

# Screening for congenital hypothyroidism in the Islamic Republic of Iran: strategies, obstacles and future perspectives

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تحري قصور الدرقي الخلقي في جمهورية إيران الإسلامية: الاستراتيجيات، والعوائق، والمنظور المستقبلي  
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**الخلاصة:** تم تقييم الجدوى العملية لبرنامج لتحري قصور الدرقي الخلقي، حيث تم أخذ عينات ممثلة في قطرات من دم الحبل السري في سبعة مستشفيات في طهران وداخل الشبكة الصحية لمنطقة دماوند. وتم اعتبار المستويات الطبيعية للهرمون المنشط للغدة الدرقيّة المأخوذة من الحبل السري، بما يعادل 20 ميكرو وحدة/لتر أو أكبر، وتم البدء في المعالجة بدواء ليفوثيروكسين بعد تشخيص قصور الدرقيّة مباشرة. وكان 22 من الولدان من جملة 107 عينة مقبولة مصابين بقصور الدرقيّة (أي بنسبة 1:914 من المواليد)، أي بمعدل 1.3%. وبلغت نسبة التغطية بالتحريّ 90% من المواليد الأحياء. وكان متوسط العمر عند التشخيص ثمانية أيام، وعند بدء المعالجة 12 يوماً. وتخلص الدراسة إلى جدوى تحريّ قصور الدرقيّة. ونظراً لارتفاع معدل وقوعها، يستلزم الأمر تنفيذ برنامج وطني للتحريّ.

**ABSTRACT** The operational feasibility of a congenital hypothyroidism (CH) screening programme was assessed. Cord blood spot specimens were collected at seven Teheran hospitals and within the Damavand District health network. Cord thyroid-stimulating hormone (TSH) levels  $\geq 20$  mU/L were recalled and levothyroxine (L-T<sub>4</sub>) therapy was started immediately after diagnosis of CH. Of 20 107 acceptable specimens, 22 neonates had CH (1:914 births). The recall rate was 1.3%. Screening coverage was 90% of live births. Of all cord samples, only 0.2% were unacceptable either because of delay in transportation or improper specimen collection. Median ages at the time of diagnosis and starting treatment were 12 and 8 days respectively. Screening for CH is feasible and a national screening programme is a necessity.

## Dépistage de l'hyperthyroïdie congénitale en République Islamique d'Iran : stratégies, obstacles et perspectives futures

**RESUME** La faisabilité opérationnelle d'un programme de dépistage de l'hyperthyroïdie congénitale a été évaluée. Des échantillons de sang du cordon ombilical ont été recueillis dans sept hôpitaux de Téhéran et dans le réseau de santé du District de Damavand. Les nouveau-nés ayant un taux d'hormone de libération de la thyroïdostimuline (TSH) dans le cordon supérieur ou égal à 20 mU/L ont été rappelés et un traitement par lévothyroxine (L-T<sub>4</sub>) a été mis en route immédiatement après le diagnostic d'hyperthyroïdie congénitale. Sur les 20 107 échantillons acceptables, 22 nouveau-nés avaient une hyperthyroïdie congénitale (1 pour 914 naissances). Le taux de rappel était de 1,3 %. La couverture du dépistage s'élevait à 90 % des naissances vivantes. Sur tous les échantillons de cordon, 0,2 % seulement étaient inacceptables du fait soit du retard dans le transport soit du mauvais recueil des échantillons. Les âges médians au moment du diagnostic et de la mise en route du traitement étaient de 12 et 8 jours respectivement. Le dépistage de l'hyperthyroïdie congénitale est possible, et un programme national de dépistage est nécessaire.

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## Introduction

Congenital hypothyroidism (CH) occurs in 1:3000–4000 births [1] and represents one of the most common preventable causes of mental retardation [2]. Delayed diagnosis and treatment may result in poor neurointellectual outcome [3]. Screening for CH was first introduced in Canada in 1974 [4,5]. It has since become routine in all industrialized and some developing countries [6]. Primary tests measuring thyroid-stimulating hormone (TSH) or serum thyroxine ( $T_4$ ) on dried blood spots have been extensively employed for detection of neonatal hypothyroidism. Primary TSH screening is presently performed in all European countries (except the Netherlands) and in Japan, Australia and parts of the United States of America and Canada. In the two latter, primary  $T_4$  tests are used more frequently [7].

In 1987, the Islamic Republic of Iran was an iodine deficient area and Azizi et al. introduced the first CH screening in Teheran using cord blood TSH measurement. Iodine deficiency induces hyperthyrotropinaemia and subsequently has a high recall rate of neonates. Because the recall rate of the first screening programme was unusually high (i.e. 5%), the programme was temporarily discontinued [8]. In 1990, Karamzadeh and Amirhakimi conducted a study of 4300 cord blood samples in Fars Province using primary  $T_4$  supplemented by TSH back-up tests on specimens lower than the cut-off level. The incidence rate of CH was one in 1433 births [9].

National iodine supplementation with iodized salt was implemented in 1989 and by 1994 more than 95% of households were consuming iodized salt. Median iodine excretion for school-age children was 20.5  $\mu\text{g}/\text{dL}$  in 1996 [10]. Hence, the screening programme recommenced in 1998.

In this country, most deliveries occur in hospitals or birth centres, which belong to primary health care (PHC) or non-PHC systems.

We determined CH incidence rate and assessed the operational feasibility of the programme in the Damavand District health network (PHC) and in Teheran hospitals (non-PHC), both of which offer models for a national screening programme. Proper sampling, timely transportation of samples, maximum neonate coverage, follow-up and treatment of CH neonates were also analysed.

## Methods

For 40 months between 20 February 1998 and 21 June 2001, cord blood samples were collected in seven hospitals in Teheran. For an additional 12 months therein (since July 2000), a general hospital and a rural birth centre in the health network of Damavand District were also used for sample collection. The Damavand hospital and birth centre and the Teheran hospitals offered models for PHC and non-PHC systems respectively. Damavand hospital and birth centre were 76 and 96 km respectively from the Endocrine Research Centre (ERC). The distances of the Teheran hospitals from the ERC were between 0 km and 25 km.

Cord blood samples were collected on filter papers (Whatman BFC 180, United Kingdom) immediately after birth, i.e. only after live births. Specimens were collected and shipped by trained personnel to the ERC central laboratory in Teheran according to the National Committee for Clinical Laboratory Standards and the American Academy of Pediatrics recommended guidelines for CH Screening Programmes [11,12]. The samples from the Teheran hospitals were transported to the ERC 3 to

4 times per week, whereas the samples from Damavand hospital and birth centre were transferred twice weekly. Samples with delayed transportation (i.e. samples at room temperature > 7 days between specimen collection and TSH measurement) and with improper collection and/or transportation were considered 'unacceptable specimens' for testing. In the Damavand health network, the number of days that elapsed between specimen collection to receipt at the ERC laboratory was assessed. In Teheran, however, the interval was only assessed as  $\leq 7$  or  $> 7$  days from specimen collection to receipt by the ERC, i.e. acceptable or unacceptable samples respectively. TSH concentrations of dried blood spots were measured using a two-site immunoradiometric assay method (NETRIA kits provided by Iran Atomic Energy Organization under supervision of International Atomic Energy Agency, RAW/6/003 Project).

TSH values  $\geq 20$  mU/L were considered abnormal and those neonates were recalled. In the non-PHC system, parents were informed either by telephone, if possible, or by home visits. In the PHC system, however, local health workers notified parents of recalls during at-home visits. Recalled neonates born in and discharged from Teheran hospitals were brought directly to the ERC for confirmatory tests. Considering the difficulties of bringing the neonates to the ERC from the distant rural and urban areas in Damavand District, sera of recalled neonates were collected at the Damavand general hospital and sent to the ERC central laboratory within 48 hours. Storage and transportation of sera were carried out under standard conditions [13]. If cord blood TSH values were  $\geq 100$  mU/L, either in the PHC or the non-PHC systems, the parents were asked to bring their babies directly to the ERC without delay. The recall goal was

to bring neonates to the ERC for confirmatory tests within 7–14 days of life. The diagnosis for those not brought to the ERC was considered 'undetermined'. Confirmatory tests comprised venous TSH and  $T_4$ . Normal venous TSH and  $T_4$  values were considered as 'transient hyperthyrotropinaemia'. Abnormal values were determined using reference values adjusted for age [14]. During the first 7–14 days of life, or thereafter, venous TSH  $> 10$  mU/L and  $T_4 < 6.5$   $\mu\text{g/dL}$  or venous TSH  $\geq 30$  mU/L regardless of venous  $T_4$  values were considered to be CH. Hypothyroid neonates underwent clinical examination by a trained endocrinologist. Sera of CH neonates were collected for thyroglobulin (Tg) measurement. Neonatal and maternal urinary iodine were also measured. Whenever possible, knee X-ray was taken for determination of bone age, followed by thyroid scintigraphy using  $^{99\text{m}}$ Tc pertechnetate. Replacement levothyroxine (L- $T_4$ ) therapy (10–15  $\mu\text{g/kg}$  per day) was started immediately after diagnosis of CH and for those with cord TSH  $\geq 100$  mU/L. Figure 1 gives the flow-chart of the ERC screening programme for CH.

Indicators of operational quality included total birth coverage (total number of acceptable cord blood samples  $\times 100$  per total number of live births); interval between specimen collection for Damavand health network and receipt by and TSH measurement in the ERC central laboratory; number of unacceptable primary samples due to delay in transportation in PHC and non-PHC systems; number of unacceptable primary samples due to improper technique of sampling or shipment in PHC and non-PHC systems; total recall rate; interval between birth and confirmation of diagnosis in recalled neonates; and interval between birth and starting treatment in hypothyroid neo-



nates (ideal if < 15 days and acceptable ≤ 45 days of life).

## Results

### Indicators of operational quality

A total of 20 143 cord blood samples, 18 978 (94.2%) from Teheran and 1165 (5.8%) from Damavand, were collected and sent to the ERC central laboratory. Of these, 36 (0.18%) samples were unacceptable, 28 samples from Teheran and 8 samples from Damavand. Of these 36 samples, 17 were unacceptable because of improper sampling and 19 were unacceptable because of delayed transportation. Of the improperly collected specimens, 15 were from Teheran hospitals and 2 were from the Damavand health network. Of the delayed transportation specimens, 13 were from the Teheran hospitals and 6 were from the Damavand health network. The mean interval and standard deviation between specimen collection in the Damavand health network (PHC system) and receipt and testing by the ERC central laboratory was  $2.7 \pm 1.5$  days with a median of 2 days. These data were not available for Teheran hospitals.

During the course of the programme, 20 107 neonates, i.e. acceptable samples, were screened. Of the total acceptable samples, 18 950 (94.2%) and 1157 (5.8%) were from Teheran and Damavand respectively. Coverage increased progressively during the first year until it reached 90% of total births and then it remained constant throughout the programme. Of 1169 live births in Damavand, 1157 acceptable cord samples were sent to the ERC, which meant there was almost complete coverage (98.9%) in the PHC system. In the Teheran hospitals, coverage was 88.1% (16 183 of 18 362 live births).

The recall rate (RR) was 1.3% as 256 of 20 107 neonates had primary TSH values  $\geq 20$  mU/L. Respective values were 244 of 18 950 (RR = 1.3%) in Teheran and 12 of 1157 (RR = 1.0%) in Damavand District.

Of 56 telephone recalls, 52 parents responded and brought the infant to the ERC for confirmatory tests. The mean interval between birth and confirmation of diagnosis for recalled neonates was  $13 \pm 6$  days with a median age of 12 days and a range of 5–25 days. The mean interval between birth and commencement of treatment in CH neonates was  $10 \pm 5$  days with a median age of 8 days and a range of 4–46 days. L-T<sub>4</sub> therapy was started in four CH neonates at 15, 19, 23, and 46 days of life.

### Screening results

The distribution of cord TSH values is given in Table 1. There were 19 851 neonates who had cord blood TSH values < 20 mU/L and who were not followed-up. 'Transient hyperthyrotropinaemia' was seen in 174 neonates, of whom 163, 10, and 1 neonates

**Table 1 Distribution of cord blood spot thyroid stimulating hormone (TSH) values among 20 107 neonates screened for congenital hypothyroidism**

TSH (mU/L)	No.	%	Cumulative %
0–4.9	9143	45.5	45.5
5.0–9.9	9108	45.3	90.8
10.0–19.9	1600	8.0	98.7
20.0–29.9	171	0.9	99.6
30.0–39.9	35	0.2	99.8
40.0–49.9	17	0.1	99.8
50.0–99.9	16	0.1	99.9
$\geq 100$	17	0.1	100.0
Total	20 107	100.0	

had cord TSH values between 20–49.9, 50–99.9, and  $\geq 100$  mU/L respectively. Hypothyroidism was found in 22 neonates, i.e. an incidence rate of 1:914 live births. Diagnosis for 60 neonates remained 'undetermined' because of inaccurate address (33), parental lack of interest in follow-up (18), death of the neonate (6), and other causes (3).

## Discussion

The first screening for CH in the Islamic Republic of Iran by Azizi et al. during 1987–89 was discontinued after two years because of the high recall rate due to iodine deficiency and hyperthyrotropinaemia [8]. The second study in the country was conducted by Karamizadeh and Amirhakimi on 4300 cord blood samples and found an incidence rate of 1:1433 births for CH [9]. Our study was conducted in seven hospitals in Teheran for 40 months and in a general hospital and a rural birth centre in the Damavand District health network for 12 months. The former was a representative model for non-PHC systems and the latter for PHC systems. Of all live births, 88.8% were screened and the incidence rate of CH was 1:914 live births. This was higher than reported in North American and European countries and also in Japan [15]. To determine the incidence rate of permanent CH, a prolonged study is needed to differentiate transient from permanent types of CH.

Preliminary results of our study indicated a recall rate of 1.6%. This was significantly lower than during the iodine deficiency period when the recall rate was 5% ( $P < 0.001$ ) [16]. This significant decrease in the recall rate was one of the indicators of iodine supplementation in the region and supported continuation of the programme [1]. As the programme pro-

gressed, the recall rate settled at the present rate of 1.3%.

Only 36 (0.18%) of total cord blood specimens were unacceptable for testing. The low number of improperly collected samples (17) reflected the simplicity of the specimen collection technique for cord blood sampling used by the health workers. Thus, the programme seems operational on a larger scale because it can use pre-existing human resources and would not necessarily depend upon prolonged and/or complex training courses for personnel. Only 19 (0.09% of total samples) filter paper specimens were unacceptable due to delay in transportation to the ERC central laboratory ( $> 7$  days). Of these, 13 were from Teheran hospitals and 6 were from the Damavand health network. This meant that 99.9% and 99.5% of primary samples collected in non-PHC and PHC systems respectively were transported in a timely manner to the ERC laboratory. Therefore, the transportation system performed appropriately in both PHC and non-PHC systems. The Teheran hospitals were 0–25 km from the ERC central laboratory. The Damavand general hospital and the Damavand rural birth centre were 76 and 96 km respectively from the ERC central laboratory. In remote locations like the Damavand District, the distance from the central laboratory might be a problem for timely transportation of samples and indeed we initially expected that a large number of samples would be unacceptably delayed before reaching the ERC. Therefore, in addition to the plan for the Teheran hospitals, i.e. classifying samples into two groups ( $\leq 7$  and  $> 7$  days from sample collection to receipt by the ERC), the number of days that elapsed between sample collection in Damavand District to receipt and testing at the ERC central laboratory was also regis-

tered. This mean interval was  $2.7 \pm 1.5$  days with a median of 2 days. Hence, transportation of specimens was almost perfectly accomplished in the PHC system. The timely transportation of the samples from the Damavand District health network will serve as a model for PHC systems in other regions of the country.

The interval between birth and confirmation of diagnosis in recalled neonates was used as an indicator of the quality of job performance by the specimen collectors. These collectors included in addition to workers in the PHC and the non-PHC systems, the Damavand health workers and the ERC central laboratory, tracking system and screening office personnel. The mean birth–confirmation of diagnosis interval was  $13 \pm 6$  days with a median of 12 days and a range of 5–25 days and therefore the performance of the screening programme in both PHC and non-PHC systems was acceptable [17].

Heel prick method, which is usually performed during the first 2–6 days of life, is the preferred method for specimen collection [11,12]. However, cord blood sampling is still used in some regions [18,19]. In the United States of America and Canada,  $T_4$  is initially measured and TSH is only measured for those with the lowest 10%–20% of  $T_4$  results. In other areas of the world, direct TSH screening has commonly been used. In effect, all neonatal thyroid-screening programmes include screening for elevated serum TSH concentration as the most reliable indicator of primary hypothyroidism [6]. Selection of primary TSH or  $T_4$  methods depends greatly on the local laboratory or regional screening programme preferences. The incidence of CH has been shown to be similar with both screening approaches [7]. The threshold value of significant TSH elevation in most screening programmes is 20–25 mU/L. Re-

cent increases in the number of maternal–neonatal discharges from hospitals within 48 hours of delivery have been a burden on screening programmes by increasing recall rates and false positive cases [6]; therefore, some programmes use higher values for the TSH cut-off point [6,20]. Whatever method is used, the goal of the screening programme is to obtain samples from neonates and to provide early treatment of CH while keeping the number of false positive results as low as possible, particularly because of the emotional disturbance to parents caused by a recall [21].

In the Islamic Republic of Iran, the heel prick method could possibly result in large numbers of neonates not getting screened. In addition, mothers and neonates are usually discharged within 24 hours of delivery. Therefore, in the present study, in order to obtain specimens from all neonates, the preferred method was cord blood sampling. This might have resulted in a high recall rate because of the physiologic TSH surge within the first 24 hours of life. Some studies using cord blood samples have used a higher level for the cut-off point [20,22]. Since we planned to determine incidence and to design a model to serve as the nationwide programme, we used one of the lowest cut-off points reported, i.e. 20 mU/L. Initial results of the present study supported the use of higher cut-off values, e.g. 30–35 mU/L as CH was not found in neonates with cord TSH less than 40 mU/L. However, this concept was later abandoned when three hypothyroid neonates with primary TSH values of 23.3 mU/L, 33.2 mU/L and 35 mU/L were detected.

One of the main objectives of a CH screening programme is to establish early treatment for affected neonates. Although starting treatment within 14 days of life is preferred [7,23], this is not always possible. Due to screening and early diagnosis,

treatment of affected infants has usually been initiated within 45 days of birth and IQ levels in treated infants measured at 5 to 7 years of age have been normal [6]. Some researchers have reported that the turnaround time from collection of specimen to treatment must be less than 3 months or, ideally, less than 1 month [18]. In our study, the mean interval between birth and starting treatment for hypothyroid neonates was  $10 \pm 5$  days with a median of 8 days and a range of 4–46 days. The median age of start of treatment compared favourably with reports from Europe [24,25]. That the telephone recalls worked so well indicated that parents were reasonably cooperative and reduced the need for home visits considerably (and thus reduced the cost of the programme). This is important if the programme is to be conducted on a national scale. In this regard, public awareness plays a critical role.

A few difficulties and obstacles were observed. The large number of recalled neonates with 'undetermined diagnosis' and the few CH cases with delayed treatment will necessitate public awareness as the programme continues. Also, despite regular and careful monitoring of the programme (i.e. personnel, tests and equipment), human error was inevitable. For example, de-

layed reporting by central laboratory personnel of abnormal venous TSH and  $T_4$  values of one CH neonate resulted in delayed treatment for that child until day 46 of life.

Unless the programme can be legislated and supported by the government, initiation and operation of the neonate-screening programme for CH will not result in complete participation of the population at risk. Because of the high incidence rate of CH, a national screening programme for CH is needed in the Islamic Republic of Iran. The elimination of iodine deficiency, the low recall rate and the operational feasibility of the CH screening programme for both the PHC and the non-PHC systems have laid the groundwork for a successful programme. The next step will entail obtaining parliamentary legislation, government support and public awareness via mass media in order to establish a nationwide neonate screening programme for CH.

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### **Eastern Mediterranean Approach to Non-Communicable Diseases**

We would like to draw our readers attention to the EMAN network (Eastern Mediterranean Approach to Non-Communicable Diseases Network) which provides extensive information on noncommunicable diseases, such as cancer, cardiovascular disease, diabetes, genetics, osteoporosis and other chronic diseases, and the work and activities being carried out in the Region and WHO Regional Office with regard to these conditions. Information can be obtained on the Internet at: <http://www.emro.who.int/ncd/>