

## Screening For congenital hypothyroidism In Maltese newborns using cord blood

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(on behalf of the Neonatal Thyroid Screening Committee)

**ABSTRACT:** Routine screening for congenital hypothyroidism (CHT) has been introduced because clinical features of CHT may not be evident before the baby is a few weeks old and treatment at this stage may already be too late. Since a newborn testing programme employing liquid cord blood for other conditions had already been developed in the University of Malta and the Department of Health, we explored the possibility of implementing newborn thyroid testing using liquid cord blood. A similar programme had been implemented successfully in Finland and Philadelphia. Between September 1989 and August 1995 around 32,000 newborns were tested. This is nearly complete ascertainment. Preliminary testing was by radioimmunoassay for TSH. The sera of those with TSH levels more than 13mU/l were further tested for free T4. If the free T4 level was below 12 pmol/l, the babies were recalled for clinical evaluation and repeat testing. Other babies were recalled for technical reasons, giving a total recall rate of 3.88%. CHT was identified in seven newborns and treatment started within 3 weeks of delivery. One baby was reported normal on screening but was suspected to have CHT on clinical grounds at 3 weeks of age, confirmed biochemically. The incidence of CHT in Malta is therefore 1 in 4500.

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### Introduction

The clinical diagnosis of congenital hypothyroidism during the neonatal period is difficult and often missed with grievous developmental sequelae. Consequently, a number of newborn screening programmes have been implemented worldwide in order to detect the condition prior to the onset of symptoms. The benefit of screening to detect hypothyroidism in the newborn, and the subsequent early treatment of identified infants is supported by evidence that optimum intellectual performance occurs when thyroid replacement therapy is begun as early as possible<sup>1</sup>.

The level of thyroid stimulating hormone (TSH) in cord blood is considered a true indicator of thyroid function in the newborn; the TSH level rises sharply a few minutes after birth and returns to normal within one week<sup>2</sup>. Therefore, for the detection of hypothyroidism TSH estimation should be carried out immediately after birth or at least two days later. Commonly, heel prick blood samples are collected on filter paper about 1 to 2 weeks postnatally. Considerable cost and effort is necessary to organise collections in this way. However, in countries where it is necessary to screen for other inborn errors of metabolism as well as hypothyroidism, a few days until the baby has established feeding must be allowed before the blood samples can be collected.

In this communication, we report our experience with a screening programme for congenital hypothyroidism in newborn infants by measurement of TSH levels in samples of cord blood. Cord blood was chosen because a screening programme for the detection of abnormal haemoglobins and thalassaemia based on cord blood had already been established in the Maltese Islands.

### Materials and Methods

Umbilical venous blood was collected from the placental side of the cord after every delivery and stored at 4°C until it reached the laboratory. If for any reason this was not done, a venous sample was taken from the baby at the time of routine discharge from hospital (2nd to 3rd day) or within the first week of life.

Cord blood samples were initially assayed for TSH. Between September 1989 and December 1993 a radioimmunoassay kit (Diagnostic Products Corporation, Los Angeles; KTS1) calibrated against the WHO 1st IRP 68/38 was used. This was changed to an enzyme immunoassay kit (Boehringer Mannheim Germany; 1488 635) using the ES 300 automated immunoassay analyser calibrated as above.

In a pilot study, 640 random samples of cord blood were analysed and the TSH distribution plotted as shown in Figure 1. Twenty percent of the samples had a TSH level of 13mU/L or above. This value was arbitrarily taken as a cut off level above which free thyroxine (FT4) was also estimated on these samples.

FT4 was analysed by a radioimmunoassay kit (Diagnostic Products Corporation, Los Angeles; TKF41). 200 random cord blood sera were analysed and the FT4 distribution was plotted as shown in Figure 2. The mean FT4 level was 15.9 pmol/L with a SD of 4.2. It was empirically decided that in the screening programme an FT4 level equal to or less than 12 pmol/L (1 SD or more below the mean) would be an indication for recalling the infant for a second TSH and FT4 estimation.

During the programme, infants were recalled by letter sent to the parents explaining the need for repeat testing

**Results**

In the 6 year period from September 1989 to August 1995, 31,533 infants delivered at St.Luke's Hospital (28,283), Gozo General Hospital (1,985), peripheral clinics and homes (1,265), were screened (Table 1). Of these, 1226 (3.88%) had a TSH level  $\geq 13$ mU/L and were recalled to submit a second sample but 377 (30.7%) failed to attend for re-testing. There were no patients that presented in our clinics with signs and symptoms of congenital hypothyroidism.

Table 1 - Results of screening programme

Number of infants screened (01.09.89 TO 31.08.95)	
St Luke's Hospital	28283
Gozo General Hospital	1985
Clinics / Home	1265
<b>TOTAL</b>	<b>31533</b>

RECALLS .....	1226 (3.88%)
FAILED RECALLS .....	377
	( 30.7% of recalls; 1.19% of total screened )
POSITIVE CASES .....	6
FALSE NEGATIVES .....	1

Of those that were re-tested, 6 (1 male and 5 females) were found to have congenital hypothyroidism (Table 2). One female infant (case 7, Table 2) had an initial TSH value of 5.6mU/l and was passed as normal by the screening programme. Subsequently, she developed constipation and prolonged jaundice while she was still on the special care baby unit, and TSH / FT4 assays at 3 weeks of age were consistent with a diagnosis of congenital hypothyroidism. None of the cases of hypothyroidism had a goitre.

From these figures the incidence of congenital hypothyroidism in the Maltese population was found to be 1 in 4500 which is slightly lower than the worldwide incidence of approximately 1 in 3800 to 4000<sup>3</sup>.

**Discussion**

Screening of newborns for congenital hypothyroidism is a well established practice and over the past 20 years it has proved its benefit and efficacy<sup>4</sup>. Indeed, about 9 million infants are screened every year throughout the developed world. Screening for congenital hypothyroidism commenced in Malta in September 1989 and by the end of August 1995, 31,533 newborn infants had been screened. This is believed to be an almost complete ascertainment giving a prevalence for the condition of 1 in 4500 which is lower than the rest of Europe where the prevalence is 1 in 3500.

Most centres use filter paper blood spots taken at five days of age to measure either TSH ( Europe and Asia) or

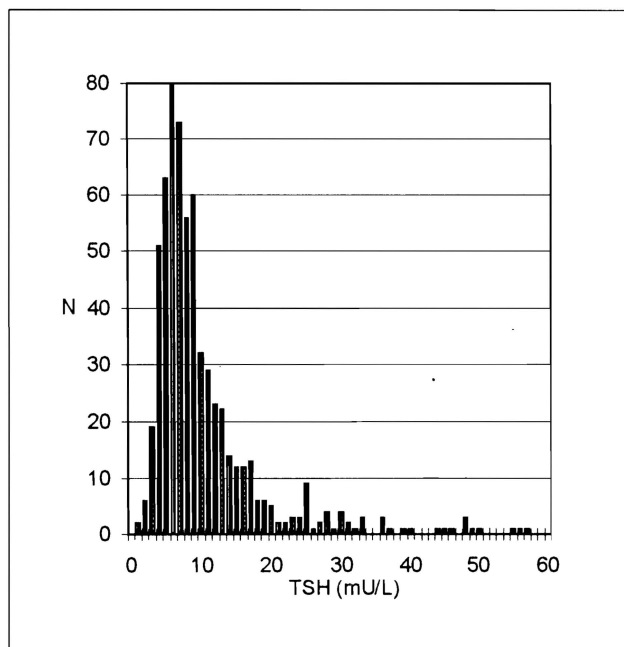


Fig. 1 - TSH distribution in 640 cord sera  
N = number of cord blood samples

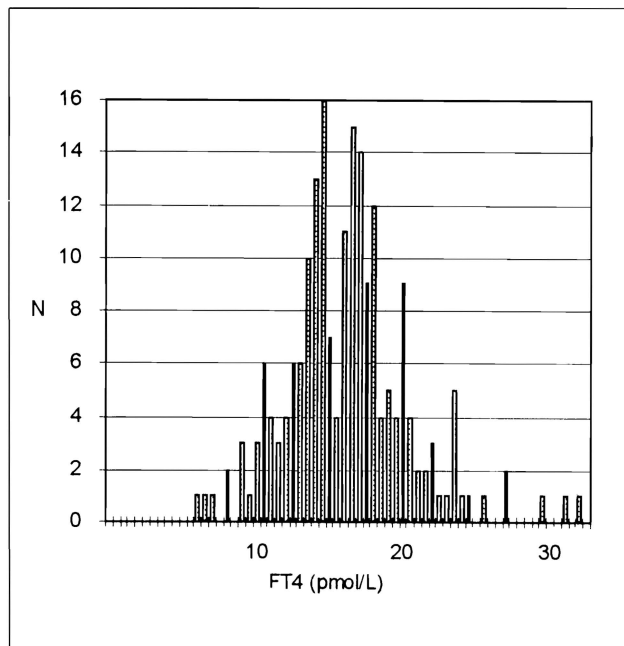


Fig. 2 - FT4 distribution in 200 cord sera  
N = number of cord blood samples

and urging them to bring their infant to the children's outpatients without delay so that a second blood sample could be taken.

The diagnosis of congenital hypothyroidism was made when the TSH level remained high (above 13 m U/l) and the FT4 level decreased or remained unacceptably low compared to the first sample (ie  $\leq 12$  p mol/l).

In this study, in an attempt to identify 'missed cases', a circular was sent to all the medical practitioners on the Island to ask whether they were aware of cases of congenital hypothyroidism that were diagnosed during the study period but which were missed by the screening programme. This circular was sent on two separate occasions but no cases were reported.

Table 2 - Data on cases with Congenital Hypothyroidism

CASE	GENDER	INITIAL		RECALL		AGE*
		TSH (mU/L)	FT4 (pmol/L)	TSH (mU/L)	FT4 (pmol/L)	
CB1	M	>60	2.8	>120	<1.6	18
CB2	F	>60	6.8	>120	<1.3	5
CB3	F	>60	9.2	NA	<1.7	11
CB4	F	5.9	4.2	> 60	<1.6	11
CB5	F	13.1	7.3	15.1	4.6	6
CB6	F	40.2	7.0	> 40	<1.7	18
CB7	F	5.6	ND	> 40	<1.3	22

\* age at the start of treatment with thyroxine  
 ND = not done      NA = not available

T4 (North America and Australia). With either approach congenital hypothyroidism will be missed in some infants<sup>5</sup>. Some centres like Finland, Philadelphia and Hong Kong have chosen to use cord blood for screening. With this method, a higher percentage of positive cases are missed due to a delay in TSH elevation in these cases<sup>6</sup>.

A number of false positive results is accounted for by the dramatic surge of TSH which peaks by 30 minutes after birth and reverts to normal within a week. By arbitrarily setting the cord blood TSH level to a cut off point >13mU/L, 3.88% of the population screened had to be followed up. This recall rate is high compared to that of Finland (0.08%) where cord blood is also used for screening<sup>7</sup>. In our series only about 70% of the patients who were recalled to the children's outpatients department actually turned up for repeat testing. This is far from satisfactory, considering that patients need only travel very short distances to reach the hospital. It suggests that more emphasis should be made on parent education about screening, and perhaps also through the content of the letter sent to parents.

In our series one case of congenital hypothyroidism (CB 7) was missed on screening because of a normal cord blood TSH value but at 3 weeks of age she had signs and symptoms suggestive of congenital hypothyroidism which was confirmed biochemically. This case underlines the need for ongoing clinical vigilance for hypothyroidism even in infants whose

thyroid function was normal on screening<sup>4</sup>. It is interesting to note that 6 out of the 7 positive cases were female. In one study from Finland it was shown that the incidence of thyroid dysgenesis was higher among female infants<sup>8</sup>.

One case (CB 5) picked up by the screening had borderline TSH values with low FT4 levels. This case was still treated as a positive case but has to be confirmed and distinguished from transient hypothyroidism in the future. It is important to start treatment with T4 as early as possible if neurodevelopmental delay is to be avoided. Two of our cases were started on treatment in the first week, two in the second week, two in the third week and one at 22 days of age.

At follow-up all patients are doing well and developing normally. The first patient who was detected in the programme also had congenital hydrocephalus that required shunting on several occasions but his mental and physical development is within normal limits. The developmental outcome of these cases, both physical and mental, will be the subject of another study in the future.

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