the present study.

The object of the study was to ascertain the effect of T_4 administration on the P value as an expres-

sion of fetal lung maturity. Thus it is clear why we discarded those cases in which we didn't have both a pre- and post treatment P value.

As amniocentesis itself is an invasive procedure it was only carried out in high risk pregnancies when the information gained justified the intervention. Most of the patients in the control groups were examined before T_4 was in use and the relative contraindications to using steroids on those patients left them without specific treatment for accelerating fetal lung maturity.

The only criterion for the readministration of T_4 in the experimental group was the P value of amniotic fluid sample obtained by a previous amniocentesis.

It is to be noted that in no case was there any difference in fetal heart rate pattern before or after T_4 administration recorded.

Table II shows that only 1 of the 16 cases (H.M.) developed RDS. This infant was delivered by Caesarean section at 30 weeks because of severe toxemia and acute fetal distress. After intensive treatment which included administration of Indomethacin in order to close the patent ductus arteriosus (according to FRIEDMAN et al. [5]), the infant made an uneventful recovery.

It is quite difficult to explain the incidental RDS in case No. 8 (H.M.) in spite of a mature P value ($= 0.306$). However, one cannot ignore the predisposing factors for RDS in this particular case such as prematurity, severe perinatal asphyxia caused by the fulminant toxemia and the urgent caesarean section.

In case No. 15 (K.N.) no RDS was developed although P value indicated immaturity of the fetal lungs ($P = 0.350$), in spite of previous T_4 injection.

Keeping in mind the possibility of false negative and false positive rates of any method, it is not impossible to presume that antenatal evaluation

of surfactant content in amniotic fluid is not the single meansto predict the development of RDS post-natally.

In the two cases of multiple pregnancy the development of fetal lung maturity, including the responsiveness of each fetus to the T_4 treatment was individual and independent. (Fig. 1).

As can be seen from Tab. II, 15 out of the 16 treated patients who delivered between 29–34 weeks did not develop RDS despite the high caesarean section rate (50%); and the high incidence of pregnancy complications.

Data from small groups cannot be evaluated statistically. However, the incidence of RDS in the test group is below the expected rate. Only one case of RDS was recorded out of the 16 treated premature pregnancies whereas 4 cases developed RDS out of 9 premature untreated infants.

There are two disadvantages for this procedure of enhancement of fetal lung maturity: a) amniocentesis has to be performed; b) It is not practical to inject T_4 intra-amniotically in cases of Premature Rupture of Membranes. It may be possible however, in these cases to inject T_4 intrafetally.

At the moment there is no way of checking the absorption of T_4 from the amniotic fluid. It is possible that in these cases requiring more than one injection there may have been malabsorption of the hormone.

This malabsorption may be due to the primary pathology of the pregnancy or a temporary response to acute fetal distress.

FISHER et al. have already demonstrated a suppression of serum Thyroid Stimulating Hormone (TSH) in human neonates 12–24 hours after injection of T_4 intraamniotically [4]. This aspect of the study is at present being investigated by measuring serum T_4 and TSH levels at birth and during the first 24 hours.

Summary

In this study we set out to examine the effect of thyroxine injection intraamniotically on the acceleration of fetal lung maturity.

183 samples of amniotic fluid from pathological pregnancies were examined at different stages of pregnancy; to determine fetal lung maturity by the evaluation of

"P" (a measurement dependent on microviscosity) previously described.

16 cases between 29–34 weeks received intra-amniotic thyroxine in order to accelerate the development of fetal lung maturity. In all 16 cases there was a significant improvement in the degree of lung maturity. 14 newborns

were definitely mature. The desired maturity was not achieved in only two cases.

The results of these 16 cases were compared to a control group (untreated) which were chosen because of an identical gestational age and the same types of pathology. There was a statistically significant difference in the pulmonary maturity value 'P' after use of thyroxine in comparison to the control groups.

In 15 of the 16 treated cases, there was no RDS (Respiratory Distress Syndrome), and this in spite of the fact that they were all born before 34 weeks of pregnancy, and nine of them by Caesarean Section.

In view of these results it seems that thyroxine treatment is one of the most efficient methods of preventing RDS in high risk pregnancies in which there is an indication for early induction of labor.

Keywords: Fetal lung maturity, respiratory distress syndrome (RDS), thyroxine treatment.

Zusammenfassung

Der Einfluß von Thyroxingaben in das Fruchtwasser auf die fetale Lungenreife beim Menschen

In der vorliegenden Untersuchung sollte der Einfluß einer intraamniotischen Thyroxininjektion auf die Beschleunigung der fetalen Lungenreife geprüft werden.

Es wurden 183 Fruchtwasserproben von pathologischen Schwangerschaften in verschiedenen Stadien entnommen. Zur Bestimmung des Lungenreifegrades wurde der Faktor "P" berechnet, der – wie beschrieben – ein Maß in Abhängigkeit von der Mikroviskosität darstellt.

In 16 Fällen wurde bei Schwangerschaften zwischen der 29. und 34. Woche Thyroxin verabreicht, um eine Beschleunigung der Lungenreife zu induzieren. Bei allen 16 Fällen konnte eine signifikante Zunahme des Reifegrades der fetalen Lunge festgestellt werden. 14 Neugeborene waren dementsprechend matur, während in 2 Fällen der gewünschte Effekt nicht erreicht werden konnte.

Die Ergebnisse in dieser Gruppe wurden mit denen einer unbehandelten Gruppe verglichen. In dieser Kontrollgruppe waren Schwangerschaften zusammengefaßt, die in Bezug auf Gestationsalter und Pathologie mit der ersten Gruppe identisch waren. Es zeigte sich ein statistisch signifikanter Unterschied zwischen der mit Thyroxin behandelten Gruppe und der Kontrollgruppe.

Bei 15 der 16 Kinder aus der behandelten Gruppe entwickelte sich kein RDS (Respiratory distress syndrome), wobei es zu berücksichtigen gilt, daß alle Kinder vor der 34. Schwangerschaftswoche geboren wurden, davon 9 durch Sectio caesarea.

Die Ergebnisse lassen vermuten, daß die Behandlung mit Thyroxin eine der effizientesten Methoden darstellt, ein RDS bei Risikoschwangerschaften, in denen eine Indikation zur vorzeitigen Entbindung vorliegt, zu verhindern.

Schlüsselwörter: Fetale Lungenreife, RDS, Thyroxinbehandlung.

Résumé

Effet de l'administration de thyroxine intraamniotique sur la maturité pulmonaire foetale chez l'homme

Nous nous sommes proposés d'examiner dans cette étude l'effet de l'injection intraamniotique de thyroxine sur l'accélération de la maturité pulmonaire foetale. Nous avons observé 183 échantillons de liquide amniotique de grossesses pathologiques à différentes périodes en vue de déterminer la maturité pulmonaire foetale par l'évaluation de «P» (mesure dépendant de la microviscosité) décrite antérieurement. 16 cas entre la 29 et la 34ème semaine de grossesse ont reçu de la thyroxine par injection intraamniotique afin d'accélérer le développement de la maturité pulmonaire foetale. Dans tous les 16 cas nous avons pu observer une amélioration significative sur ce point. 14 nouveaux-nés sur 16 ont atteint la maturité désirée.

Nous avons comparé les résultats de ces 16 cas avec ceux de groupes de contrôle (n'ayant subi aucun traitement) sélectionnés selon l'identité de l'âge gestationnel et des caractères pathologiques. Nous avons relevé une différence statistiquement significative dans la valeur «P» de maturité pulmonaire entre les sujets ayant reçu de la thyroxine et ceux des groupes de contrôle. Dans 15 des 16 cas il n'y a pas en trace d'asphyxie périnatale, et cela en dépit du fait qu'ils soient tous nés avant la 34ème semaine de grossesse et que neuf d'entre eux aient été accouchés par césarienne.

Devant ces résultats il semble que le traitement de thyroxine représente l'une des méthodes les plus efficaces de prévention d'asphyxie périnatale dans les grossesses à haut risque avec indication d'une induction précoce du travail.

Mots-clés: Asphyxie périnatale, maturité pulmonaire foetale, traitement de thyroxine.

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