# Screening for congenital hypothyroidism

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## ABSTRACT

**Objective:** To review the screening program for congenital hypothyroidism in the Riyadh Al-Kharj Hospital Programme, Riyadh, Kingdom of Saudi Arabia, and to investigate the clinical and biochemical characteristics of affected infants.

**Methods:** The study was carried out from 1985 to 2000 in the Clinical Chemistry Division, Department of Pathology, Riyadh Armed Forces Hospital, Kingdom of Saudi Arabia. Laboratory data and case notes of infants diagnosed with congenital hypothyroidism were used to supply the relevant data and information.

**Results:** One hundred and twenty-one thousand, four hundred and four infants were screened over a period of nearly 15 years. The overall incidence of congenital hypothyroidism was 1:2759 live births with a female: male ratio of 1.8:1. The incidence in a rural satellite hospital was 1:1538. No seasonal variation was observed. Apart from jaundice, signs and symptoms of congenital hypothyroidism were rarely present in the neonatal period. The neonatal and maternal parameters of affected infants did not differ significantly from those of other infants. The predominant cause of congenital hypothyroidism was athyreosis (45%), followed by thyroid ectopia (24%) and dyshormonogenesis (17%). The mean age at the start of treatment of infants diagnosed in the screening program was 10.3 days.

**Conclusion:** The screening program based on initial measurement of thyroid stimulating hormone in cord blood captures 97% of infants born in the Riyadh Al-Kharj Hospital Programme. The incidence of congenital hypothyroidism was 1:2759 live births with a female:male ratio of nearly 2:1. Congenital hypothyroidism infants had similar neonatal parameters as other infants. No seasonality in the incidence of congenital hypothyroidism was observed. In general, affected infants were started on thyroxine very soon after birth.

**Keywords:** Congenital hypothyroidism, cord blood, neonatal signs and symptoms, seasonal variation, anthropometric measurements.

**Saudi Med J 2002; Vol. 23 (5): 529-535**

Screening for congenital hypothyroidism (CH) in the Riyadh Al-Kharj Hospital (RKH), Programme Kingdom of Saudi Arabia (KSA) started as a pilot study in April 1985[1] and continues to the present day. The infants screened in RKH Program are from 2 hospitals, the Armed Forces Hospital (AFH), KSA and Al-Kharj Military Industrial Corporation Hospital (AKMICH) located in Al-Kharj approximately 100 kilometers south east of Riyadh, KSA. The pilot study of Bacchus et al[1] at AFH showed a CH incidence of 1:2476 after one year of screening. Another study[2] in 5 hospitals of the Ministry of Health (MOH) showed an incidence of 1: 2666. All the early indications suggested that the incidence of CH in KSA would be higher than in other countries as shown by innumerable studies, starting with the 1974 seminal work of Dussault et al[3] in Quebec Province, Canada, which revealed an incidence of 1:7000.

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Received 13th August 2001. Accepted for publication in final form 25th December 2001.

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Congenital hypothyroidism fulfills most of the following criteria for disease screening as set out by Wilson and Jungner.[4] In essence, the condition must be an important health problem; there must be a reliable screening test and effective treatment should be available while the cost of screening should be justifiable in relation to the overall health care expenditure. The screening programme should not produce a significant number of false-positive results. Neonatal CH screening protocols are based on either the measurement of thyroid-stimulating hormone (TSH) in heel prick blood spot collected around the age of 5 days or, as in Finland, measurement of cord blood TSH. Duplication of the screening protocols is not a common practice. The screening programme in RKH is based on the measurement of cord blood TSH. The uptake is 97%. However, to ensure that late onset CH is not missed a heel prick blood spot is collected from the infants around 5 days after birth. The uptake is around 70% as the majority of infants are discharged after one day and a high proportion do not return. The cut-off levels are 30 mIU/L for cord blood and 25 mIU/L for blood spot TSH. All assays are subject to strict internal quality control. In addition, the laboratory participates in the United Kingdom National External Quality Assessment Schemes (UKNEQAS) for TSH and neonatal TSH. Although, the endocrinology laboratory plays an essential part, the definitive diagnosis of CH is solely and entirely the responsibility of the neonatologists who provide a diagnostic gold standard based on clinical examination, laboratory results and clinical imaging. Hypothyroidism is a very variable condition both in severity and over time, making it difficult to apply the usual concepts of false-positive and false-negative in evaluating screening performance. The draft Newborn Screening Lexicon 1996[5] defines a positive test as a "test result which indicates that the infant from whom the specimen is taken has a greater likelihood than the population frequency of having the condition screened for." The current screening protocol for cord blood followed in RKH Programme is shown in **Figure 1**. The protocol has evolved with the benefit of experience to identify any cases of primary hypothyroidism as well as secondary or tertiary hypothyroidism and hyperthyroidism. After validation, all results are downloaded into the hospital information system (HIS). Senior laboratory staff are reminded at the time of logging into the laboratory information system (LIS) of any abnormal cord blood TSH results. Abnormal results are communicated directly to a designated physician coordinator in the pediatric team. The present study examines the incidence of CH in the population screened, sex distribution, seasonal variation, neonatal signs and symptoms, etiology, biochemical abnormalities and anthropometric measurements at birth. Laboratory records and case notes of mothers and children were used to provide the necessary data and qualitative information.

Methods. The study was carried out from 1985 to 2000 in the Clinical Chemistry Division, Department of Pathology, Riyadh Armed Forces Hospital, Kingdom of Saudi Arabia. Laboratory data and case notes of infants diagnosed with congenital hypothyroidism were used to supply the relevant data and information.

Results. The reference ranges currently used in the laboratory for cord blood analytes[6] are shown in **Table 1**. As most infants were assumed to be euthyroid, the reference ranges were derived from the hospital newborn population after exclusion of outliers. **Table 2** shows the number of infants born between April 1985 and December 1999 and the number of CH cases diagnosed. During the period, the ratio of male:female births was 1.04:1. The total number of infants screened by cord blood TSH measurement was 117,592, representing 96.8% of the total live births. The distribution of cases of CH diagnosed according to months is shown in **Table 3**. The statistical properties of the thyroid function data obtained on cord blood of infants diagnosed with CH are shown in **Table 4**. There were insufficient data to analyze for FT3, thyroid-binding globulin (TBG) and thyroglobulin. **Figures 2 and 3** are scatter diagrams of cord blood TSH and free T4 values in CH of different etiologies. In vivo isotopic tests ($^{123}$I uptake and perchlorate discharge) and imaging were used to confirm and determine the etiology of CH in suspected infants (based on laboratory screening results). For the infants who were fully investigated by in vivo isotopic tests, the frequency of the different etiologies of CH is shown in **Table 5. Table 6** shows the frequency of ABO blood groups among Saudi women attending antenatal clinic and mothers of children diagnosed with CH. The maternal and neonatal parameters of CH infants are summarized in **Table 7**.

Discussion. The reference range for cord blood TSH (**Table 1**) was 2.4 – 20.6 mIU/L but the cut-off of 30 mIU/L which was selected for the pilot study has been retained. However, analysis of the available data showed that a cut-off of 50 mIU/L which is used in several screening programmes[7,8] would be more appropriate. The median value for false-positive cord blood TSH was 50 (range 31 - 109) mIU/L while the median for CH infants was 330 (range 9 – 1055) mIU/L (**Table 4**). The latter data include 5 infants with late on-set CH who had false-negative cord blood TSH and were diagnosed either in the parallel blood spot TSH screening programme or on clinical suspicion. The mean cord blood free T4 for CH infants was 7.93 (sem 0.48) pmol/L (**Table 4**). There

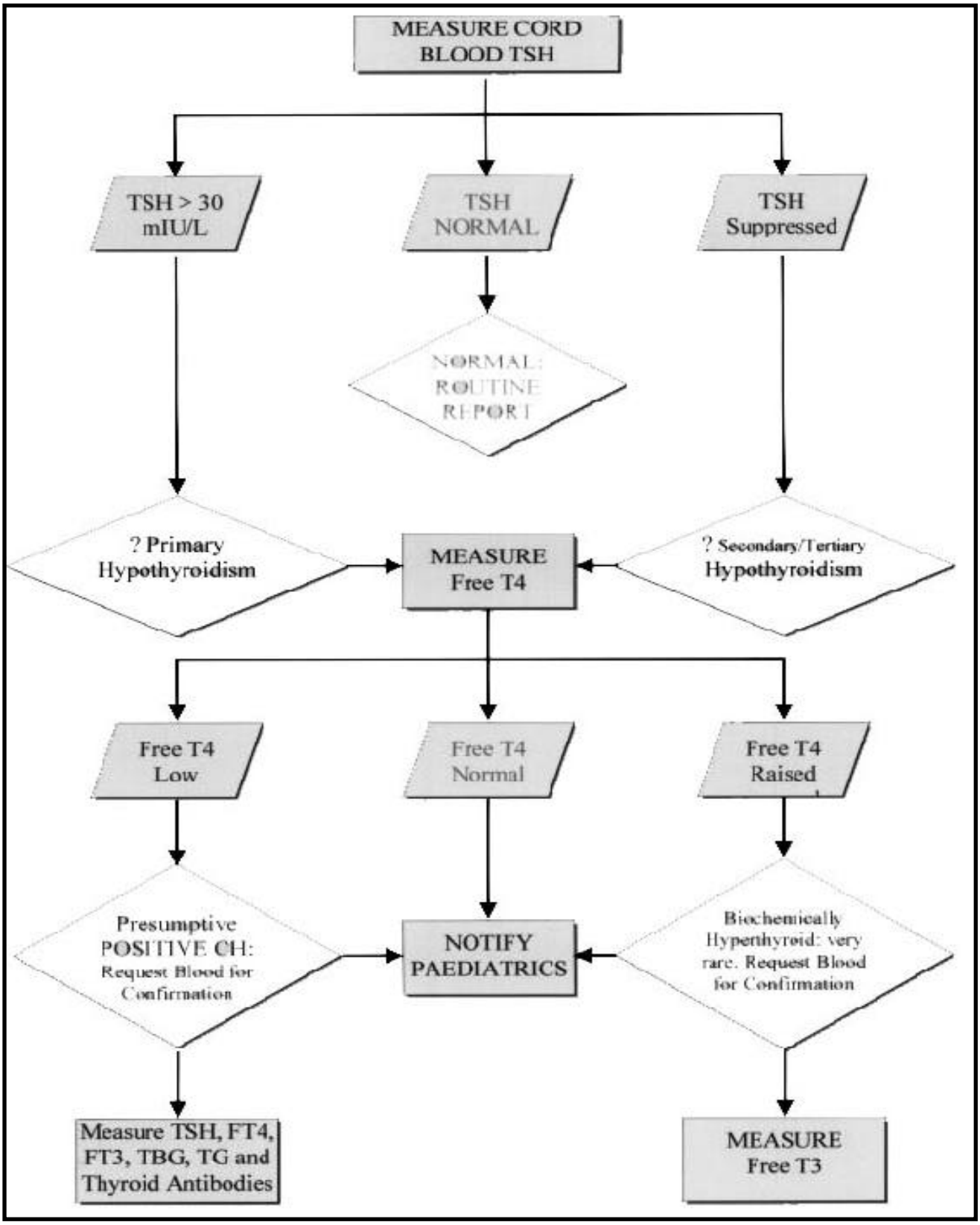


**Figure 1** - Protocol for screening of thyroid-stimulating hormone in cord blood. TSH - thyroid stimulating hormone, T4 - thyroxine, CH - congenital hypothyroidism, FT4 - free thyroxine, FT3 - free triiodothyronine, TBG - thyroxine binding globulin, TG - thyroid globulin.

**Table 1** - References ranges for cord blood analytes.

| Analytes | Reference ranges | Analyser |
|---|---|---|
| TSH | 2.4 - 20.6mlU/L | BM ES 700 |
| Free T4 | 12.0 - 19.6pmol/L | BM ES 700 |
| Free T3 | <2.3pmol/L | Abbott AxSYM |
| TBG | 18.4 - 37.7mg/L | DPC Immulite |
| Thyroglobulin | 12.2 - 113.5µg/L | DPC Immulite |

TSH - thyroid- stimulating hormone,
T3 - triiodothyronine,
T4 - thyroxine
TBG - thyroxine-binding globulin,
BM - Boehringer-Mannheim, ES - enzyme system,
DPC - Diagnostic Products Corporation,

**Table 2** - Annual births in Riyadh Al Kharj Hospital Programme and incidence of congenital hypothyroidism.

| Year | Total live births | Results for Al Kharj Hospital | Male CH | Female CH | Total CH | Annual Incidence of CH |
|---|---|---|---|---|---|---|
| 1985* | 4439 | 1342 | 0 | 1 | 1 | 1:4439 |
| 1986 | 6584 | 1472 | 2 | 0 | 2 | 1:3292 |
| 1987 | 6569 | 1495 | 1 | 1 | 2 | 1:3284 |
| 1988 | 7033 | 1617 | 1 | 2 | 3 | 1:2344 |
| 1989 | 7529 | 1668 | 1 | 3 | 4 | 1:1882 |
| 1990 | 8172 | 1826 | 2 | 4 | 6 | 1:1362 |
| 1991 | 6226 | 1593 | 1 | 2 | 3 | 1:2086 |
| 1992 | 8964 | 2048 | 1 | 2 | 3 | 1:2988 |
| 1993 | 9053 | 2038 | 0 | 3 | 3 | 1:3018 |
| 1994 | 9214 | 2132 | 1 | 2 | 3 | 1:3004 |
| 1995 | 9260 | 1929 | 1 | 2 | 3 | 1:3087 |
| 1996 | 9866 | 2065 | 1 | 1 | 2 | 1:4933 |
| 1997 | 9818 | 2144 | 3 | 1 | 4 | 1:2455 |
| 1998 | 9083 | 2183 | 0 | 1 | 1 | 1:9083 |
| 1999 | 9594 | 2136 | 1 | 3 | 4 | 1:2399 |
| **Total** | **121404** | **27688** | **18** | **26** | **44 (18)** | **1:2759 (1:1538)** |

* - from 1 April 1985, ( ) - results for Al-Kharj Hospital,
CH - congenital hypothyroidism.

was no statistically significant difference between cord blood free T4 values used for determining the reference range and those of cord blood with false-positive TSH.

The overall incidence of CH was one per 2759 live births. This incidence is lower in comparison to earlier published data for KSA which quoted an incidence of 1:1988[1] to 1:2666.[2] However, later data for KSA[9] showed an incidence of 1:3417. Further breakdown of the RKH Programme data shows an incidence of CH of 1:1538 for AKMICH and 1:3604 for AFH. The hospital in Al-Kharj serves a mainly rural population which may be genetically more homogeneous while the incidence of parental consanguinity may also be higher. The possible influence of parental consanguinity on the incidence of CH has been observed among infants of Asian origin in North West England[10] and infants of Pakistani origin in the West Midlands.[11] There were wide fluctuations in the annual incidence of CH, ranging from 1:1362 in 1990 to 1:9083 in 1998 (**Table 2**). Such fluctuations have been reported in other countries.[12,13] These figures merely underline the need for substantial data before reaching any reliable conclusions on the incidence of diseases. Among infants with CH the female:male ratio was 1.8:1 which is in line with most international studies. However, the pilot study[1] showed a strikingly different sex ratio of female:male of 1:2. The incidence and sex ratio in CH have been shown to vary with race[14] and the sex ratio for CH infants diagnosed in the RKH Programme is close to the Caucasian average.[15] Delange,[16] Thalhammer[17] and Virtanen et al[18] have observed a seasonal variation in the incidence of CH in Belgium, Austria and Finland. Recently a similar observation has been made in the English West Midlands by Hall et al[11] but no evidence of seasonality could be established in Israel[13] or the Netherlands.[19] Inspite of a peak in the month of April (**Table 3**), there was no evidence of any seasonal variation in the incidence of CH in the RKH Programme. The number of cases was almost evenly distributed between the hottest 6 months and the rest of the year. An earlier study[20] in KSA had not demonstrated any seasonal periodicity in the incidence of the disease. Once hypothyroidism was established biochemically the suspected infants were investigated by in vivo isotopic tests and imaging using $^{123}I$ to establish the presence and location of any thyroid tissue. The frequency of the different etiologies of CH is shown in **Table 5**. Among the fully documented cases, athyreosis accounted for 45% of the cases, followed by thyroid ectopia (24%) and dyshormonogenesis (17%). These findings contrast sharply with those of Al-Jurrayan et al[8] who found 24% athyreosis, 50% ectopia and 26% dyshormonogenesis. There was no statistically significant difference between the cord blood TSH and free T4 levels obtained in CH of different

**Table 3 -** Distribution of cases of congenital hypothyroidism detected by months: 1985 - 1999.

| Months | N of cases |
|---|---|
| January | 4 |
| February | 2 |
| March | 1 |
| April | 8 |
| May | 1 |
| June | 5 |
| July | 2 |
| August | 5 |
| September | 5 |
| October | 3 |
| November | 4 |
| December | 1 |

N - number

**Table 4 -** Thyroid function data on cord blood of congenital hypothyroidism infants.

| Analytes | N | Median | Mean | SEM | Range | Units |
|---|---|---|---|---|---|---|
| TSH | 33 | 330 | 348.6 | 43.2 | 9 - 1055 | mIU/L |
| Free T4 | 35 | 7.3 | 7.9 | 0.4 | 3.4 - 14.5 | pmol/L |

N - number, TSH - thyroid stimulating hormone, T4 - thyroxine, SEM - standard error of mean

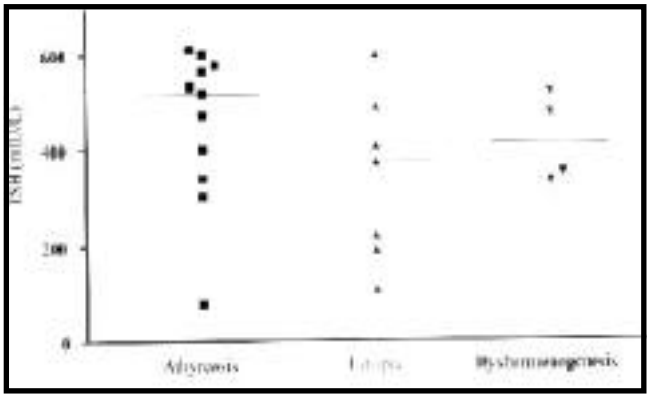

**Figure 2 -** Scatter diagram of cord blood thyroid stimulating hormone of different etiologies. TSH - thyroid stimulating hormone.

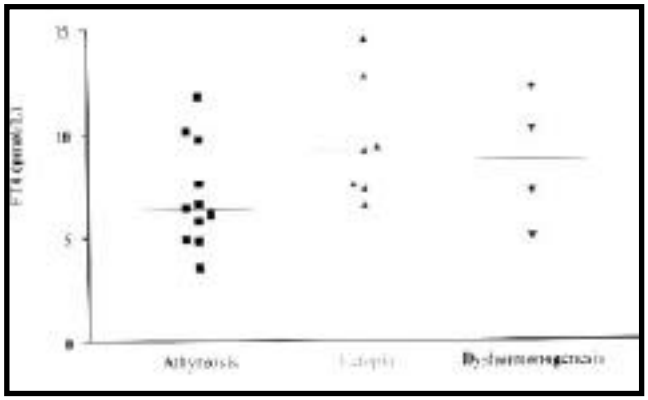

**Figure 3 -** Scatter diagram of cord blood free thyroxine values obtained in congenital hypothyroidism of different etiologies. FT4 - free thyroxine.

**Table 5 -** Frequency of the different etiologies on congenital hypothyroidism in Riyadh Al-Kharj Hospital Programme.

| Etiology | N of cases | (%) |
|---|---|---|
| Athyreosis | 13* | (29.5) |
| ***Ectopic thyroid*** | | |
| Lingual | 5 | (11.5) |
| Midline | 2 | (4.5) |
| Goitrous | 1 | (2) |
| Hypoplastic | 0 | (0) |
| Dyshormonogenesis | 5 | (11.5) |
| Apparently normal | 3 | (7) |
| Undocumented | 15 | (34) |
| **Total** | **44** | **(100)** |

* - documented, N - number.

**Table 6 -** Blood group distribution among antenatal clinic attendees and mothers of congenital hypothyroidism children.

| Blood groups | % frequency | |
|---|---|---|
| | Antenatal clinic | Mothers of CH children |
| O | 44 | 30 |
| A | 36 | 52 |
| B | 16 | 18 |
| AB | 4 | 0 |

CH - congenital hypothyroidism

**Table 7** - Maternal and neonatal parameters of congenital hypothyroidism infants.

| Parameters | N | Median | Mean | SEM | Range |
|---|---|---|---|---|---|
| Maternal age (year) | 29 | 26 | 26 | 0.89 | 18 - 37 |
| Gestational age (weeks) | 30 | 40.2 | 39.5 | 0.57 | 31 - 43 |
| Birth weight (g) | 34 | 3270 | 3231 | 112.60 | 1700 - 4180 |
| Birth length (cm) | 31 | 50 | 49.6 | 0.55 | 42 - 54 |
| OFC (cm) | 30 | 34.75 | 34.3 | 0.45 | 25 - 37 |
| Apgar score at 1m | 31 | 8 | 7.3 | 0.25 | 4 - 9 |
| Apgar score at 5m | 31 | 9 | 8.5 | 0.27 | 1 - 10 |
| Days to treatment | 30 | 9 | 10.3 | 1.24 | 1 - 31 |

N - number, SEM - standard error of mean, OFC - occipital forehead circumference, m - minute, g - gram, cm - centimeter.

etiologies (**Figures 2 & 3**). On the other hand, although few data were available, thyroglobulin levels were low in athyreosis and raised in thyroid ectopia. Cord blood thyroglobulin may serve as an aid in the characterization of CH. The characteristic signs and symptoms of CH are rarely seen in the neonatal period. This explains why, before the advent of mass screening, approximately 10% of infants were diagnosed clinically in the first month and 35% within 3 months.[20] The conventional wisdom supported by various studies[21,22] is that initiation of treatment before the age of 3 months generally conduces to satisfactory physical and mental development in affected infants. In the present study, jaundice was observed in 40% of cases of CH. The other signs and symptoms such as umbilical hernia, macroglossia, micrognathia, enlarged anterior fontanelle or depressed nasal bridge were rarely seen. Al-Jurrayan et al[9] also noted a similar scarcity of neonatal signs and symptoms of CH in KSA. In Finland, Virtanen[23] found jaundice in 57% of CH infants within one month. It has been observed[24] that infants with low cord blood total T4 had a higher incidence of jaundice and other signs and symptoms of CH in the neonatal period. Analysis of our data showed no significant difference in the free T4 levels of CH infants with and without jaundice. **Table 7** is a summary of the maternal and neonatal parameters of CH infants. The gestational age and anthropometric measurements of CH infants were not significantly different from those of Saudi infants in general.[25] Virtanen[23] had observed that CH infants in Finland had prolonged gestation and high birth weight. Similarly, Grant et al[24] had noted that in UK 44% of CH infants had birth weight in excess of 3500g. The maternal blood group distribution of CH infants was compared with that of women attending the antenatal clinics. Mothers of CH infants were 52% blood group A and 30% group O as opposed to 36% and 44% among the antenatal clinic attendees. The association between congenital hypothyroidism and human leukocyte antigen (HLA) types AW24 and BW44 has been observed previously[16] but there is no record of any blood group association. The number of CH infants in this study was quite small but the association of CH with blood group deserves further investigation. The most significant data concerns the mean age at start of treatment which was 10.3 days (range 1 – 31). In the final analysis this is the real measure of the success of the screening programme.

In conclusion, the screening programme based on initial measurement of TSH in cord blood captures nearly 97% of infants born in the RKH Programme. Between 1985 and 1999, the overall incidence of CH was 1:2759 live births with a female:male ratio of nearly 2:1. No seasonal variation was observed. Apart from jaundice, signs and symptoms of congenital hypothyroidism were rarely present in the neonatal period. The neonatal and maternal parameters of affected infants did not differ significantly from those of other infants, thus making it difficult to draw a profile of affected babies. The main cause of CH was athyreosis (45%), followed by thyroid ectopia (24%) and dyshormonogenesis (17%). The mean age at start of treatment of infants diagnosed in the screening programme was 10.3 days. The most reliable modality for diagnosing congenital hypothyroidism is by neonatal screening. However, no screening programme can achieve 100% sensitivity or specificity and neonatologists should remain vigilant in looking for CH.

Acknowledgment. We are grateful to Syed Mujeebuddin, BSc MSc (Pathology Department, Security Forces Hospital, Riyadh, Kingdom of Saudi Arabia) for his expert assistance with the statistics and graphics.

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