Antenatal corticosteroids for threatened labor facilitate thyroid maturation among preterm neonates

Journal:	*Clinical Endocrinology*
Manuscript ID	CEN-2020-000290.R3
Manuscript Type:	3 Original Article - Australia, Japan, SE Asia
Date Submitted by the Author:	n/a
Complete List of Authors:	Hanaoka, Shintaro; Kyoto University Graduate School of Medicine Faculty of Medicine, Pediatrics Iwanaga, Kougorou; Fac. Medicine, Kyoto University, Pediatrics Tomotaki, Seiichi; Kyoto University Graduate School of Medicine Faculty of Medicine, Pediatrics Niwa, Fusako; Kyoto university, Pediatrics; Takita, Junko; Kyoto University Graduate School of Medicine Faculty of Medicine, Pediatrics Kawai, Masahiko; Fac. Medicine, Kyoto University, Pediatrics
Key Words:	antenatal corticosteroids, preterm, Thyroid, Cortisol < Hormones/related: < Adrenal, Thyrotropin-Releasing Hormone < Hormones/related: < Hypothalamus

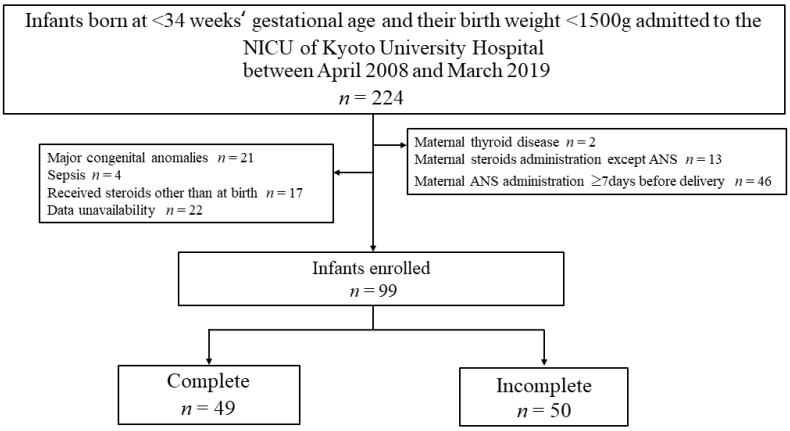

Figure 1. Flowchart of subject enrollment

338x190mm (96 x 96 DPI)

Antenatal corticosteroids for threatened labor facilitate thyroid maturation among preterm neonates

Antenatal steroids induce thyroid maturation

Shintaro Hanaoka, MD, Kogoro Iwanaga, MD, Seiichi Tomotaki, MD, Fusako Niwa, MD, PhD ,Junko Takita,MD, PhD, Masahiko Kawai, MD ,PhD

Department of Pediatrics, Graduate School of Medicine, Kyoto University, 54 Kawara-machi, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.

Tel.: +81 75 751 3554; Fax: +81 75 752 3638

Corresponding Author: Shintaro Hanaoka, Department of Pediatrics, Graduate School of Medicine, Kyoto University, 54 Kawara-machi, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.

Tel.: +81 75 751 3554. Fax: +81 75 752 3638. E-mail: hanaokas@kuhp.kyoto-u.ac.jp

Acknowledgments: We thank James Cummins, PhD, from EDANZ Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Word count: 2090 words

Conflict of interest:

The authors do not declare any conflict of interest or financial involvement with this manuscript.

Abstract

Objective:

To examine the effect of Antenatal corticosteroids (ANS) on the maturation of thyroid function in the preterm infants.

Context:

ANS reduce mortality and morbidities in preterm neonates. Organ maturation by the glucocorticoids is the key, at least in part. However, the effect of ANS on thyroid are controversial.

Patients:

A study group of 99 very low birthweight neonates (<34 weeks' gestational age) with the exception of those born more than 7 days after ANS administration were divided into a complete group (n = 49) whose mothers completed two doses of betamethasone and who were born more than 24 h after the completion of ANS administration, and an incomplete group (n = 50) who were not exposed to any ANS or were born within 24 h after the completion of ANS administration. Serum free thyroxine and thyroid stimulating hormone (TSH) levels were measured and thyrotropin-releasing hormone **(**TRH) stimulation tests were performed at about 2 weeks of age.

Results:

The incidence of hyperthyrotropinemia (TSH > 15 mIU/L) in the complete group was significantly lower than in the incomplete group (6% vs, 22%, P = 0.023). Exaggerated responses to TRH tests were more frequent in the incomplete group (17% vs. 44%; P = 0.053). TSH_{30} was significantly lower in the complete group, (P = 0.046). Multivariate logistic regression analysis showed that the incidence of

hyperthyrotropinemia was associated with complete ANS administration (adjusted odds ratios 0.39).

Conclusions:

ANS administration might facilitate thyroid maturation in preterm neonates.

Keywords:

Aantenatal corticosteroids**,** preterm**,** thyroid, cortisol, thyrotropin-releasing hormone

Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Main Text File

Main text

1.| INTRODUCTION

Advances in perinatal care have improved the prognosis for preterm neonates.[1,2] Among them, the

administration of antenatal corticosteroids (ANS) is one of the most effective. Since Liggins et al. first reported that maternal ANS administration reduced the incidence of neonatal respiratory distress syndrome (RDS) in 1972,[3] its clinical efficacy has been verified in many studies.[4-6] The beneficial effects of ANS have been reported not only in reducing the incidence of RDS, but also in reducing the incidence of mortality, intraventricular hemorrhage, periventricular leukomalacia, and necrotizing enterocolitis.[7,8] As the mechanism of ANS in reducing the incidence of RDS is considered to involve organ maturation in the lungs by facilitating differentiation into Type 2 pulmonary epithelial cells, this effect might contribute to a reduction in other morbidities in preterm neonates, at least in part. On the other hand, the suppression of somatic cell growth by ANS might result in unfavorable effects on the somatic and developmental outcome, is of concern.[9,10] With increasing numbers of mothers receiving ANS, it is important to examine both the favorable and unfavorable effects of this intervention.

Endocrine function is one of the key factors that might influence psychomotor development in preterm neonates.[11–13] Thyroid function is considered a key issue among them.[14–16] Although preterm neonates do not often have primary hypothyroidism with elevated thyroid stimulating hormone (TSH) levels,[17] preterm infants frequently show thyroidal dysfunctions. Many have transient hypothyroxinaemia of prematurity (THOP),[18] however there is no consensus for the treatment with thyroid hormones. Delayed elevation of TSH is also common in preterm infants, but treatments for this condition remain controversial. Although the links between such thyroid status specific to preterm infants and subsequent neurological outcomes are tenuous at best,[19] thyroid maturation might be associated with a good outcome for preterm neonates. Maturation of thyroid function is accelerated in the third trimester of pregnancy, coinciding with a cortisol surge in the fetus.[20,21] Glucocorticoids are involved in the process.[22,23] Therefore, we hypothesized that ANS might promote the maturation of thyroid function, in addition to organs such as the lungs. In human studies, the effects of ANS on the maturation of thyroid function is controversial: one report claimed that administration of ANS reduced thyroid dysfunction in neonates,[24] but others found no such effect.[25,26] Therefore, we conducted a study to examine the effects of ANS on thyroid function in preterm neonates. We evaluated not only basal free thyroxine (FT4) and TSH levels but also TRH stimulation tests, which are

helpful in defining thyroid dysfunction in older children and full-term neonates.[27–29] In preterm neonates, we previously reported that the hypothalamic–pituitary–thyroid (HPT) axis could respond to TRH stimulation tests appropriately even in very low birth weight neonates born at < 30 weeks of gestation at about 2 weeks after birth.[30] Therefore, we consider that TRH stimulation tests are helpful for defining thyroid function.

2 | METHODS

2.1 | Subjects

Preterm neonates who were born at <34 weeks of gestational age and with birth weights <1500 g, and were admitted to Kyoto University Hospital Neonatal Intensive Care Unit (NICU) between April 2008 and March 2019 were included in this retrospective study. An ANS course consisted of two 12-mg doses of betamethasone injected intramuscularly to the mothers at risk of preterm labor 24 h apart. Neonates whose mothers had thyroid diseases or major congenital anomalies, who suffered sepsis, who received steroids before 2 weeks of age or for whom some data were missing were excluded from this study. To clarify the effects of ANS, we also excluded neonates who were born more than 7 days after the initiation of ANS administration and whose mother had already received glucocorticoids other than ANS. We divided the subjects into two groups: complete and incomplete ANS treatment. It has been reported that ANS had no effect on reducing the incidence of RDS if neonates were born within 24 h after completion of a course of ANS, so the interval between ANS administration and birth is important to detect significant effects on organ maturation.[3] Therefore to clarify the effect of ANS, neonates who were born within 24 h after the completion of ANS administration were assigned to the incomplete group. Thus, the complete group consisted of neonates whose mother had completed two doses of betamethasone and who were born between 24 h and 7 days after the completion of ANS administration, and the incomplete group consisted of neonates who were not exposed to any ANS or were born within 24 h after the completion of ANS administration.

Ethics approval was obtained from Kyoto University Graduate School and Faculty of Medicine Ethics Committee, and written informed parental consent was obtained before each procedure.

2.2 | Serum FT4 and TSH measurements and TRH stimulation tests

We measured serum FT4 and TSH values for very low birth weight (VLBW) neonates at about 2 weeks of age. Generally, we do not initiate levothyroxine sodium (LT4) treatment for neonates with low FT4 and normal TSH concentrations, considered as transient hypothyroxinemia of prematurity, but we initiate LT4 therapy for neonates with elevated TSH values (> 15 mIU/L). For neonates with TSH values <15 mIU/L, we repeat serum FT4 and TSH measurements at 1- or 2-week intervals until about 40 weeks postmenstrual age, so that neonates with delayed TSH elevation are not missed. FT4 and TSH were measured using enhanced chemiluminescence (ECLIA) kits (Roche Diagnostics, Tokyo, Japan).

In addition, we performed TRH stimulation tests for almost all VLBW neonates at about 2 weeks of age to evaluate the hypothalamic–pituitary–thyroid (HPT) axis and thyroid function during 2008−2010 and 2015−2017 among cases where parental consent for such testing was obtained. ~~As we did not peforem~~ TRH stimulation tests were not performed during the period 2011-2014, resulting in fewer TRH tests ~~the number of infants who were pefomed by the tests were lower~~ than the total number of subjects. The test was performed as follows: 7 μg/kg TRH (Tanabe Mitsubishi Pharmaceutical Company, Osaka, Japan) was injected intravenously and serum was collected before and 30 min after the injection.[30,31] If the TSH value at 30 min (TSH_{30}) was above 35 mIU/L, it was considered as an exaggerated response indicating thyroid dysfunction.[31]

2.3 | Outcomes

The primary outcome was an elevated serum TSH value (> 15 mIU/l), resulting in the initiation of LT4. Therapy. Secondary outcomes were serum TSH and FT4 levels at about 2 and 4 weeks of age, at about 40 weeks postmenstrual age and the outcomes of TRH stimulation tests.

2.4 | Statistical analysis

Data are expressed as medians and interquartile ranges. The Mann–Whitney nonparametric *U*-test was used to compare continuous variables, and the chi-squared test was used for analyzing categorical data. $P < 0.05$ was considered statistically significant. Multivariate logistic regression analysis was performed to adjust for

potential cofounders and identify risk factors for the incidence of hyperthyrotropinemia and TRH stimulation tests. All statistical analyses were conducted using IBM SPSS Statistics (version 20; IBM Corp., Armonk, NY, USA).

3 | RESULTS

3.1 | Profiles of the subjects

Two hundred twenty-four neonates born at <34 weeks of gestational age with birth weights < 1500g were admitted to the NICU between April 2008 and March 2019 (Fig. 1). We excluded 125 for the reasons given above, so the final enrollment was 99. Characteristics of neonates in the complete and incomplete ANS groups are shown in Table 1. There was a significant difference only in the variable "history of surgery" (P = 0.004). Most surgeries involved ductus arteriosus ligation. Other variables were not significantly different between the two groups.

The time from administration of ANS to delivery in the complete group was a median of 60 h (range 43–92), and that in the incomplete group was all within 12h. In the incomplete group, 22 neonates (44%) were not exposed to ANS.

3.2 | Thyroid function of the subjects

Regarding thyroid function, the incidence of hyperthyrotropinemia (TSH > 15 mU/L) at about 2 weeks was significantly lower in the complete group (6% vs 22%; P = 0.023) although there were no significant differences in median serum TSH, FT4 values and the incidence of hypothyroxinemia (FT4 < 10.5 pmol/L~~0.8 ng/dL~~) (Table 2). At the two later time points, there were no significant differences in median serum TSH and FT4 values between the two groups (data not shown), but in the incomplete group three neonates developed delayed elevation of TSH after 3 weeks of age (days 21, 21, and 39). We initiated LT4 therapy for neonates with hyperthyrotropinemia and adjusted the dose so that serum TSH values were < 5 mIU/L; almost all those neonates continued to be administered the drug at the time of discharge. Serum TSH values in all cases except for three with delayed TSH elevation remained < 15 mIU/L and decreased spontaneously throughout the study.

3.3 | Risk factors for the incidence of hyperthyrotropinemia

Variables used in the multiple logistic regression analysis were complete ANS therapy, gestational age, birth weight (SD), use of iodinated contrast agents, and history of surgery, as these are known risk factors for thyroid dysfunction. Results of the analysis are shown in Table 3. The incidence of hyperthyrotropinemia (TSH > 15 mU/L) was independently associated with complete ANS administration with an adjusted odds ratio (aOR) value of 0.39.

3.4 | TRH stimulation test

Outcomes of the TRH stimulation test are shown in Table 4. TSH_{30} values in most of the subjects were > 10 mIU/L, indicating that the test had been performed correctly, and that no pituitary dysfunction was found in most of the neonates. Comparing the two groups, the TSH_{30} level in the complete group was significantly lower than in the incomplete group (22.3 ~~μIU/ml~~ mIU/L vs 33.8 ~~μIU/ml~~ mIU/L; $P = 0.046$). This finding suggested that thyroid function of the neonates in the complete group was more mature than that in the incomplete group. As defined at 35 ~~μIU/ml~~ mIU/L, the incidence of an exaggerated response was lower in the complete group but not significantly (17% vs 44%; $P = 0.053$). The aOR value of complete ANS (by gestational age, birth weight (± SD), use of iodinated contrast agents, and history of surgery) was 0.21 (95% confidence interval, 0.041−1.09; P = 0.064).

4 | DISCUSSION

Here we found that the incidence of hyperthyrotropinemia (TSH >15 mIU/L) in the complete group was significantly lower than in the incomplete group (6% vs 23%; $P = 0.023$). In addition, ANS reduced the incidence of exaggerated response to the TRH stimulation test at about 2 weeks of age. Thus, we consider that thyroid function in the complete group was more mature than that in the incomplete group. Our multivariate logistic regression analysis showed that hyperthyrotropinemia was independently associated with complete ANS administration (aOR = 0.39). Thus, the incidence of hyperthyrotropinemia decreased by 61% following complete ANS administration.

In contrast, the decrease in TSH by ANS might be interpreted as an unfavorable effect on the HPT

axis, as glucocorticoids are known to have suppressive effects on this and can cause hypothyroidism.[33] However, in our study there was no difference in the serum FT4 level between the two groups, and no suppression of FT4 by ANS was found. Therefore, we consider that the decrease in TSH levels by ANS therapy indicated maturation of the HPT axis but not its suppression.

Although the mechanism by which maternal corticosteroids might affect fetal thyroid function was not evaluated in our studies, it was reported that cortisol infusion to the preterm fetus raised its hepatic, renal, and perirenal adipose tissue deiodinase (D)1 levels and reduced renal and placental D3 activities in animal studies.[22] The report concluded that the prepartum cortisol surge induces tissue-specific changes in D activity. It also reported that dexamethasone infusion to pregnant animals changed the D1 and D3 activities of preterm fetuses similarly to cortisol infusion to the fetus, so ANS treatment has a maturational effect on the thyroid function of preterm fetus in addition to the preterm cortisol surge.[23] Based on these reports, we speculated that ANS might be associated with fetal thyroid maturation not only in animal models but also in humans. Thus, ANS therapy might reduce the incidence of thyroid dysfunction in preterm neonates by promoting thyroid maturation.

This study had several limitations. First, it was a relatively small retrospective study in a single institution and should be verified in a larger study. Second, in this study ANS administration might have been at a low incidence. Many pregnant women with serious problems such as abruptio placentae, non-reassuring fetal status, poor blood pressure control, and premature rupture of the membranes are transferred to our hospital just before delivery, so that the number of cases where ANS was not given in time tended to be higher. Third, TRH stimulation tests were performed only for 45% of the subjects (45/99); but the profiles of these neonates were similar to those of the total study population, as shown in Appendices 1 and 2. Considering these points, we integrated the findings with TRH stimulation tests in this study. Fourth, urinary iodine concentration was not measured in this study, although iodine deficiency or excess is one of the most common causes of hypothyroidism.[33] Japan is surrounded by ocean, and seaweed is our primary source of iodine. Thus Japan is a country with iodine sufficiency, and iodine deficiency is rarely seen.[34] On the contrary, iodine overexposure could be a problem. Based on these observations, iodine overexposure

during surgical treatment or with the use of iodine contrast agents is a matter of concern in discussing thyroid function. In the present study, the incidence of previous surgical treatment was lower in the complete group, which might explain the favorable effects of ANS therapy. However, there was no significant difference in the incidence of hyperthyrotropinemia between the groups with and without a history of surgery (28% vs 12%, $P = 0.09$). Furthermore, our multivariate logistic regression analysis showed that hyperthyrotropinemia was not associated with a history of surgery (Table 4). Based on these considerations, we consider that the possible contribution of iodine exposure to the incidence of hyperthyrotropinemia was minor compared with the effects of ANS therapy. Fifth, the impact of cardiorespiratory severity on thyroid dysfunction cannot be completely ruled out because the severity was not included in the variables for the multivariate analysis due to the small number of cases.

CONCLUSIONS

Here we found that complete ANS administration could reduce the incidence of hyperthyrotropinemia in preterm neonates. This might reflect maturation of thyroid function. Therefore, it is desirable that any maternal administration of ANS should be done completely, not only for its effects on the respiratory and circulatory systems of the progeny, but also for thyroid maturation in the progeny.

CONFLICT OF INTEREST

The authors do not declare any conflict of interest or financial involvement with this manuscript.

REFERENCES

1. Itabashi K, Horiuchi T, Kusuda S.et al. Mortality rates for extremely low birth weight infants born in Japan in 2005. *Pediatrics.* 2009; 123:445-450.

2. Fanaroff AA, Hack M, Walsh MC. The NICHD neonatal research network: changes in practice and outcomes during the first 15 years. *Semin Perinatol.* 2003; 27:281-287.

3. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics*.1972; 50:515-525.

4. Gyamfi-Bannerman C, Thom EA. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants *N Engl J Med*. 2016; 375:486-487

5. Saccone G, Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials. *BMJ.* 2016; 355: i5044.

6. Ecker JL, Kaimal A, Mercer BM. et al. Obstetric Care consensus No. 6: Periviable Birth. *Obstet Gynecol*. 2017; 130: e187-e199.

7. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev. 2017; 3:CD004454.*

8. Leviton A, Dammann O, Allred EN. Antenatal corticosteroids and cranial ultrasonographic abnormalities. *Am J Obstet Gynecol.* 1999; 181:1007-1017.

9. Ford LR, Willi SM, Hollis BW, Wright NM. Suppression and recovery of the neonatal hypothalamic-pituitary-adrenal axis after prolonged dexamethasone therapy. *J Pediatr.* 1997; 131:722-726.

10. Barrington KJ. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. *BMC Pediatr.* 2001; 1:1

11. Williams GR. Neurodevelopmental and neurophysiological actions of thyroid hormone. *J Neuroendocrinol.* 2008; 20:784-794.

12. Fernandez EF, Watterberg KL. Relative adrenal insufficiency in the preterm and term infant. *J Perinatol.* 2009; Suppl 2: S44-9.

13. Kawai M. Late-onset circulatory collapse of prematurity. *Pediatr Int.* 2017; 59:391-396.

14. de Zegher F, Pernasetti F, Vanhole C, Devlieger H, Van den Berghe G, Martial JA. The prenatal role of thyroid hormone evidenced by fetomaternal Pit-1 deficiency. *J Clin Endocrinol Metab.* 1995; 80:3127-3130.

15. Vulsma T, Gons MH, de Vijlder JJ. Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. *N Engl J Med.* 1989; 321:13-16.

16. Frank JE, Faix JE, Hermos RJ.et al. Thyroid function in very low birth weight infants: effects on neonatal hypothyroidism screening. *J Pediatr.* 1996; 128:548-554.

17. Kaluarachchi DC, Colaizy TT, Pesce LM, Tansey M, Klein JM. Congenital hypothyroidism with delayed thyroid-stimulating hormone elevation in premature infants born at less than 30 weeks gestation. *J Perinatol.* 2017; 37:277-282.

18. van Wassenaer AG, Kok JH, de Vijlder JJ.et al. Effect of thyroxine supplementation on neurologic development in infants born at less than 30 week' gestation. *N Engl J Med.* 1997; 336:21-26.

19. Hollanders JJ, Israels J, van der Pal SM.et al. No association between transient hypothyroxinemia of prematurity and neurodevelopmental outcome in young adulthood. *J Clin Endocrinol Metab.* 2015; 100:4648-4653.

20. Thorpe-Beeston JG, Nicolaides KH, Felton CV, Butler J, McGregor AM. Maturation of the secretion of thyroid hormone and thyroid-stimulating hormone in the fetus. *N Engl J Med*. 1991; 324:532-536.

21. Dattani MT, Gevers EF. Endocrinology of fetal development. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology* 13th edition: Amsterdam, Netherlands, Elsevier; 2015:858-861.

22. Forhead AJ, Curtis K, Kaptein E, Visser TJ, Fowden AL. Developmental control of iodothyronine deiodinases by cortisol in the ovine fetus and placenta near term. *Endocrinology.* 2006; 147:5988-5994.

23. Forhead AJ, Jellyman JK, Gardner DS.et al. Differential effects of maternal dexamethasone treatment on circulating thyroid hormone concentrations and tissue deiodinase activity in the pregnant ewe and fetus. *Endocrinology*. 2007; 148:800-805.

24. Kaluarachchi DC, Zhao Q, Colaizy TT. Antenatal steroids and thyroid hormone function in preterm infants. J *Perinatol.* 2018; 38:1466-1470.

25. Franklin RC, Purdie GL, O'Grady CM. Neonatal thyroid function: prematurity, prenatal steroids, and respiratory distress syndrome. *Arch Dis Child.* 1986; 61:589-592.

26. Lee JH, Kim SW, Jeon GW, Sin JB. Thyroid dysfunction in very low birth weight preterm infants. *Korean J Pediatr.* 2015; 58:224-229.

27. Foley TP Jr, Jacobs LS, Hoffman W, Daughaday WH, Blizzard RM. Human prolactin and thyrotropin concentrations in the serums of normal and hypopituitary children before and after the administration of synthetic thyrotropin-releasing hormone. *J Clin Invest.* 1972; 51:2143-2150.

28. Jacobsen BB, Andersen H, Dige-Petersen H, Hummer L. Thyrotropin response to thyrotropin-releasing hormone in full term, euthyroid and hypothyroid newborns. *Acta Paediatr Scand.* 1976; 65:433-438.

29. Jacobsen BB, Andersen H, Dige-Petersen H, Hummer L. Pituitary-thyroid responsiveness to thyrotropin-releasing hormone in preterm and small-for-gestational age newborns. *Acta Paediatr Scand.* 1977; 66:541-548.

30. Niwa F, Kawai M, Kanazawa H.et al. Hyperthyrotropinemia at 2 weeks of age indicates thyroid dysfunction and predicts the occurrence of delayed elevation of thyrotropin in very low birth weight infants. *Clin Endocrinol (Oxford).* 2012; 77:255-261.

31. Rapaport R, Sills I, Patel U.et al. Thyrotropin-releasing hormone stimulation tests in infants. *J Clin Endocrinol Metab.* 1993; 77:889-894.

32. No authors listed. Committee Opinion No. 713 Summary: Antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol.* 2017; 130:493-494.

33. Re RN, Kourides IA, Ridgway EC, Weintraub BD, Maloof F. The effect of glucocorticoid administration on human pituitary secretion of thyrotropin and prolactin. *J Clin Endocrinol Metab.* 1976; 43:338-346.

34. Dattani MT, Gevers EF. Endocrinology of fetal development. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology.* 13th edition: Amsterdam, Netherlands; 2015:423-433

35. Fuse Y. Iodine and thyroid function: historical review of goiter and the current iodine status in Japan.

Pediatr Endocrinol Rev. 2017; 14:260-270

TABLE 1 Characteristics of the two groups of neonates and their mothers' medical history. Data are expressed as medians and interquartile ranges or numbers and percentages.

Clinical characteristics	Complete (*n* = 49)	Incomplete (*n* = 50)	*P*
Male, *n* (%)	24 (49)	25 (50)	0.92
GA (weeks)	28.0 (26.8–30.3)	28.6 (26.4-30.2)	0.61
BW (g)	948 (618–1225)	892 (746–1174)	0.49
Small for gestational age, *n* (%)	26 (53)	17 (34)	0.06
Caesarean section, *n* (%)	44 (90)	48 (96)	0.23
Apgar score (1 min)	5 (2–7)	4 (2–7)	0.53
Apgar score (5 min)	7 (6–9)	7 (6–9)	0.53
Postnatal steroids, *n* (%)	7 (14)	8 (16)	0.81
DOA/DOB infusion, *n* (%)	5 (10)	8 (16)	0.39
NO inhalation, *n* (%)	3 (6)	1 (2)	0.30
Use of surfactant, *n* (%)	23 (47)	30 (60)	0.14
Duration of mechanical ventilation (days)	6 (0–25)	8 (3-28)	0.38
BPD36, *n* (%)	25 (51)	19 (42)	0.26
Use of mechanical ventilation at 2 weeks of age, *n* (%)	21 (43)	21 (42)	0.93
Use of oxygen at 2 weeks of age, *n* (%)	31 (63)	36 (72)	0.35
Use of iodinated contrast agents, *n* (%)	3 (6)	6 (12)	0.31
History of surgery, *n* (%)	2 (4)	12 (24)	0.004
Intraventricular hemorrhage grade III, IV, *n* (%)	1 (2)	5 (10)	0.10

BPD36, bronchopulmonary dysplasia at 36 weeks; GA, gestational age; BW, birth weight; DOA, dopamine; DOB, dobutamine; NO, nitric oxide–

TABLE 2 Incidence of hyperthyrotropinemia, TSH and FT4 levels at about 2 weeks of age of the two groups of neonates. Data are expressed as medians and interquartile ranges or numbers and percentages.

	Complete (n = 49)	Incomplete (n = 50)	P
Incidence of hyperthyrotropinemia, n (%)	3 (6)	11 (22)	0.02
Incidence of hyporthyroxinemia, n (%)	19 (9/47)	17 (8/47)	0.79
Postnatal days when elevated TSH was detected	14 (12.5–15)	14.5 (14–18.5)	0.70
TSH at about 2 weeks of age (mIU/L)	5.80 (3.68–10.68)	7.47 (4.23–9.05)	0.44
FT4 at about 2 weeks of age (pmol/L)	15.3 (12.5–19.2)	15.2 (11.8–18.4)	0.69

TABLE 3 Multivariate logistic regression analysis on factors involved in the incidence of hyperthyrotropinemia among neonates (TSH > 15 mIU/L)

Variable	Adjusted odds ratio	95% confidence interval	*P*
Complete ANS treatment in pregnancy	0.39	0.18–0.85	0.02
Gestational age	0.79	0.60–1.04	0.09
Birth weight	0.56	0.33–0.97	0.04
Use of iodinated contrast agents	0.49	0.054–4.42	0.52
History of surgery	1.34	0.23–7.87	0.75

TABLE 4 Results of TRH stimulation tests in the two groups of neonates

	Complete (n = 18)	Incomplete (n = 27)	P
TSH_{30} (mIU/L)	22.3 (18.85–32.44)	33.8 (26.78–42.89)	0.046
TSH_{30} >35, n (%)	5 (17)	12 (44)	0.053

TSH_{30}, serum TSH level at 30 min after TRH stimulation. Data are expressed as medians and interquartile ranges or as numbers and percentages.

TSH_{30} >35, the incidence of subjects who showed an exaggerated response higher than 35 mIU/L at 30 min after TRH stimulation.

FIGURE LEGENDS

FIGURE 1 Flowchart of subject enrollment

ANS, antenatal corticosteroids.

Appendix **TABLE 1** Characteristics of the two groups undergoing TRH stimulation tests. Data are expressed as numbers and percentages or as medians and interquartile ranges.

	Complete (n = 18)	Incomplete (n = 27)	P
Male, n (%)	9（50）	15（55）	0.71
GA (weeks)	27.3 (26.6–28.1)	28.0 (26.0–28.8)	0.86
BW (g)	943 (607–1100)	854 (731–1121)	0.49
Small for gestational age, n (%)	7（39）	6（22）	0.23
Caesarean section, n (%)	16（89）	26（96）	0.33
Apgar score (1 min)	4 (2–6.7)	4 (2–5)	0.83
Apgar score (5 min)	7 (5.2–9)	6 (6–7)	0.65
Postnatal steroids, n (%)	3 （17）	2 （7）	0.33
DOA/DOB infusion, n (%)	3（17）	6 （22）	0.65
NO inhalation, n (%)	2（11）	0（0）	0.08
Use of iodinated contrast agents, n (%)	2（11）	2（7）	0.31
History of surgery, n (%)	2（11）	7（26）	0.22
Intraventricular hemorrhage grade III or IV; n (%)	1（5）	2（7）	0.85

GA, gestational age; BW, birth weight; DOA, dopamine; DOB, dobutamine; NO, nitric oxide

Appendix **TABLE 2** Incidence of hyperthyrotropinemia, TSH and FT4 levels in mIU/L at about 2 weeks of age in the two groups of neonates subjected to TRH stimulation tests. Data are expressed as medians and interquartile ranges.

	Complete (n = 18)	Incomplete (n = 27)	P
Incidence of hyperthyrotropinemia, n (%)	1 （5）	6 （22）	0.13
Postnatal days when elevated TSH was detected	13.5 (12–14)	14 (10.5–14)	0.70
TSH (mIU/L)	6.20 (3.47–8.10)	7.61 (3.67–10.63)	0.29
FT4 (pmol/L)	14.2 (10.8–17.5)	13.5 (10.9–17.0)	0.35