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Neonatal Outcomes of Pregnancies Complicated by Maternal Hyperthyroidism

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Abstract

Objective. This study aimed to determine the proportion, clinical characteristics, hormonal status, median time for normalization of serum thyroxine (FT4) and thyroid-stimulating hormone (TSH) and factors affecting time to thyroid function test (TFT) normalization of neonates born to mothers with maternal hyperthyroidism admitted in our institution.

Methodology. This was a retrospective cohort study that included 170 newborns admitted to the Neonatal Intensive Care Unit (NICU) of Hospital Universiti Sains Malaysia (HUSM) with a history of maternal hyperthyroidism from January 2013 until December 2018. We analyzed their baseline demographic and clinical characteristics, maternal thyroid status and antibody levels. Finally, we analyzed newborn thyroid function and thyroid antibodies.

Results. The proportion of neonates born to mothers with maternal hyperthyroidism was 0.8% (170 of 20,198 neonates within the study period). Seven (4.1%) developed overt hyperthyroidism, while four (2.4%) had thyroid storm. The median time for thyroid function test normalization was 30 days (95% CI: 27.1 to 32.8). The median time for TFT normalization was longer among neonates of mothers with positive thyroid antibodies [46.6 days (95% CI, 20.6 to 39.4)] and of mothers who received anti-thyroid treatment [31.7 days (95% CI, 23.5 to 39.9)].

Conclusion. Neonates born to mothers with hyperthyroidism is uncommon. These babies were observed to have a longer time for normalization of thyroid function tests if their mothers had thyroid antibodies or received anti-thyroid treatment.

Key words: neonatal thyrotoxicosis, maternal hyperthyroidism, Graves' disease (GD)

INTRODUCTION

Thyroid hormones are important for linear growth, central nervous system myelination and regulation of many metabolic activities in infancy.[1] Routine newborn screening for congenital hypothyroidism was introduced in 1993 by the American Academy of Pediatrics. Newborn screening for congenital hypothyroidism in Malaysia was started in October 1998.[2]

There is a lack of consensus in identifying neonates who are at risk for hyperthyroidism. Neonates born to hyperthyroid mothers, particularly those with Grave's disease (GD), are at risk for significant morbidity and mortality.[3] The prevalence of hyperthyroidism in pregnancy ranges from 0.7 to 2.8% worldwide.[4,5] In Malaysia, studies have shown that the incidence of hyperthyroidism in pregnancy is 0.9 per 1000 deliveries, with GD as the most common etiology.[6] Other etiologies of hyperthyroidism in pregnancy are toxic adenoma, toxic nodular goiter, thyroiditis, gestational hyperthyroidism and mutations in the TSH receptor.[7]

The causative antibodies in GD are thyroid-stimulating hormone receptor antibodies (TRAb) that belong to the immunoglobulin G class. TRAbs cross the placenta freely, particularly during the second half of pregnancy.[8] TRAbs are of two types: TSH-receptor stimulating antibodies that bind to the TSH receptor on thyroid follicular cells and lead to autonomous thyroid hormone production, and TSH-receptor blocking antibodies that bind to the TSH-receptor but do not initiate intracellular signaling, and result in suppression of thyroid hormone synthesis.[9]

Fetal thyroid development is established at seven weeks of gestation. At ten to 12 weeks of gestation, thyroid hormone synthesis begins and becomes functionally mature by 25 weeks. Transfer of these stimulating TRAbs to the fetus can cause *in utero* and/or postnatal hyperthyroidism.[10]

Neonatal thyroid storm is a serious complication of neonates born to mothers with GD. The European Society for Pediatric Endocrinology (ESPE) Consensus Guidelines recommend that babies born to mothers with hyperthyroidism need

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repeat TFT in the first week of life, or on the third to fifth day of life.[11] However, there are no clear guidelines on subsequent management and follow-up of neonates born to mothers with hyperthyroidism. Hence, we sought to study the outcomes of neonates born to mothers with hyperthyroidism, specifically to estimate the median time to normalization of thyroid function and to identify factors that may affect time to normalization of thyroid function.

OBJECTIVES

We aimed to determine the proportion, clinical characteristics, hormonal status, median time for serum FT4 and TSH normalization and factors affecting time to normalization of TFTs of neonates born to mothers with maternal hyperthyroidism admitted to the NICU of Hospital Universiti Sains Malaysia.

METHODOLOGY

Study Design

We conducted a retrospective cohort study covering the period of January 2013 until December 2018. We included neonates born to mothers with hyperthyroidism and admitted to the NICU.

Subjects and Procedures

In HUSM, all neonates born to mothers with hyperthyroidism are routinely admitted at the NICU. Records of neonates of mothers with hyperthyroidism admitted from January 1, 2013 to December 31, 2018 were reviewed.

We excluded subjects with inadequate crucial data, specifically those lacking the date of diagnosis, three or more sociodemographic variables of interest (birth weight, length, head circumference, gestational age, gender, mode of delivery) and follow-up records.

We collected demographic, anthropometric (birth weight, length and head circumference) and clinical data (heart rate, blood pressure, respiratory rate) during initial admission. Maternal demographic characteristics, TFTs, presence of thyroid antibodies and anti-thyroid treatment were also collected.

TFT monitoring was done through cord blood as part of the congenital hypothyroidism screening program and on the third to fifth day of life. Serial TFTs were monitored in babies who had abnormal results, with determinations from cord blood on days 3 to 5, 15, 30, 45, 60, 90 and 180 of life.

Statistical Analysis

Data analysis was done using Statistical Package for Social Science (SPSS) IBM version 26.0. Continuous data were presented as mean (standard deviation, SD) or median (interquartile range, IQR) based on their probability distribution. Categorical data were presented as frequency (percentage). The proportion of neonates born to mothers with hyperthyroidism was calculated by using the total number of newborns admitted to the NICU within the study period as the denominator. The median time for normalization of TFTs was analyzed with Kaplan-Meier survival analysis. Cox proportional hazard regression test was used to calculate associated factors in TFT normalization.

The sample size determination was conducted based on calculation for survival analysis (log-rank test) using G*power software. The median time to normalization among newborns without maternal thyroid antibodies (designated as group *m1*) is four weeks, based on a previous study/expert opinion. The expected time of normalization among newborns with maternal thyroid antibodies (group *m2*) is 12 weeks. Given the accrual time of 312 weeks and additional follow-up time of 52 weeks, the ratio *m2* and *m1* is 0.4. The required sample sizes were 49 for *m1* and 25 for *m2*, for a total of 74 newborns, at 5% type I error and 80% power. Anticipating missing data of 10%, the corrected sample size was 82.

Ethical Approval

This study was approved by the Human Research Ethics Committee USM with reference USM/JEPeM/20100533.

RESULTS

There were 20,198 newborns admitted during the study period. Of these, we identified 186 neonates born to mothers with hyperthyroidism. A total of 170 (0.8%) were included in the study. Sixteen were excluded: three died a few hours after birth due to prematurity and another 13 were born to mothers who had hypothyroidism rather than hyperthyroidism.

Tables 1 and 2 summarize the demographic, clinical and biochemical characteristics of the included neonates. Seventy-seven (45.3 %) were male. The mean gestational age was 38.2 ± 1.5 weeks, and mean birth weight was 2.9 ± 0.5 kg. Majority (81.8%) were delivered via spontaneous vaginal delivery, and had an APGAR score of at least 7 at five minutes (97.1%). Most had normal vital signs: mean heart rate was 131.3 ± 15.9 beats per minute; mean respiratory rate 46.9 ± 8.8 breaths per minute; and mean systolic and diastolic pressures of 73.2 ± 5 mmHg and 44.8 ± 3.3 mmHg, respectively. Median length of stay was 22.3 ± 24.4 days. Mean cord TSH was 15.0 ± 23.1 mIU/L [reference value (RV) 0.001-101 mIU/L], while mean cord FT4 was 25.1 ± 29.6 pmol/L (RV 5.0-85.2 pmol/L). Most (60.0%) had abnormal TFTs at days 3 to 5. These abnormal TFTs were classified into seven categories: subclinical hyperthyroidism; subclinical hypothyroidism; isolated high FT4; overt hyperthyroidism; overt hypothyroidism; high FT4, high TSH; and sick euthyroid (Table 3).

Table 1. Clinical characteristics of newborns with maternal hyperthyroidism

Variable	Mean ± SD[a] / Frequency (%)[b]
Anthropometry	
Birth weight, kg	2.9 ± 0.5
Head circumference, cm	32.3 ± 1.7
Length, cm	49.8 ±3.3
Age of gestation, week	38.2 ± 1.5
Male gender	77 (45.3)
Race	
Malay	162 (95.3)
Others	8 (4.7)
APGAR score	
Poor	5.2 (2.9)
Good	165 (97.1)
Vital signs	
Heart rate, beats per minute	131.3 ± 15.9
Respiratory rate, beats per minute	46.9 ± 8.8
Systolic blood pressure, mmHg	73.2 ± 5.0
Diastolic blood pressure, mmHg	44.8 ± 3.3
Mode of delivery	
Spontaneous vaginal delivery	139 (81.8)
Lower segment Caesarean section	31 (18.2)
Length of stay, day	22.3 ± 24.4

[a]Mean ± SD (standard deviation) for numerical variables
[b]Frequency and percentages for categorical variables

Table 2. Biochemical and clinical characteristics of newborns with maternal hyperthyroidism

Variable	Mean ± SD[a] / Frequency (%)[b]	Reference value
Maternal autoantibodies present	21 (12.4)	
Maternal anti-thyroglobulin, kIU/L	711.7 ± 1299.0	Up to 115 kIU/L
Maternal anti-thyroid peroxidase, kIUL	117.8 ± 173.5	Up to 34 kIU/L
Mother received treatment	105 (61.8)	
Neonatal anti-thyroglobulin, kIU/L	45.88 ± 143.26	Up to 115 kIU/L
Neonatal anti-thyroid peroxidase, kIU/L	25.89 ± 53.54	Up to 34 kIU/L
Cord thyroid function tests		
TSH, mIU/L	15.0 ± 23.0	<20 mIU/L
Free thyroxine, pmol/L	25.1 ± 29.6	15 pmol/L
Day 3 to 5 thyroid function tests		
TSH, mIU/L	5.7 ± 10.1	0.5-6.0 mIU/L
Free thyroxine, pmol/L	27.3 ± 18.5	12-15 pmol/L
Day 15 thyroid function tests		
TSH, mIU/L	5.7 ± 9.7	0.5-4.0 mIU/L
Free thyroxine, pmol/L	34.6 ± 33.1	10-24 pmol/L
Neonate diagnosed overt hyperthyroidism	7 (4.1)[c]	
Neonate diagnosed with thyroid storm	4 (2.4)	

[a]Mean ± SD (standard deviation) for numerical variables
[b]Frequency and percentages for categorical variables
[c]Characteristics described in Tables 4 and 5

Eighteen (10.6%) newborns had normal TFTs at days 3 to 5. At day 15 of life, fewer newborns had abnormal TFTs (from 102 to 19, 11.2%). Most were seen in groups with isolated high FT4 (28, 15.5%); overt hyperthyroidism (4, 2.2%) and high FT4, high TSH (7, 3.9%). However, there was an increase in subclinical hyperthyroidism (from 1 to 2, 1.1%), subclinical hypothyroidism (from 7 to 9, 5.0%) and overt hypothyroidism (from 2 to 5, 2.8%). Thirty-nine (22.9%) newborns had normalization of TFTs on day 15. At days 3 to 5, mean TSH was 5.7 ± 10.1 mIU/L, while mean FT4 was 27.3 ± 18.5 pmol/L. At day 15, mean TSH was 5.7 ± 9.7 mIU/L and mean FT4 was 34.6 ± 33.1 pmol/L (Figure 1).

Seven newborns had overt hyperthyroidism. Of these, four had thyroid storm and were started on Lugol's iodine, carbimazole and propranolol. Medications were stopped in all four newborns with subsequent normalization of TFTs from one to four months of life. All seven newborns were born to mothers with GD: three were diagnosed before pregnancy, while four had mothers who were diagnosed during the second trimester. Serum TRAb was not routinely done in all mothers and newborns: only three newborns and 2 mothers had TRAb done, which were positive (Tables 4 and 5).

Majority of the mothers were diagnosed with hyperthyroidism without specific etiology (142, (83%) (Table 4). The rest had GD (7, 4.1%), gestational hyperthyroidism (3, 1.8%), thyroid nodule (1, 0.5%), goiter (15, 8.8%) and post-total thyroidectomy (2, 1%). Most of the mothers were diagnosed with hyperthyroidism before pregnancy. Only four (2.3%) were diagnosed with GD in the second/third trimester. There were 21 (12.4%) mothers who had thyroid antibodies and 149 (87.6%) who did not have thyroid antibodies. TRAb was only measured in one patient whose mother which turned out to be positive. Mean maternal anti-thyroglobulin (anti-Tg) level was 711.7 ± 1299.0 kIU/L, and mean maternal anti-thyroid peroxidase (anti-TPO) was 117.8 ± 173.5 kIU/L. Most of the mothers received treatment (105, 61.8%) for hyperthyroidism, and most received anti-thyroid drugs (ATDs) only (95, 55.8%).

Differences in median time of TFTs to normalize by presence of maternal thyroid autoantibodies and maternal

Table 3. Categories of abnormal thyroid function tests in newborns

Category	TSH	FT4	Total T3[a] or Free T3[a]
Subclinical hyperthyroidism	Low or undetectable, <0.5 mIU/L	Normal, 10-24 pmol/L	Normal
Overt hyperthyroidism	Low, <0.5 mIU/L	High, >24 pmol/L	
Subclinical hypothyroidism	High, First 30 days of life: 6-20 mIU/L After 30 days of life: 6-10 mIU/L	Normal, First 30 days of life: 10-24 pmol/L After 30 days of life: 10-22 pmol/L	
Overt hypothyroidism	High, First 30 days of life: ≥20 mIU/L After 30 days of life: ≥6 mIU/L	Low, First 30 days of life: ≤15 pmol/L After 30 days of life: ≤10 pmol/L	
Isolated elevated FT4	Normal, 0.5-6.0 mIU/L	High, >24 pmol/L	
High FT4, high TSH	High, >6 mIU/L	High, >24 pmol/L	
Sick euthyroid/central hypothyroidism	Low, 6-10 mIU/L or low	Low, ≤10 pmol/L	

[a]T3, triiodothyronine

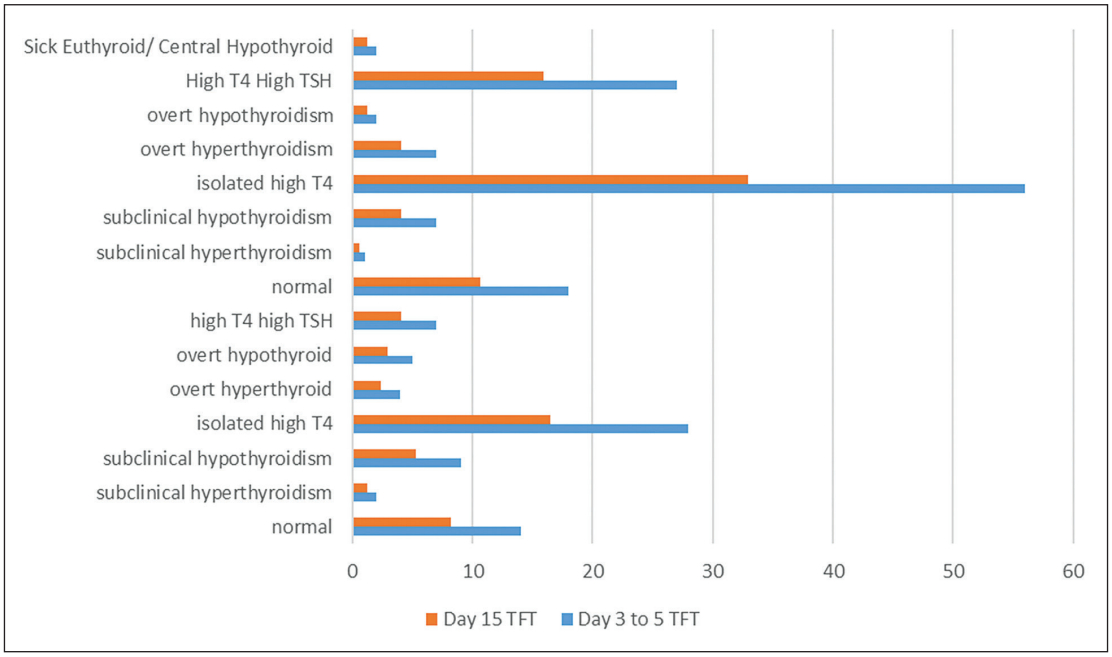

Figure 1. Comparison of categories of abnormal thyroid function tests on day 3 to 5 and day 15 of life. *TFT, thyroid function test.*

treatment are summarized in Table 6. Kaplan-Meier analysis revealed that the overall median time for TFTs to normalize was 30 days (95% CI, 27.1 to 32.8). Among newborns with mothers who had thyroid antibodies, the median time of TFT normalization was longer at 46.6 days (95% CI, 20.6 to 39.4) compared to newborns whose mothers did not have thyroid antibodies [26.2 days (95% CI, 22.0 to 30.4). In terms of maternal thyroid treatment, TFT normalization appeared to be slowest among neonates whose mothers were on thyroxine, at 95.0 days (95% CI, 11.2 to 178.7). Cox proportional hazard regression analysis revealed that none of the variables were significant.

Table 4. Summary of maternal thyroid function tests and antibodies of newborns with overt hyperthyroidism

Case	At diagnosis		At delivery		Antibodies			Treatment
	TSH, mIU/L	FT4, pmol/L	TSH, mIU/L	FT4, pmol/L	Anti-TPO[a], kIU/L	Anti-Tg[b], kIU/L	Anti-TRAb[c], U/L	
1	0.01	23.2	0.01	24.5	156.4	<10	-	Prophylthiuracil, Propanolol
2	0.25	47.4	0.01	29.4	Not done[d]	Not done[d]	Not done[d]	Carbimazole
3	0.01	25.0	28.6	9.5	>600	>4000	-	Thyroxine
4	0.001	52.6	0.01	18.3	22.4	21.1	-	Carbimazole
5	0.67	25.0	0.005	47.0	8.5	<10	-	not mentioned
6	0.01	72.0	0.01	91.0	11.5	88.28	39.8	Carbimazole
7	0.09	59.0	0.01	68.0	-	-	-	Propanolol, Carbimazole

[a]Anti-TPO, thyroid peroxidase antibody
[b]Anti-Tg, thyroglobulin antibody
[c]Anti-TRAb, thyroid receptor antibody
[d]Mother had thyroid storm during pregnancy

Table 5. Summary of thyroid function tests and antibodies of newborns with overt hyperthyroidism

Case	Day 3-5		Day 15		Day 30		Antibodies			Treatment given
	TSH, mIU/L	FT4, pmol/L	TSH, mIU/L	FFT4, pmol/L	TSH, mIU/L	FT4, pmol/L	Anti-TPO[a], kIU/L	Anti-Tg[b], kIU/L	Anti-TRAb[c], U/L	
1	0.01	>100	0.01	21.7	2.6	21.9	7.92	11.73	-	Yes
2	0.04	63.0	0.03	38.2	1.8	16.2	6.1	<10	Not done[d]	Yes
3	-	52.4	2.6	44.7	2.6	26.4	-	356.4	-	No
4	0.01	8.3	0.001	21.9	0.02	27.3	13.5	51.8	-	No
5	0.05	55.0	0.04	25.7	0.01	20.0	<5	<10	28.3	Yes
6	0.02	38.0	0.04	10.3	0.7	3.8	20.25	21.82	37.1	Yes
7	0.03	29.0	0.02	29.0	0.05	23.3	78.9	16	18.6	No

[a]Anti-TPO, thyroid peroxidase antibody
[b]Anti-Tg, thyroglobulin antibody
[c]Anti-TRAb, thyroid receptor antibody
[d]Mother had thyroid storm during pregnancy

Table 6. Analysis of time to normalization of thyroid function tests in newborns with maternal hyperthyroidism

Variable	N (%)	Median, days (95% CI)	Log rank (df)	*p* value
Presence of maternal autoantibodies			4.602 (1)	0.03
Yes	21 (12.4)	46.6 (20.6-39.4)		
No	149 (87.6)	26.2 (22.0-30.4)		
Mother received treatment during pregnancy			3.898 (1)	0.05
Yes	105 (61.8)	31.7 (23.5-39.9)		
No	61 (35.9)	21.4 (16.2-26.5)		
Type of medication received by mother			10.861 (3)	0.01
Carbimazole	49 (28.8)	29.4 (23.7-35.0)		
Propylthyiouracil (PTU)	33 (19.4)	25.8 (18.5-33.0)		
Combined Carbimazole and PTU	13 (76)	21.6 (10.8-32.3)		
Thyroxine	9 (5.3)	95.0 (11.2-178.7)		

[a]Kaplan-Meier analysis
[b]*p* value <0.05 statistically significant
[c]Characteristics described in Tables 5 and 6

DISCUSSION

The proportion of newborns affected by maternal hyperthyroidism at the NICU of HUSM from 2013 until 2018 was 0.8%. This finding is consistent with the study by Laurberg and Andersen where the prevalence of maternal hyperthyroidism was 0.7%.[4] Our finding was slightly lower in comparison to the study by Dulek et al., which reported a prevalence of 2.8%.[5] We found that male and female newborns were equally affected, consistent with other studies.[10,12,13] This implies that TRAbs from mothers are transferred to the fetus regardless of gender. Most of the newborns were born term with normal birth weight, similar to most studies.[12,13] Most of our newborns were delivered via SVD with good APGAR scores. These findings may reflect that majority of the babies born to mothers with hyperthyroidism had stable thyroid disease with or without maternal treatment with anti-thyroid drugs.

Our study had longer mean length of hospital stay (22.3 ± 24.4 days) in contrast to the study by Männistö (10 days).[14] The longer hospital stay may be explained by the delay in the onset of neonatal hyperthyroidism. This may be due to both the effect of maternal transplacental passage of TRAb and maternal transplacental passage of ATD, wherein more than 95% of newborns may develop symptoms anytime between day 1 until day 29 of life, peaking in the first 2 weeks of life.[15] Because TRAb measurement is not routinely performed in mothers with hyperthyroidism in our hospital, it becomes a challenge to foresee who would eventually develop neonatal hyperthyroidism.

Among seven newborns who had overt hyperthyroidism, four had thyroid storm and were started on Lugol's iodine, carbimazole and propranolol. All four had mothers diagnosed with GD. Though TRAb levels are not routinely measured at our institution, most mothers were screened for anti-TPO and anti-Tg. The presence of anti-TPO/anti-Tg is suggestive of autoimmune thyroiditis, but it is not specific for GD. About 10% of GD may also test positive for anti-TPO/anti-Tg.

Thyroid storm or thyrotoxic crisis is an acute, life threatening, hypermetabolic state induced by excessive release of thyroid hormone.[16] The hypermetabolic state is characterized by hemodynamic instability, manifesting as tachycardia, tachypnea, fever and hypertension. Neurologically, babies appear irritable with wide open eyes, jitteriness and difficulty in sleeping.[17] Babies with thyroid storm may also exhibit increased appetite, diarrhea and vomiting. Severe thyroid storm may result in heart failure, pulmonary hypertension and convulsions.[18] All four babies who were treated as thyroid storm had not only overt hyperthyroidism biochemically, but also had systemic manifestations characterized by tachycardia (heart rate 160 to 200 beats per minute), respiratory distress, irritability, jitteriness, increased appetite and diarrhea. Three of the babies had onset of thyrotoxicosis at day 3 to 4 of life; while one was first diagnosed at day five. Anti-thyroid drugs were stopped between day 60 to 90 of life with the resolution of the symptoms and normalization of thyroid function tests. Long-term outcomes associated with suboptimal or delayed diagnosis and treatment are intellectual impairment; central hypothyroidism; craniosynostosis; and neuropsychological, emotional and behavioral problems.[17] Three of our patients who were initially treated for thyroid storm had defaulted long-term follow-up. One of the patients with thyroid storm had normal growth and development and was last seen at the age of five years.

For the diagnosis of GD in mothers, three were diagnosed before pregnancy based on clinical manifestations consistent with thyrotoxicosis, thyroid eye signs and biochemical results compatible with overt hyperthyroidism. Four had clinical manifestations, biochemical results compatible with overt hyperthyroidism and positive thyroid autoantibodies (one with TRAb, three with anti-TPO/anti-Tg).

There was a total of three out of seven newborns who had TRAb. Overt neonatal hyperthyroidism can present at birth; however, the onset can be delayed due to maternal ATD or the coexistence of TSH-receptor blocking antibodies. Several studies have demonstrated that in more than 95% of newborns who developed symptoms, the manifestations occur between 1 and 29 days of life, with most patients diagnosed within the first 2 weeks. Although rare, development of hyperthyroidism as late as day 45 of life has been described.[19]

The time of TFTs to normalize in our study was 30 days. Overall, the thyroid disorder is a self-limiting disease, with anticipated clearance of thyroid antibodies in one month's time.[20] Our findings show that newborns with maternal GD are at risk for neonatal hyperthyroidism and thyroid storm even with the small population size.

Mean initial cord TSH was 15.0 ± 23.1 mIU/L, while mean FT4 was 25.1 ± 29.6 pmol/L. Abnormal cord blood results do not predict subsequent neonatal thyroid status. Newborns born to mothers with GD may not manifest immediately after delivery: thyroid functions tests may show isolated high FT4 or other abnormal values, as ATDs from the mother are expected to be cleared only after 72 hours. In the study by Besançon et al., among 33 newborns born to mothers with thyroid antibodies, seven developed hyperthyroidism at day 7 of life. Among these seven newborns, initial cord blood showed subclinical hyperthyroidism in three patients and hypothyroidism in two.[21] In a review of 69 newborns by Polak et al., only six had neonatal hyperthyroidism: two had initial cord TFTs consistent with hyperthyroidism while the rest had hypothyroidism and normal cord blood.[22] These findings demonstrate that cord blood TFTs do not reliably predict the risk of neonatal hyperthyroidism.

There are limited studies on the median time of normalization of TFTs in newborns with maternal hyperthyroidism. Our median time for TFT normalization in newborns with maternal hyperthyroidism was 30 days. Rovelli et al., observed that spontaneous normalization of TFTs in newborns with autoimmune thyroid antibodies occurred mostly within 15 days of life (93.3%) and a few within one month (0.1%).[23] The resolution of abnormal TFTs was due to disappearance of maternal stimulating TSH receptor antibodies in transient neonatal hyperthyroidism.[24]

High levels of maternal thyroid antibodies were observed. The median time of TFT normalization was longer among newborns with mothers who have thyroid antibodies compared to those without maternal thyroid antibodies.

Antithyroid antibodies, including TRAb, anti-TPO and anti-Tg, have established associations with thyroid autoimmune diseases.[25] Thyroid receptor antibodies can be subdivided into TSH receptor-stimulating (TSAbs), TSH receptor-blocking (TBAbs) and neutral thyroid receptor (N-TRAbs). TSAbs are typical antibodies in GD which can bind and activate TSH receptors, causing increased thyroid hormone production. TBAbs bind to TSH receptors without causing activation and prevent TSH binding to the TSH receptor, resulting in hypothyroidism. N-TRABs do not block the binding of TSH to the TSH receptor, but they are able to induce local infiltration of inflammatory cells into the thyroid gland and eyes.[8] TRAbs can cross the placental barrier freely to disturb thyroid function of both the pregnant woman and the fetus.[26] Thyroid peroxidase (TPO) serves as the core enzyme during the synthesis of thyroid hormones. Elevated TPOAb level is essential in diagnosing Hashimoto's thyroiditis and supportive in the work-up of GD. Anti-Tg is mainly composed of IgG and mainly attacks different antigenic determinants of thyroglobulin. Anti-TPO and anti-Tg are frequently present in the same individual.[27] The pregnant women included in this study were all hyperthyroid. Those with positive thyroid antibodies showed delayed normalization of TFT, which may be due to passage of thyroid antibodies to newborns impairing neonatal TFTs. TFT normalization was also longer among those with maternal ATDs compared to those who were not on ATDs.

Carbimazole and propylthiouracil (PTU) were used in the treatment of maternal hyperthyroidism. Carbimazole and PTU are all thought to be equally effective in controlling hyperthyroidism.[28] PTU is associated with increased risk of severe liver injury, while carbimazole is linked to embryopathy.[3] Management strategies to reduce these risks using PTU in the first trimester and carbimazole thereafter. Of the 61.8% of mothers who received treatment, 95% received ATDs and 5% received L-thyroxine. The delayed time for TFT to normalize may indicate active thyroid disease. We were unable to explain why some of the mothers with hyperthyroidism were not treated in this study.

Many of these newborns exhibited different types of TFT status. There were similar studies that identified different TFT abnormalities in newborn with maternal GD. Levy-Shraga et al., identified 83 out of 96 newborns with maternal GD that had subclinical hyperthyroidism; all were otherwise well and asymptomatic.[13] Lee et al. noted in their case series that some of the newborns showed TFT abnormalities mimicking central hypothyroidism.[29] The variation of TFT status is most likely related to TRAbs which can be either thyroid receptor-stimulating or -blocking antibodies. In some newborns, both antibodies could either co-exist or vary from time to time contributing to the different TFT abnormalities.

Measurement of TRAb levels have been incorporated in guidelines on the management of maternal hyperthyroidism in some countries. However, it is not yet offered as a routine investigation in Malaysia and other countries due to its high cost. TRAbs should be checked in a pregnant woman with a history of GD, active GD or maternal hyperthyroidism secondary to suspected GD. If TRAb levels are low or undetectable in early pregnancy, no further TRAb testing is recommended. If maternal TRAb is positive or patient is being treated with ATD, TRAb should be measured again between 18 and 22 weeks of gestation.[11] In those with levels near three to four times above upper limit of normal, TRAb should be repeated during 30 to 34 weeks of gestation. Maternal TRAb serum concentration greater than two to three times the upper limit of the reference range in the third trimester is a risk factor for neonatal hyperthyroidism.[11] If TRAb testing is not available, all infants born with maternal hyperthyroidism should be considered at risk of acquiring TSH receptor antibodies,

especially those born to mothers who developed clinical thyrotoxicosis during the second and third trimester or with babies who have a history of neonatal GD, and those with fetal signs of thyrotoxicosis during prenatal screening.[3] Besançon et al., studied 68 newborns with maternal GD which were divided into three groups based on TRAb and ATD status in the mother. None of the infants born to TRAb negative mothers with GD developed neonatal thyrotoxicosis. Of the 33 TRAb positive and ATD positive, 24 (72%) had positive TRAb on cord blood assays, and seven of them developed neonatal thyrotoxicosis.[21]

Our results were very reassuring since most often the abnormal thyroid function tests would normalize at a median time of 30 days. None had abnormal thyroid status beyond six months of life. Infants who are completely asymptomatic at three months of life can be safely discharged.

Limitation of study

Our study had a few limitations as it was retrospective in nature. Because TRAb was not routinely done in all mothers and newborns with hyperthyroidism, we could not explore its usefulness in managing infants with maternal hyperthyroidism. Finally, most of the medical records showed a short follow-up which might miss persistent thyroid dysfunction in newborns who were initially treated for overt hyperthyroidism or thyroid storm.

CONCLUSION

The proportion of neonates born to mothers with hyperthyroidism is rare at 0.8%, consistent with international studies. Neonates whose mothers had positive thyroid antibodies and received anti-thyroid treatment had longer time for normalization of thyroid function tests.

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None.

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