RESEARCH

Usefulness of thyroid function assessment in infants born to mothers with thyroid dysfunction during pregnancy

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Abstract

Introduction: Maternal thyroid disease is considered as a risk factor for abnormal thyroid function at birth, as well as for long-term morbidity in offspring. The potential harmful effects on the neonate had led to the clinical practice of thyroid function assessment in infants born to mothers with thyroid disease during pregnancy. In this study, we evaluated the usefulness of routine thyroid function tests for every newborn of a mother with thyroid dysfunction.

Methods: Data were collected retrospectively from the medical files of mothers diagnosed with thyroid disease and their infants (496 mother–neonate pairs). All mothers with diagnosed thyroid disease who gave birth in the years 2016–2019 at our medical center were included.

Results: Hypothyroidism was the most common maternal diagnosis (91.4%), among which 48.7% had Hashimoto's thyroiditis. Hyperthyroidism was diagnosed in 8.6% of the cohort – 71.6% of them with Graves' disease. None of the newborns was diagnosed with congenital hypothyroidism in the screening program. Thyroid-stimulating hormone was >10 mIU/L in 14.6% and >20 mUI/L in 2.2%; all had free thyroxine within normal range. Serum thyroid function test identified four infants with thyroid disease; two had congenital hypothyroidism not related to maternal thyroid disease, one had transient familial congenital hypothyroidism and one had neonatal Graves' disease.

Conclusions: Thyroid function testing for all newborns of mothers with thyroid dysfunction seems redundant. However, in cases of congenital hypothyroidism in siblings, thyroid function test, in addition to newborn thyroid screening, is recommended, and more careful follow-up is indicated. In maternal Graves' disease, thyroid function test on days 2–3 of life is recommended.

Key Words

- thyroid function tests (TFT)
- subclinical hypothyroidism (SCH)
- Hashimoto's thyroiditis
- Graves' disease
- congenital hypothyroidism (CH)

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https://doi.org/10.1530/ETJ-22-0055

Introduction

Maternal thyroid diseases are considered a risk factor for abnormal thyroid function at birth (1, 2, 3, 4, 5), as well as for long-term morbidity in offspring (1, 6, 7, 8, 9, 10, 11). Maternal hyperthyroidism and hypothyroidism both affect the fetal and neonatal thyroid. Hyperthyroidism is mainly caused by Graves' disease, and hypothyroidism during pregnancy in most women is attributed to Hashimoto's thyroiditis. In Graves' disease, fetal and newborn thyrotoxicosis results from thyroid-stimulating immunoglobulin (TSI) crossing the placenta. The presence of thyroid-stimulating hormone (TSH) receptor-blocking antibodies (TBAb) is associated with transient hypothyroidism in the offspring. Antithyroid drugs such as propylthiouracil and methimazole are additional reasons for transient hypothyroidism in the offspring (12, 13). Maternal Hashimoto's thyroiditis is associated with transient hypothyroidism or hyperthyrotropinemia of the newborn due to the passage of thyroid autoantibodies (14). Maternal subclinical hypothyroidism (SCH) has been shown to be associated with adverse obstetric outcomes and neuro-intellectual impairment in the child (15, 16). These observations have led to the recommendation of maintaining TSH values in pregnant women below 2.5 mU/L (15, 16).

In most Western countries, newborn thyroid screening is standard, and its main purpose is to identify and initiate early supplemental thyroxine (T4) therapy in infants with primary congenital hypothyroidism (CH) (17, 18). The potential effects of maternal thyroid disease on offspring have led to the clinical practice of recommending serum thyroid function tests (TFT), including free T4 (FT4) and TSH, in infants born to mothers with thyroid disease during pregnancy. In clinical practice, newborn TFT are performed at either 2 weeks or 2–3 days after birth (19).

The usefulness of this clinical approach has been examined in several studies. Some have shown no clinical benefit of performing TFT in addition to the newborn screening (20, 21, 22, 23, 24, 25), whereas others have shown that the TFT are essential (3, 26, 27, 28, 29, 30).

In our neonatal department, the clinical practice is to perform a TFT at the age of 2–3 days for infants born to mothers with any diagnosis of thyroid disease. In this study, we retrospectively evaluated the TFT results and the management of infants born to mothers with thyroid dysfunction in our medical center neonatology department to determine whether routine testing is necessary.

Subjects and methods

All mothers with a diagnosis of thyroid dysfunction who gave birth between the years 2016 and 2019 at our medical center were enrolled in the study. Data were collected retrospectively from the computerized medical files of the mothers and their infants.

The diagnosis of maternal thyroid dysfunction included Hashimoto's thyroiditis when thyroid antibodies (against thyroid peroxidase (TPO) and/or thyroglobulin (Tg)) were positive, non-autoimmune hypothyroidism when thyroid antibodies were negative, CH, hypothyroidism post-surgery or post-radioactive iodine therapy, goiter, Graves' disease, multinodular goiter and SCH. SCH was defined when TSH was above 2.5 mIU/L.

National newborn screening results were retrieved retrospectively from the computerized data for all newborns. The study was approved by the institute's committee on human research.

Neonatal screening

Blood samples were collected by heel puncture 48–72 h after birth. Between 1987 and 2006, the Israeli National Newborn Screening Laboratory performed the tests using Diagnostic Products Corp. (Los Angeles, CA, USA) RIA total T4 (TT4) and TSH kits. Since 2006, Perkin Elmer B065-112 AutoDELFIA neonatal TT4 and B032-312 AutoDELFIA neonatal TSH kits have been employed, both of which utilize time-resolved fluoroimmunoassays (PerkinElmer Life and Analytical Sciences, Wallac Oy, Turku, Finland). The Israeli neonatal screening program is based on TT4 level, followed by confirmatory TSH test when the level of TT4 is below the 10th percentile for age. TSH values above 20 mIU/L are considered indicative of primary CH and the results are immediately reported to the pediatric endocrinologist in charge of the geographical area.

Hormone analyses

TSH and FT4 were measured by direct automated chemiluminescent IRMA using the ADVIA Centaur immunoassay system (Bayer Corporation). TSH reference values provided by our laboratory were 0.4–4.2 mIU/L and for FT4, 10–20 pmol/L. Normal references for the first week of life in our laboratory were 0.4–10 mIU/L for TSH and 10–26.8 pmol/L for FT4. Tg and TPO antibodies (Ab) were measured by direct automated chemiluminescent IRMA using an Immulite 2000 immunoassay system (Siemens). TgAb and TPOAb levels above 35 U/mL were considered positive.

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https://doi.org/10.1530/ETJ-22-0055

Statistical analysis

Statistical analyses were performed using the SAS software package version 9.4 (SAS Institute, Cary, NC, USA). Continuous variables were expressed as mean ± S.D. and percent, and categorical variables were expressed as percent. The association between maternal and newborn thyroid function and between thyroid function results of the newborn screening and TFT of our laboratory were compared by Pearson correlation. Significance was set at $P < 0.05$.

Results

Baseline data

Data on pregnancies and obstetric complications were based on 701 mothers. Data on newborns were based on 496 samples, because 205 samples were either not collected (112) by the neonatology department or eliminated (93) due to technical problems, mainly too low sample volume.

Maternal and obstetric data

Maternal thyroid diseases are presented in Table 1. Hypothyroidism was the most common diagnosis, among them, 48.7% had Hashimoto's thyroiditis. Hyperthyroidism was diagnosed in 8.6% among them, 71.6% had Graves' disease (Table 1). Pregnancy outcomes and perinatal complications are presented in Table 2. The number of cesarean sections, preterm delivery, gestational diabetes and toxemia was higher than our medical center's average. The incidence of newborn deaths was higher, but not significantly so, than the mean incidence in Israel (8.5 compared to 3.4:1000 live births, CI: 3.1–18.5) (https://www.cbs.gov.il/he/publications/doclib/2020/3.shnatonhealth/st03_13x.pdf).

Hashimoto's thyroiditis and Graves' disease

Pregnancy outcomes for mothers with Hashimoto's thyroiditis and Graves' disease are summarized in Table 3. A high incidence of cesarean sections and preterm deliveries was observed. No case of CH due to maternal antibodies was detected. No association was shown between the levels of maternal antithyroid antibodies and TFT in the newborns.

Newborn TFT results

All newborns underwent neonatal thyroid screening. None of the newborns was diagnosed with CH in the screening program. TSH above 10 mIU/L was found in 14.6% of the newborns, all with serum FT4 levels within the normal newborn range (Table 4). Eleven newborns (2.2%) had TSH levels above 20 mIU/L, with FT4 levels within the normal reference range (Table 4). Newborns with elevated TSH (above 10 mIU/L) were followed by repeated TFT until TSH levels normalized.

Newborns with thyroid diseases

Four infants were diagnosed with thyroid disease, three with hypothyroidism and one with hyperthyroidism. The details of the four patients are reported in Table 5.

Patient 1 was a female twin born to a mother who was treated with LT4 throughout her pregnancy due to SCH. She was diagnosed with multiple pituitary hormone deficiency (MPHD). Patient 2 was a male infant born to a mother

Table 1 Clinical characteristics of maternal thyroid dysfunction.

	Mean ± S.D.	%
n	701	
Age (years), mean ± S.D. (range)	30.6 ± 5.8 (18–48)	
Hypothyroidism	641	91.4
Hashimoto's thyroiditis	313	48.7
Non-autoimmune hypothyroidism	259	40.4
SCH (TSH > 2.5 mIU/L)	34	5.3
Post-thyroidectomy due to thyroid malignancy	15	2.1
Goiter	11	1.7
Congenital hypothyroidism	5	0.8
Others	4	0.6
LT4 therapy	596	93
Hyperthyroidism	60	8.6
Graves' disease	43	71.6
Non-autoimmune hyperthyroidism	14	23.3
Toxic MNG	3	5.0

MNG, multinodular goiter; SCH, subclinical hypothyroidism.

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Table 2 Pregnancy outcomes and perinatal complications.

	n	%	Incidence in our center (%)
Cesarean section	175	25	18.2
GA < 37 weeks	62	8.8	7.7
GA < 35 weeks	32	4.6	3.7
Gestational diabetes	74	10.5	7.8
Toxemia	3	5.0	2.7
Delivery complications	19	2.7	NA
	Mean ± S.D.		**Range**
Newborns			
Gender (M/F)	342/359		
GA (weeks)	38.3		23–42
Birth weight (kg)	3.2 ± 0.6		0.6–4.7
Head circumference (cm)	34.0 ± 1.3		30–38
Perinatal complications	30	4.3	
Phototherapy	54	8.5	
Deaths[a]	6	0.85	

[a]8.5 deaths to 1000 live births. In Israel, 3.4 deaths to 1000 live births (according to the OECD).
GA, gestational age.

with Hashimoto's thyroiditis. TFT after birth were within the normal range with negative thyroid autoantibodies. Persistent elevated TSH led to initiation of LT4 therapy at the age of 2 years. Patient 3 was born to a mother with non-autoimmune hypothyroidism who was on LT4 supplemental therapy throughout her pregnancy. His parents were first cousins, and his older sister was diagnosed with transient CH. First laboratory TFT showed elevated TSH of 22.5 mIU/L, and therefore, repeated TFT were carried out revealing, at the age of 19 days, overt hypothyroidism (TSH of 116 mIU/L and FT4 of 9.04 pmol/L) and LT4 therapy was initiated. Antithyroid antibodies were negative in the mother and offspring. At the age of 2 years, after LT4 withdrawal, ^{99}TC scan demonstrated normal thyroid gland with normal TFT. Patient 4 was born to a mother with hypothyroidism after thyroidectomy due to Graves' disease. At 6 days, he was diagnosed with neonatal Graves' disease and methimazole and beta blockers were initiated.

Discussion

The results of our study indicate that screening TFT of newborns from mothers with thyroid dysfunction is

Table 3 Pregnancy outcomes of mothers with Graves' disease and Hashimoto's thyroiditis.

	Mean ± S.D.	Range	%	Mean ± S.D.	Range	%
	Graves' disease (*n* = 43)			Hashimoto's thyroiditis (*n* = 313)		
Mothers						
Age (years)	32.3 ± 6	19–43		31.0 ± 5.5	19–48	
Gestational age (weeks)	37.9 ± 3	25–42		38.3 ± 2.1	23–42	
Post-I^{131} ablation or thyroidectomy (*n*)	19		44.1			
Without any medications (*n*)	13		30.2			
Antithyroid medications (*n*)	11		25.6			
TSH (mIU/L)	1.6 ± 2.7	0.01–16.9		3.72 ± 5.4	0.03–74.3	
FT4 (pmol/L)	15.5 ± 5.6	4.2–50.13		14.1 ± 2.5	4.2–29.3	
Measurement of thyroid antibodies (*n*)	35		81.4	133		42.6
Positive TPOAb (*n*)	11		25.6	114		85.7
Positive TSI (*n*)	13		40.6	ND		
Preterm delivery (*n*)	10		23.3	29		9.3
Cesarean section (*n*)	13		30.2	76		24.4
Newborns						
Birth weight (kg)	3.0 ± 0.7	0.65–4.3		3.2 ± 0.6	0.6–4.7	
Head circumference (cm)	34.3 ± 1.2	32–36.6		34. 0	25.5–37.5	
Phototherapy (*n*)	4		12.1	15.3		9.4
Age at first thyroid function test (days)	3 ± 0.8	2–5		3		2–7
TSH (mIU/L)	6.3 ± 4.9	0.03–25.0		6.34 ± 47	0.85–34.9	
FT4 (pmol/L)	29.2 ± 7.2	10.9–47		27.2 ± 5.4	13.7–48.9	
Neonatal Graves' disease (*n*)	1		2.3			
LT4 therapy (*n*)				1		0.32
Measurement of thyroid antibodies (*n*)	3		7.0	21		6.7
Positive thyroid antibodies (*n*)	1			7		33.3

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Table 4 Elevated TSH values in newborns.

	TSH > 10 mIU/L (n = 87)			**TSH > 20 mIU/L** (n = 11)		
	Mean ± S.D.	Range	%	Mean ± S.D.	Range	%
Mothers						
Age (years)	30 ± 6	20–44		30 ± 5	23–43	
GA (weeks)	39 ± 1	37–42		38 ± 1	37–40	
Cesarian section (*n*)	6		8.9	0		0
Hashimoto's thyroiditis (*n*)	33		38.4	4		40
TPOAb (U/mL)	191 ± 541	10–3305		71 ± 53	10–101	
TGAb (U/mL)	51 ± 119	20–609		29 ± 15	20–46	
Newborns						
Birth weight (kg)	3.2 ± 0.4	2.4–4.5		3.3 ± 0.3	2.8–3.7	
Head circumference (cm)	34 ± 1	31–38		34 ± 1	33–35	
Phototherapy (*n*)	6		9	0		0
Age at first TFT (days)	2.6 ± 0.7	2–5		2.8 ± 0.9	2–5	
TSH (mIU/L)	14.8 ± 4.8	10.0–35.0		24.0 ± 5.1	20.1–35	
FT4 (pmol/L)	28.1 ± 4.5	17.4–40.0		25.3 ± 3.8	17.9–31.3	

GA, gestational age; TFT, thyroid function tests.

unnecessary in most cases. In the current study, we evaluated the usefulness of this clinical practice by retrospective assessment of data from mothers with thyroid diseases who gave birth in our center between the years 2016 and 2019.

Of 589 newborn samples, 127 (22%) were excluded due to small serum sample volume, mainly because of high hematocrit which is a very common occurrence in newborns. The study ultimately included TFT results from 496 newborns. The need for repeated blood collection during hospitalization or after the babies' discharge was associated with parental anxiety, and in many cases, repeat blood samples were not performed. Another problem was how to interpret the results of the TFT, which reflects the TSH surge at birth with a subsequent increase in T4 levels

Table 5 Clinical and biochemical characteristics of the four newborns with thyroid diseases.

Patient no.	**1**	**2**	**3**	**4**	**Normal range**
Gender	F	M	M	M	
Maternal disease	SCH	Hashimoto's thyroiditis	Non-autoimmune hypothyroidism	Hypothyroidism post-thyroidectomy due to Graves' disease	
Maternal treatment	LT4	LT4	LT4	LT4	
Screening TT4 (µg/dL)	9.0	14.2	12	20.22	>10
Screening TSH (mIU/L)	6.5	ND	ND	ND	<20
Age (day)	4	4	3	6	
TSH (mIU/L)	7.26	13.3	22.5	<0.03	0.4–10[a]
FT4 (pmol/L)	8.9	24.9	21.9	46.98	10–26.8[a]
Thyroid antibodies	Negative	Negative	Negative	Positive	1.0–2.5
Medications	LT4	LT4	LT4	(TSI = 12.8 mIU/L) Methimazole Beta-blockers	
Day of therapy initiation	8 days	2 years	19 days	6 days	
Diagnosis	MPHD (TSH, ACTH, GH)	Persistent congenital hyperthyrotropinemia	Transient familial CH	Neonatal Graves' disease	

[a]Normal range for the first week of life.

CH, congenital hypothyroidism; F, female; M, male; MPHD, multiple pituitary hormone deficiency; SCH, sub-clinical hypothyroidism; TSI, thyroid-stimulating immunoglobulin.

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over the following days (17). To avoid unnecessary repeated blood collection, we used our normal ranges for newborns, which are higher than those for adults.

The incidence of obstetric complications, including cesarean section and preterm delivery, was higher for mothers with thyroid dysfunction compared to the average incidence at our center. A high risk of obstetric complications has been reported in pregnancies involving maternal hypothyroidism (2, 4, 8).

Mothers with hypothyroidism, hyperthyroidism and SCH were included in this study. Most of the mothers had hypothyroidism, about half due to Hashimoto's thyroiditis. The prevalence of hypothyroidism during pregnancy in the United States is estimated at approximately 2–3%, most of which (2–2.5%) is subclinical (30). Maternal immunoglobulins in Hashimoto's thyroiditis, including TPOAb, TgAb and TBAb, can cross the placenta from mid gestation and affect fetal thyroid development and function (22). Whereas TPOAb and TgAb have only a minor effect on the fetal thyroid (14), maternal TBAb inhibits fetal thyroid hormone production and may cause transient neonatal CH (14, 31, 32, 33, 34, 35). However, CH due to maternal TBAb is very rare, with incidence ranging between 1:84,700 and 1:310,000 (27). Only a few laboratories can perform TBAb measurements and therefore, we have no data on the presence of TBAb in our cohort. Although 87 infants had elevated TSH (>10 mIU/L), FT4 levels were within the normal range and repeated TSH tests were normal, excluding CH in these infants. Hyperthyroidism was found in 8.6% of our cohort, among them, 71.6% due to Graves' disease. Maternal Graves' disease is associated with obstetric complications such as stillbirth, preterm delivery and pre-eclampsia and fetal complications such as intrauterine growth retardation (12, 13). Newborn thyrotoxicosis results from the passage of TSI through the placenta which induces fetal thyroid hormone production (12). High maternal TSI is the main predictor of fetal and newborn Graves' disease. Nevertheless, the incidence of neonatal Graves' disease has been estimated at only 1–5% of infants born to mothers with Graves' disease (14). Luton *et al.* (35) showed a high rate of fetal thyroid disease (6% with Graves' disease and 10% with hypothyroidism) among a cohort of 72 mothers with past or present Graves' disease. However, in our study, among the 43 mothers with Graves' disease, only 1 infant (Patient 4) developed neonatal Graves' disease. It has been recommended that in cases of high maternal TSI (≥3.7 times the upper reference limit), or when results are not available, umbilical cord blood be taken for TSI, TSH and FT4 determinations and the infant be examined for signs of hyperthyroidism (2, 14).

Maternal SCH that was diagnosed during pregnancy was found in only 5% of the cohort. Treatment of women with SCH (TSH > 2.5 mIU/L) during pregnancy is debated, with no consensus regarding the outcome of these pregnancies and its effect on the newborns (10, 27, 36, 37, 38, 39).

The usefulness of newborn TFT screening has been examined in several studies but the results are inconsistent (3, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30). Underland *et al.* (26) found 7 infants with CH who required LT4 therapy in a cohort of 352 newborns of mothers with thyroid dysfunction; among them, 3 (0.9%) were not detected by the newborn screens. These three were classified as having SCH and were still being treated at the age of 3 years. Based on their findings, they proposed that infants with a maternal history of thyroid disease may require additional testing beyond the newborn screening. Haim *et al.* (20) studied 1392 newborns of mothers with hypothyroidism and found 8 babies with CH. However, all of these infants were detected by the newborn screening program. Their conclusion was that TFT for infants from mothers with hypothyroidism, additional to the newborn screening, have no clinical benefit (20).

In our cohort, we found 87 infants with TSH above 10 mIU/L and 11 infants with TSH above 20 mIU/L. All of them had FT4 within the normal range. The newborn screening of these infants did not detect any CH. LT4 therapy was initiated for three infants. Patient 1 was a female twin who had central hypothyroidism as part of MPHD. The diagnosis of MPHD in this baby was not related to her mother's thyroid dysfunction. Patient 2 was born to a mother with Hashimoto's thyroiditis, but he was not affected by maternal autoantibodies. He had non-autoimmune euthyroid persistent hyperthyrotropinemia and LT4 supplement therapy was initiated only at the age of 2 years. Patient 3 was born to first cousin parents. His mother had non-autoimmune hypothyroidism and his older sister had transient CH. Newborn screening and the first laboratory TFT were normal; however, overt hypothyroidism was detected at the age of 19 days following repeated TFT. He was ultimately diagnosed with transient familial CH, probably due to a thyroid synthesis enzyme defect. This finding indicates that in the case of CH in a sibling, serum TFT is justified. Importantly, screening of all babies of mothers with thyroid dysfunction comes at a significant expense, causing infant stress due to blood drawing as well as parental anxiety.

This study is one of the larger ones including mothers with thyroid dysfunction, regardless of the specific diagnosis; other reports have included only mothers

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with hypothyroidism or autoimmune hypothyroidism. The limitation of our study is that it is retrospective study and lacks a control group, as well as data on maternal and newborn thyroid autoantibodies. Our results have important practical clinical implications for the neonatal departments as well as for the pediatric endocrinologists.

In conclusion, our findings indicate that performing TFT as routine practice for all newborns of mothers with thyroid dysfunction is redundant. However, in cases of CH in siblings, TFT, in addition to newborn thyroid screening, are recommended and more careful follow-up is indicated. In maternal Graves' disease, TFT on umbilical cord blood or blood drawn on day 2–3 of life are recommended.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Statement of ethics

The current study complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Due to its retrospective nature, informed consent to collect medical file's data was not obtained from each participant and the study protocol, design and data collection method were approved by the Ha'Emek Medical Center Ethics Committee (0111-18-EMC).

Data availability statement

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

Author contribution statement

Z S B-Z and Y T R designed the study, analyzed and interpreted the data and wrote, reviewed and revised the manuscript. M P designed the study, analyzed and interpreted the data and reviewed and revised the manuscript. S A collected the newborn screening results and reviewed and revised the manuscript. C F, S A W, and A L reviewed and revised the manuscript. All authors approved the final manuscript and agreed to be accountable for the content of the work.

Acknowledgements

The authors thank Camille Vainstein for professional English editing, Shiraz Vered and Naama Schwartz for statistical analyses and the families for kind collaboration.

References

1 Negro R & Westman JH. Thyroid disease in pregnancy. *Best Practice and Research: Clinical Endocrinology and Metabolism* 2011 **25** 927–943. (https://doi.org/10.1016/j.beem.2011.07.010)

2 Korevaar TIM, Medici M, Visser TJ & Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. *Nature Reviews: Endocrinology* 2017 **13** 610–622. (https://doi.org/10.1038/nrendo.2017.93)

3 Ozdemir H, Akman I, Coskun S, Demirel U, Turan S, Bereket A, Bilgen H & Ozek E. Maternal thyroid dysfunction and neonatal thyroid problems. *International Journal of Endocrinology* 2013 **2013** 987843. (https://doi.org/10.1155/2013/987843)

4 Wikner BN, Sparre LS, Stiller COS, Källén B & Asker C. Maternal use of thyroid hormones in pregnancy and neonatal outcome. *Acta Obstetricia et Gynecologica Scandinavica* 2008 **87** 617–627. (https://doi.org/10.1080/00016340802075103)

5 Pop VJ, Brouwers EP, Vader HL, Vulsma T, Van Baar AL & De Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. *Clinical Endocrinology* 2003 **59** 282–288. (https://doi.org/10.1046/j.1365-2265.2003.01822.x)

6 Gutvirtz G, Walfisch A, Wainstock T, Landau D & Sheiner E. Maternal hypothyroidism and future pediatric neurological morbidity of the offspring. *Archives of Gynecology and Obstetrics* 2019 **299** 975–981. (https://doi.org/10.1007/s00404-019-05092-1)

7 de Escobar GM, Obregón MJ & Escobar del Rey F. Maternal thyroid hormones early in pregnancy and fetal brain development. *Best Practice and Research in Clinical Endocrinology and Metabolism* 2004 **18** 225–248. (https://doi.org/10.1016/j.beem.2004.03.012)

8 Cignini P, Cafà EV, Giorlandino C, Capriglione S, Spata A & Dugo N. Thyroid physiology and common diseases in pregnancy: review of literature. *Journal of Prenatal Medicine* 2012 **6** 64–71.

9 Smallridge RC & Ladenson PW. Hypothyroidism in pregnancy: consequences to neonatal health. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 2349–2353. (https://doi.org/10.1210/jcem.86.6.7577)

10 Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, Teng X, Guo R, Wang H, Li J, *et al.* Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25–30 months. *Clinical Endocrinology* 2010 **72** 825–829. (https://doi.org/10.1111/j.1365-2265.2009.03743.x)

11 Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, *et al.* Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *New England Journal of Medicine* 1999 **341** 549–555. (https://doi.org/10.1056/NEJM199908193410801)

12 Cooper DS & Laurberg P. Hyperthyroidism in pregnancy. *Lancet: Diabetes and Endocrinology* 2013 **1** 238–249. (https://doi.org/10.1016/S2213-8587(13)70086-X)

13 van der Kaay DC, Wasserman JD & Palmert MR. Management of neonates born to mothers with Graves' disease. *Pediatrics* 2016 **137** e20151878. (https://doi.org/10.1542/peds.2015-1878)

14 van Trotsenburg ASP. Management of neonates born to mothers with thyroid dysfunction, and points for attention during pregnancy. *Best Practice and Research: Clinical Endocrinology and Metabolism* 2020 **34** 101437. (https://doi.org/10.1016/j.beem.2020.101437)

15 Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, *et al.* 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid* 2017 **27** 315–389. (https://doi.org/10.1089/thy.2016.0457)

16 De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, Eastman CJ, Lazarus JH, Luton D, Mandel SJ, *et al.* Management of thyroid dysfunction during pregnancy and

postpartum: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 2543–2565. (https://doi.org/10.1210/jc.2011-2803)
17 van Trotsenburg P, Stoupa A, Léger J, Rohrer T, Peters C, Fugazzola L, Cassio A, Heinrichs C, Beauloye V, Pohlenz J, *et al.* Congenital hypothyroidism: a 2020–2021 consensus guidelines update – an endo-European reference network initiative endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology. *Thyroid* 2021 **31** 387–419. (https://doi.org/10.1089/thy.2020.0333)
18 Eng L & Lam L. Thyroid function during the fetal and neonatal periods. *NeoReviews* 2020 **21** e30–e36. (https://doi.org/10.1542/neo.21-1-e30)
19 Ogilvy-Stuart AL. Neonatal thyroid disorders. *Archives of Disease in Childhood: Fetal and Neonatal Edition* 2002 **87** F165–F171. (https://doi.org/10.1136/fn.87.3.f165)
20 Haim A, Wainstock T, Almashanu S, Loewenthal N, Sheiner E, Hershkovitz E & Landau D. Thyroid function tests in newborns of mothers with hypothyroidism. *European Journal of Pediatrics* 2021 **180** 519–525. (https://doi.org/10.1007/s00431-020-03895-y)
21 Banakar MK & Formosa M. Serum thyroid function tests in neonates of mothers with thyroid disease. *Indian Journal of Pediatrics* 2011 **78** 870–873. (https://doi.org/10.1007/s12098-010-0337-1)
22 Balomenou F, Siomou E, Kolios G, Bairaktari E, Tzoufi M & Giapros V. Are thyroid function tests in neonates born to mothers with hypothyroidism clinically useful? *Early Human Development* 2019 **139** 104877. (https://doi.org/10.1016/j.earlhumdev.2019.104877)
23 Habeb AM, Zubier M, Pairaudeau P & Mathew V. Do we need to assess the thyroid function in the infants of mothers with Hashimoto's thyroiditis? *Archives of Disease in Childhood: Fetal and Neonatal Edition* 2003 **88** F258. (https://doi.org/10.1136/fn.88.3.f258)
24 McGovern M, Reyani Z, O'Connor P, White M & Miletin J. Thyroid function testing in neonates born to women with hypothyroidism. *European Journal of Pediatrics* 2016 **175** 2015–2018. (https://doi.org/10.1007/s00431-016-2793-8)
25 Fernandez Rodriguez B & Perez Diaz AJ. Evaluation of a follow up protocol of infants born to mothers with antithyroid antibodies during pregnancy. *Journal of Maternal-Fetal and Neonatal Medicine* 2018 **31** 312–319. (https://doi.org/10.1080/14767058.2017.1285886)
26 Underland L, Kenigsberg L, Derrick KM, Crespi R, Kaushal T & Lam L. Thyroid function testing in neonates with maternal history of disease. *Clinical Pediatrics* 2018 **57** 436–441. (https://doi.org/10.1177/0009922817729484)
27 Weber G, Vigone MC, Rapa A, Bona G & Chiumello G. Neonatal transient hypothyroidism: aetiological study. Italian Collaborative Study on Transient Hypothyroidism. *Archives of Disease in Childhood: Fetal and Neonatal Edition* 1998 **79** F70–F72. (https://doi.org/10.1136/fn.79.1.f70)
28 Rovelli R, Vigone MC, Giovanettoni C, Passoni A, Maina L, Corrias A, Corbetta C, Mosca F, Chiumello G & Weber G. Newborn of mothers affected by autoimmune thyroiditis: the importance of thyroid function monitoring in the first months of life. *Italian Journal of Pediatrics* 2010 **36** 24. (https://doi.org/10.1186/1824-7288-36-24)
29 Büyükgebiz A. Newborn screening for congenital hypothyroidism. *Journal of Clinical Research in Pediatric Endocrinology* 2013 **5** (Supplement 1) 8–12. (https://doi.org/10.4274/jcrpe.845)
30 Saki F, Dabbaghmanesh MH, Ghaemi SZ, Forouhari S, Omrani GR & Bakhshayeshkaram M. Thyroid autoimmunity in pregnancy and its influences on maternal and fetal outcome in Iran (a prospective study). *Endocrine Research* 2015 **40** 139–145. (https://doi.org/10.3109/07435800.2014.966384)
31 Mahadik K, Choudhary P & Roy PK. Study of thyroid function in pregnancy, its feto-maternal outcome; a prospective observational study. *BMC Pregnancy and Childbirth* 2020 **20** 769. (https://doi.org/10.1186/s12884-020-03448-z)
32 Rakover Y, Sadeh O, Sobel E, Shneyour A & Kraiem Z. A case of transient hypothyroidism: sequential serum measurements of autoantibodies inhibiting thyrotropin-stimulated thyroid cAMP production in a neonate. *Acta Endocrinologica* 1990 **123** 118–122. (https://doi.org/10.1530/acta.0.1230118)
33 Brown RS, Alter CA & Sadeghi-Nejad A. Severe unsuspected maternal hypothyroidism discovered after the diagnosis of thyrotropin receptor-blocking antibody-induced congenital hypothyroidism in the neonate: failure to recognize and implications to the fetus. *Hormone Research in Paediatrics* 2015 **83** 132–135. (https://doi.org/10.1159/000368671)
34 Evans C, Gregory JW, Barton J, Bidder C, Gibbs J, Pryce R, Al-Muzaffar I, Ludgate M, Warner J, John R, *et al.* Transient congenital hypothyroidism due to thyroid-stimulating hormone receptor blocking antibodies: a case series. *Annals of Clinical Biochemistry* 2011 **48** 386–390. (https://doi.org/10.1258/acb.2011.011007)
35 Luton D, Le Gac I & Vuillard E, Castanet M, Guibourdenche J, Noel M, Toubert ME, Léger J, Boissinot C, Schlageter MH, *et al.* Management of Graves' disease during pregnancy: the key role of fetal thyroid gland monitoring. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 6093–6098. (https://doi.org/10.1210/jc.2004-2555)
36 Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R & Vaidya B. 2014 European Thyroid Association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *European Thyroid Journal* 2014 **3** 76–94. (https://doi.org/10.1159/000362597)
37 Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, *et al.* Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2011 **21** 1081–1125. (https://doi.org/10.1089/thy.2011.0087)
38 Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, Reddy UM, Wapner RJ, Thorp JM Jr, Saade G, *et al.* Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. *New England Journal of Medicine* 2017 **376** 815–825. (https://doi.org/10.1056/NEJMoa1606205)
39 Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina A, Rees R, Chiusano E, John R, Guaraldo V, George LM, *et al.* Antenatal thyroid screening and childhood cognitive function. *New England Journal of Medicine* 2012 **366** 493–501. (https://doi.org/10.1056/NEJMoa1106104)

Received in final form 15 May 2022
Accepted 25 May 2022
Accepted Manuscript published online 25 May 2022