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Who Needs Thyroid Function Testing at Birth?

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Abstract and Introduction

Introduction

There have been notable advances in terms of what biochemistry laboratories can measure, how quickly they can measure and how much sample is required to do the measuring. This has improved many aspects of clinical care but ease of access and rapid feedback may increase the likelihood of babies undergoing blood tests unnecessarily. Checking thyroid-stimulating hormone (TSH) and thyroid hormone concentrations in neonates is a good case in point. Many different neonatal (and adult) symptoms and signs can be linked to abnormal levels of thyroid hormone and so it is easy to understand why doctors are keen to check thyroid function. The potential impact of maternal thyroid disease on neonatal thyroid status also needs to be considered. Approximately 10% of adult women have autoimmune thyroid disease and many babies may be considered eligible for thyroid function testing because of this.[1]

What Is Normal?

Interpreting thyroid biochemistry requires the clinician to know what normal is in the first place. The biochemistry report of TSH and thyroxine concentrations may be accompanied by an 'adult' reference range which can lead to concerns about possible hypothyroidism or thyroid gland overactivity in healthy babies. Discussions about the threshold above which TSH concentrations can be said to be significantly raised are highly pertinent in the neonatal period.[2,3] Is a serum TSH of 9 mU/L of any clinical significance? What is the differential diagnosis? Is this result within the normal spectrum at this age? Should the baby undergo further investigation? Should the baby be treated with thyroxine?[2,3] If the biochemistry is thought to be mildly abnormal, then thyroid function tests are sometimes repeated regularly even though the likelihood of a recognised abnormality of thyroid development is remote.

Delivery is associated with a profound change in circulating TSH and thyroid hormone concentrations. Mean free thyroxine (FT4) concentrations around day 7 of life in a term baby are considerably higher than in adults because of thyroid gland stimulation by the partum-related rise in TSH secretion. Paediatricians should familiarise themselves with the pattern of changes that are seen in the early neonatal period. shows the 97.5th centile for thyroid biochemistry (TSH, FT4 and FT3) derived from well neonates in three separate studies using three different assay systems.[4–6] This does not represent a comprehensive summary of normative data but the studies selected are relatively recent, involve a respectable (although not optimal) number of healthy babies and use assays from different companies. The upper bound for serum TSH and FT4 concentrations in neonates around 1 week of life is assay dependent to a degree but lies in the vicinity of 6.5–12.0 mU/L (TSH) and 34–79 pmol/L (FT4).[4–7] It should be noted that TSH concentrations in whole blood collected on filter paper as part of neonatal screening will be approximately half the serum value because of the inclusion of the red cell volume in the assay process. One of the reasons that the UK screening programme for primary congenital hypothyroidism (CHT) samples around day 5 of life is to avoid the maximum peak TSH concentration that has normally occurred beforehand.

Table 1. Reference data (97.5th centile) for TSH, FT4 and FT3 in well babies in early life from three separate sources obtained using three different assays[4–6]

Electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). Mutlu *et al* [4]					
Age	**Day 1 N=29**	**Day 7 N=30**	**Day 14 N=22**	**Day 28 N=19**	**Adult N=50**
TSH (mU/L)	26.5	12.1	7.9	4.8	3.8
Free T4 (pmol/L)	33.6	34.6	28.7	25.0	18.3
Free T3 (pmol/L)	11.5	8.7	9.5	7.6	6.5
Chemiluminescence assay system (Immulite, DPC Los Angeles, USA). Elmlinger *et al* [5]					
	Days 1–7 N=45		**Days 8–15 N=40 Adult**		**N=20**
TSH (mU/L)	9.7		8.0		2.4
Free T4 (pmol/L)	79.2		63.6		20.5

Free T3 (pmol/L)	11.7	11.9		6.3
CALIPER (Canadian Laboratory Initiative on Paediatric Reference Intervals) data obtained using an Abbott (Abbott Laboratories. Abbott Park, Illinois, USA) Architect Immunoassay Analyser (http://www.sickkids.ca/caliperproject)				
TSH (mU/L)	4 days to 6 months			14–18 years
	4.8			3.4
	N=139			N=259
Free T4 (pmol/L)	Days 5–14	Days 15–29		Adult
	41.3	32.5		17.6
	N=66	N=55		N=952
Free T3 (pmol/L)	4 days to 1 year			15–18 years
	7.5			5.9 (M) and 5.7 (F)
	N=360			N=133 (M) and 124 (F)

FT4, free thyroxine; M, male; F, female; TSH, thyroid-stimulating hormone.

Key Causes of Abnormal Thyroid Function in the Neonate

The key causes of abnormal thyroid function in babies that need prompt treatment are CHT and neonatal hyperthyroidism arising because of maternal Graves' disease (autoimmune hyperthyroidism) and associated transplacental antibody transfer.

Congenital Hypothyroidism

Most cases of CHT in Europe and North America are detected by neonatal screening and here the paediatrician need not worry greatly about 'missing' primary CHT due to abnormalities of thyroid gland development. A small number of babies will rightly have formal thyroid function tests prior to screening because clinicians suspect severe CHT on the basis of features such as lethargy, poor feeding, facial dysmorphism, macroglossia, large anterior fontanelle, wide sutures and umbilical hernia.[8] Thyroid function may also be checked prior to formal screening if there is a sibling with CHT. The CHT neonatal screening programme will detect the vast majority of clinically significant abnormalities of thyroid gland development (primary CHT), although babies with secondary hypothyroidism due to abnormally low TSH secretion will not be identified by screening programmes that rely on TSH elevation as a marker of disease. Some programmes in Europe and North America therefore measure thyroid hormone concentrations in addition to TSH.[9] It is difficult to measure FT4 on blood spot samples and so thyroid-binding globulin can be measured as well in order to gauge the 'free' thyroid hormone component. A proportion of babies with secondary hypothyroidism (around 25–30%) will have isolated TSH deficiency (hypopituitarism with only one pituitary axis affected) rather than TSH deficiency as a component of combined pituitary hormone deficiency (CPHD) where more than one pituitary axis is affected.[10,11] Some babies with CPHD will have symptoms and signs such as microphallus, hypoglycaemia and conjugated hyperbilirubinaemia in early life because of gonadotrophin, adrenocorticotrophic hormone and growth hormone deficiency. While they may, therefore, be diagnosed rapidly outwith a formal screening programme, this is not always the case.[10,11]

Maternal Graves' Disease

Maternal Graves' disease, its treatment and the presence of stimulating or blocking antibodies to the TSH receptor can result in virtually every possible permutation of TSH and thyroid hormone concentrations in the baby. This includes high TSH, low FT4; low TSH, high FT4/FT3 and low TSH, low FT4. In Maternal Graves' disease, antibodies can cross the placenta and stimulate excess thyroid hormone release from the neonatal thyroid gland (suppressed or low TSH, high FT4/FT3). Excessive transfer of antithyroid drug or blocking antibodies can result in a primary hypothyroid picture (high TSH and low FT4).[12] Excessive transplacental passage of FT4 from an inadequately treated thyrotoxic mother can suppress the pituitary–thyroid axis in the baby (leading to low TSH, low FT4 in the baby).[13]

It follows that the paediatrician must establish whether the mother has the circulating immunological markers of Graves' disease (Graves' autoimmune hyperthyroidism), which may be present even if she has had definitive treatment with thyroidectomy or radioiodine (RI) and is now on thyroid hormone replacement.

Establishing the risk that maternal Graves' (predefinitive or postdefinitive treatment with surgery or RI) will lead to hyperthyroidism in the neonate is therefore best undertaken by measuring TSH receptor antibodies. Measuring the

thyroid receptor antibody (TRAb) titre, which may also be reported as thyroid-binding inhibitory immunoglobulin (TBII), is a key component of good antenatal care. If the TRAb or TBII titre is normal (low), then the baby is not at significant risk of thyrotoxicosis and formal neonatal thyroid function testing, above and beyond the normal blood spot neonatal screen for CHT, is not required.[14] If the titre is raised, then the baby is at risk of thyroid gland overactivity (~30% of cases) and requires a detailed clinical assessment and thyroid function testing. Maternal thyroid status and whether or not she is receiving treatment with anti-thyroid drug are important additional considerations.

The precise timing of neonatal thyroid function testing in the case of elevated maternal TRAb or TBII titre is open to debate but in the at-risk baby a reasonable strategy is to measure thyroid function (TSH and FT4) in cord blood and then to sample again at around 5–7 days of age.[14] TRAb levels can also be measured in cord blood if they have not been tested before, although feedback from the laboratory may take days. A suppressed TSH in cord blood or at 5–7 days of age suggests that the baby has been affected by antibody or abnormal thyroid hormone transfer from mother. Clear advice to the family regarding the signs of thyroid hormone excess is important and it may be wise to monitor high-risk babies in hospital for a period of time before discharge.

There are rare non-autoimmune causes of thyrotoxicosis due to mutations that give rise to a constitutively active TSH receptor.[15] The underlying defect can be inherited in a dominant manner, but somatic mutations giving rise to neonatal hyperthyroidism have been described.[16]

Other Common Clinical Scenarios Linked to Abnormal Neonatal Thyroid Function

Maternal Autoimmune Thyroid Disease Besides Graves' Disease

Approximately 10% of adult women have clinical, biochemical or immunological evidence of autoimmune thyroid disease.[1] Maternal autoimmune thyroid disease is most commonly Hashimoto's thyroiditis and hence a disease process that involves primarily destructive antibodies (such as thyroid peroxidase). This disease is not usually associated with abnormal neonatal thyroid function. The baby born to the mother who is on thyroid hormone replacement because of Hashimoto's disease or autoimmune hypothyroidism does not, therefore, need formal thyroid function tests.[17,18] There may be an effect of the transplacental passage of 'blocking' antibodies on neonatal thyroid function in maternal autoimmune thyroid disease but this is uncommon (2% of CHT) and these babies will be detected by the neonatal screening programme.[12] The only indication for formal thyroid function in the case of autoimmune thyroid disease besides Graves' is where the baby is thought to be hypothyroid on clinical criteria before the neonatal blood spot screening result is available.

The Jaundiced Baby

CHT can result in both conjugated and unconjugated hyperbilirubinaemia. Prolonged jaundice (jaundice beyond 2 weeks of age in the term baby) is one of the commoner clinical features of CHT[8] and yet an audit of 385 thyroid function tests undertaken for prolonged jaundice between 2005 and 2008 in two hospitals in South-West England did not identify any baby with an underlying disorder of thyroid function.[17] It is likely that babies with CHT and associated low thyroid hormone concentrations will have other clinical manifestations of hypothyroidism prior to the evolution of prolonged jaundice, which may be the stimulus for thyroid function testing and early diagnosis.[8] Babies with primary CHT may also be identified by the neonatal screening programme before jaundice becomes a concern and it is of note that most babies with primary CHT in the UK are now diagnosed prior to 2 weeks of age.[19] While CHT may be unlikely in the baby with early or prolonged unconjugated hyperbilirubinaemia who is feeding appropriately and who has none of the other features of CHT outlined above, babies with primary and secondary CHT and very low thyroid hormone concentrations may have very little in the way of clinical signs.[8,11]

The Preterm Baby

The preterm baby is frequently said to have an immature hypothalamo-pituitary axis with a different biochemical response to a physiological or pathophysiological scenario when compared with the term baby.[20] A concern has been that babies with a primary thyroid problem may not mount an appropriate TSH response despite an anatomically abnormal or poorly functioning thyroid gland and hence not be detected by a screening programme that uses a cut-off derived from TSH concentrations in term babies.[21] This is the rationale for repeat CHT testing in preterm babies in many European nations; in the UK, babies born before 32 weeks gestation are retested 4 weeks later or on discharge home, whichever is the sooner. Preterm babies with elevated TSH values at initial or on repeat screening may have CHT but elevated (and low) TSH values may reflect a host of other factors, including iodine exposure (a little or a lot), illness or concomitant medication such as dopamine. The majority of preterm babies with CHT detected by newborn screening ultimately prove to have normal thyroid anatomy and function. For example, Vigone and colleagues[22] found that only 5 out of 23 preterm babies (<36 weeks gestation and all <2000 g at birth) detected by newborn screening for CHT in Lombardy (Italy) were detected on the basis of an elevated TSH on days 2–4 of life; most were identified by a second TSH blood spot screen between days 15 and 30 of life. However, only three of the 23 babies had thyroid dysgenesis and only five of these babies required treatment beyond 2–3 years of age. Hence, the pathogenesis of the 'CHT' detected in preterm babies is not the same as the 'classical' term baby with CHT where a markedly raised TSH

and low thyroid hormone concentration are observed in the context of abnormal thyroid gland development or a dyshormonogenesis.[23,24] It is unclear whether the true 'classical' CHT that was the original target of neonatal screening programmes is more or less common in preterm babies and the extent to which preterm babies with transient hypothyroidism benefit from thyroxine treatment is also unknown. It is of note that thyroid dysgenesis and dyshormonogenesis increase the risk of babies being born beyond their due date.

Summary

A concern for many paediatricians and biochemistry departments has been the lack of an appropriate, age-related reference range for many of the parameters measured in babies in early life. Establishing what is normal is easy in principle but not always in practice because obtaining blood samples from a healthy cohort of children—and babies in particular—is not straightforward. Data from initiatives such as the Canadian Laboratory Initiative on Paediatric Reference Intervals (CALIPER) project in Canada are helping to address this issue.[6] Checking thyroid function in babies whose mothers have Hashimoto's disease is unnecessary but vital in neonates where mother has Graves' disease (ongoing or definitively treated with surgery or RI) and who has been found to have a raised TRAb/TBII titre. The neonatal screening programme will not detect all babies with CHT and so if CHT is suspected on clinical criteria, then formal thyroid function tests should be performed.

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