

## Interpreting thyroid function tests in babies of mothers with thyroid disease

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Dear Sir,

Measurement of cord blood thyroid-stimulating hormone (TSH) levels has been the primary screening strategy for congenital hypothyroidism in Singapore.<sup>(1)</sup> Screening is important, as affected infants may not present with overt clinical manifestations at birth. Prompt initiation of therapy will help to prevent long-term consequences, including intellectual disability and delayed bone maturation.<sup>(2)</sup> However, umbilical cord blood TSH levels can be difficult to interpret in babies of mothers with pre-existing or undetected thyroid conditions. Graves' disease (GD) is a common cause of hyperthyroidism in pregnancy, affecting 0.2% of pregnant women.<sup>(3)</sup> Maternal GD has a considerable impact on neonatal outcome, depending on the interplay of changes in maternal thyroid function, presence of TSH receptor antibodies (TRAb) and use of anti-thyroid drugs (ATDs).<sup>(4)</sup> Herein, we report on two cases of babies born to mothers with hyperthyroidism to illustrate the intricacies in balancing the various factors affecting fetal-neonatal thyroid function antenatally and postnatally.

The baby in Case 1 was born at term with good weight to an apparently healthy primiparous mother. The mother was noted to have sinus tachycardia at six hours postpartum. Investigations showed that she had a raised free thyroxine (fT4) level of 26.3 (normal range [NR] 8.8–14.4) pmol/L, low TSH level < 0.010 (NR 0.65–3.70) mU/L, raised TRAb level of 4.94 (NR < 1.76) IU/L and thyroid-stimulating immunoglobulin (TSI) > 4,054% (NR 50%–179%). Notably, the mother did not exhibit other signs or symptoms of hyperthyroidism, in particular Graves' ophthalmopathy, despite the high TSI level.<sup>(5)</sup> She was diagnosed with GD and treated with carbimazole and propranolol from postpartum Day 2. Routine cord blood screening revealed a low TSH level < 0.010 (NR 0.65–3.70) mU/L, while neonatal thyroid function on Day 4 of life showed fT4 level of 14.3 pmol/L, TSH level of 0.063 mU/L and high TRAb level of 5.20 IU/L. Subsequent testing showed low and rapidly declining fT4, with improving TSH and TRAb (Table I). The baby breastfed well. Breastfeeding was withheld temporarily for three days from Day 15 to eliminate the theoretical risk of passage of ATDs through breast milk.<sup>(6)</sup> However, the patient's fT4 level decreased further, with inappropriately normal TSH. An ACTH stimulation test showed appropriate response, and evaluation of the hypothalamic-pituitary axis returned normal results: insulin-like growth factor 1 of 62 (NR < 25–129) mcg/L, testosterone level of 2.9 nmol/L, follicle-stimulating hormone level of 1.0 IU/L, luteinising hormone level of 0.9 IU/L and prolactin level of 114.5 µg/L.

Several differentials could be considered in Case 1: (a) transient TSH suppression due to transplacental passage of maternal TSI, which could bind to the neonatal pituitary TSH receptor, resulting in suppression of neonatal TSH via a paracrine feedback loop;

**Table I. Investigation results of the babies in Cases 1 and 2.**

Age (day)	No. (normal range)		fT3 (pmol/L)	TRAb (IU/L)	ACTH stimulation test: cortisol (nmol/L)			Treatment
	TSH (mU/L)	fT4 (pmol/L)			0 min	30 min	60 min	
<b>Case 1</b>								
0 (cord blood)	< 0.010 (2.100–16.800)							
4	0.063 (1.230–11.500)	14.3 (11.4–29.4)		5.20				
8	0.259 (1.230–11.500)	10.4 (11.4–29.4)						
15	0.823 (1.230–11.500)	7.0 (11.4–29.4)		3.08				
18	1.130 (1.230–11.500)	6.9 (11.4–29.4)	4.8					
21	1.060 (0.500–6.500)	8.8 (11.6–28.3)	4.9					
25	1.410 (0.500–6.500)	7.3 (11.6–28.3)	5.3		164	415	500	
32	0.120 (0.500–6.500)	12.1 (10.3–25.7)		1.21				LT4 25 mcg OM
46	0.010 (0.500–6.500)	13.8 (10.3–25.7)	6.2					LT4 25 mcg OM
60	0.200 (0.500–6.500)	10.8 (10.3–25.7)						LT4 25 mcg OM
<b>Case 2</b>								
0 (cord blood)	75.300 (2.100–16.800)	insufficient						
2	137.000	12.1						
4	51.300 (1.230–11.500)	24.4 (11.4–29.4)						
11	5.440 (1.230–11.500)	19.8 (11.4–29.4)						
16	3.300 (1.230–11.500)	15.5 (11.4–29.4)						
32	5.210 (0.500–6.500)	14.7 (11.6–28.3)						

ACTH: adrenocorticotropic hormone; fT3: free triiodothyronine; fT4: free thyroxine; LT4: levothyroxine; OM: every morning; TRAb: TSH receptor antibody; TSH: thyroid-stimulating hormone

**Table II. Investigations and treatment of the mother in Case 2.**

Gestation week	Postpartum age (wk)	No. (normal range)					Treatment (mg/day)
		TSH (mU/L)	fT4 (pmol/L)	fT3 (pmol/L)	TRAb (IU/L)	TSI (%)	
12		0.010 (0.450–4.500)	26.0 (8.0–16.0)				
15		0.030 (0.450–4.500)	17.0 (8.0–16.0)				
18		0.010 (0.450–4.500)	10.0 (8.0–16.0)	4.7 (3.5–6.0)	0.7 (0.0–1.0)		
21		0.090 (0.450–4.500)	9.0 (8.0–16.0)				
29		0.050 (0.450–4.500)	10.0 (8.0–16.0)		0.6 (0.0–1.0)		PTU 50
33		0.040 (0.450–4.500)	12.0 (8.0–16.0)				PTU 100
37		0.134 (0.650–3.700)	9.3 (8.8–14.4)				PTU 150
	4.6	0.800 (0.450–4.500)	12.0 (8.0–16.0)				100 (50–179)
	14.0	0.610 (0.450–4.500)	15.0 (8.0–16.0)				
	23.0	0.440 (0.450–4.500)	15.0 (8.0–16.0)				

fT3: free triiodothyronine; fT4: free thyroxine; PTU: propylthiouracil; TRAb: TSH receptor antibody; TSH: thyroid-stimulating hormone; TSI: thyroid-stimulating immunoglobulin

(b) evolving neonatal thyrotoxicosis; or (c) evolving central hypothyroidism, either from neonatal hypopituitarism or congenital central hypothyroidism in the face of prolonged fetal exposure to high maternal thyroid hormones throughout pregnancy. Without knowledge of fT4 levels at birth, it was reasonable to presume that the low cord TSH was caused by transplacental passage of maternal TSI. However, subsequent testing revealed inappropriately normal TSH with rapidly decreasing fT4 levels. When it became clear that transient TSH suppression and neonatal thyrotoxicosis were unlikely diagnoses, the next step was to exclude adrenal insufficiency through a synacthen test, prior to starting thyroxine treatment. This would avoid precipitating an iatrogenic adrenal crisis by inappropriately starting thyroxine in an infant with undiagnosed hypopituitarism. The baby was started on levothyroxine 25 mcg daily from Day 25, with normalisation of fT4 levels. Our approach was guided by repeated monitoring using several thyroid function tests in the first two weeks of life in order to narrow the range of differentials. When it became clear to us that the diagnosis in Case 1 was not primary hypothyroidism but congenital central hypothyroidism, we undertook a cautious approach of excluding potential hypopituitarism first. This would allow us to be truly certain of the diagnosis before prescribing thyroxine therapy to the baby.

The newborn achieved good growth and age-appropriate developmental milestones for the two years of follow-up. However, uncertainty remains with regard to the permanence of low thyroid function, and long-term follow-up is imperative to understand the impact of chronic exposure of the developing fetus to undetected maternal GD.

In Case 2, the baby was born at term with good weight to a healthy multiparous mother. Maternal thyroid function test in the first trimester showed a high fT4 level of 26.0 pmol/L (NR in Table II) and suppressed TSH of 0.010 mU/L, with normal TRAb. These levels normalised in the second trimester. However, in the third trimester, the mother was found to have normal fT4 level at 9.3 pmol/L, with a suppressed TSH level of 0.134 mU/L. She was treated elsewhere with propylthiouracil (PTU) 50 mg/day from 29 weeks' gestation, which was increased to 100 mg/day at 33 weeks' gestation and further increased to 150 mg/day at 37 weeks' gestation because of persistently suppressed TSH. The baby's routine cord blood screening showed a very high TSH of 75.300 mU/L. Repeat thyroid function testing on Day 4 showed persistently elevated TSH (Table II).

High cord TSH exceeding 40 mU/L generally triggers the 'reflex' initiation of thyroid replacement<sup>(7)</sup> to avoid the prospect of delayed treatment, with consequences for cognitive development.<sup>(8)</sup> However, when the maternal treatment history of escalating PTU dosages was clarified, a diagnosis of transiently oversuppressed neonatal thyroid gland from maternal ATD use became more obvious. The persistently high TSH on Day 4 of life posed a dilemma of whether thyroid replacement would be indicated or could be delayed to allow spontaneous recovery of thyroid function, knowing the effect of maternal PTU intake on neonatal thyroid status.<sup>(9)</sup> With parental understanding and compliance to close thyroid function monitoring, spontaneous recovery of the infant's thyroid function by Day 11 led us to conclude that watchful waiting was indeed appropriate.

These two cases describe two less common presentations of babies of mothers with thyroid conditions, namely congenital central hypothyroidism and transient primary hypothyroidism. It is imperative to consider undiagnosed maternal thyroid conditions, transplacental passage of thyroid auto-antibodies, maternal anti-thyroid medications and their potential transfer during breastfeeding as factors that potentially influence neonatal thyroid function outcomes. Ideal management of such patients requires close multidisciplinary collaboration between the neonatologist, paediatric endocrinologist and adult endocrinologist for optimal outcome.

Yours sincerely,

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