An-Najah National University
Faculty of Graduate Studies

Congenital Hypothyroidism among Palestinian Children of the West Bank

By
Issa Ibrahim Ishtieh

Under the Supervision
Of

Dr. Nael Abu-Hassan and Dr. Kamel Adwan

2001

Congenital Hypothyroidism among Palestinian Children of the West Bank

By

Issa Ibrahim Ishtieh

Under the Supervision

of

Dr. Nael Abu-Hasan and Dr. Kamel Adwan

An-Najah National University
Faculty of Graduate Studies
Nablus, Palestine
May, 2001

Congenital Hypothyroidism among Palestinian Children of the West Bank

By

Issa Ibrahim Ishtieh

Under the Supervision

of

Dr. Nael Abu-Hassan and Dr. Kamel Adwan

Submitted in partial fulfillment of the requirements for the degree of Masters of Science in Biology

An-Najah National University
Faculty of Graduate Studies
Nablus, Palestine
May, 2001

DEDICATION

To

My Parents

Brothers and Sisters

For their love, support and continuous encouragement

To all I loved and lost

ACKNOWLEDGMENTS

My sincere appreciation, and heartfelt gratitude go first to my supervisors committee, Dr. Nael Abu-Hassan, Dr. Kamel Adwan, Dr. Ryad Ameen and Dr. Faysal Awartani for their guidance, help and support through out this project. It is with affection and appreciation that I acknowledge my indebtedness to Prof. Dr. Joseph Sack for his enthusiastic encouragement, the priceless gifts of his time and wisdom, friendship, patience, support and valuable suggestions.

I would like to extend my deep appreciation to the physicians, nursing staff of the regional preventive medicine department and my colleagues in the Public Health Laboratory for their personal interactions and assistance.

Also, it is not possible to enumerate the dedicated, conscientious, tireless, and outstanding efforts of Dr. Mohammed Mosa, Dr. Ameen Thalgi, Dr. Aymen Daragmeh, Mr. Mohammed Asia, and Mr. Murad Abu-Hassan.

I wish to thank all families, whose children are participating in the follow-up study, for taking part in this study.

Special thanks for all in the Palestinian Ministry of Health and the director of the Preventive Medicine Department, Dr Asa'd Ramlawi, for their encouragement and support through my educational endeavors.

Last but not least my deep thanks to my family whom I owe much.

TABLE OF CONTENTS

Table of contents		Page
LIST OF TABLES		X
LIST OF FIGURES		XII
ABSTRACT		XIII
Chapter I	INTRODUCTION	1
1. 1	Development and physiology of the thyroid system	2
1. 2	Regulation Of the thyroid hormones	4
1. 3	Congenital hypothyroidism	5
1. 3. 1	Incidence of CH	5
1. 3. 2	Etiology	6
1. 3. 2. 1	Permanent CH	6
1. 3. 2. 2	Temporary or transient CH	7
1. 4	Iodine deficiency disorders	8
1. 5	Clinical signs and symptoms	9
1. 6	Newborn screening	10
1. 6. 1	Newborn screening for CH in Palestine	10
1. 6. 2	Socioeconomic impact	11
1. 7	Screening methodology	12
1. 7. 1	T4 and sequential TSH measurement	12
1. 7. 2	TSH and sequential T4 measurement	13
1. 7. 3	Specimens	14
1. 7. 4	Attitudes of health care providers	14
1. 7. 5	Collection and handling of specimens	14

1. 7. 6	Transport of specimens	14
1. 7. 7	Follow-up	15
1. 8	Imaging	15
1. 9	Treatment	16
1. 10	Prevention	17
1. 11	Outcomes of screening	18
	Aims of the study	20
Chapter II	**MATERIAL and METHODS**	21
2. 1	Newborn screening program in the west bank	22
2. 2	Screened population	23
2. 3	Neonatal TSH procedure (IRMA assay)	25
2. 4	Neonatal T4 procedure	25
2. 5	Evaluation of the newborn screening program	26
2. 6	The incidence of PCH in the west bank	26
2. 7	Study cases	26
2. 8	Transitory hypothyroidism	27
2. 9	Statistical analysis	27
Chapter III	**RESULTS**	28
3. 1	Newborn screening program for CH in the west bank	29
3. 1. 1	Coverage rate	29
3. 1. 2	Recall rate	30
3. 1. 3	Sample collection and testing	31
3. 2	Incidence of CH in west bank	33
3. 3	Follow up of suspected permanent CH cases	34
3. 3. 1	Demographic characteristics of CH subjects	34

3. 3. 2	Laboratory findings of CH subjects	35
3. 3. 3	Clinical findings of CH	37
3. 3. 4	Growth and development	38
3. 3. 5	Health services for CH subjects	41
3. 3. 5. 1	Identification of cases	41
3. 3. 5. 2	Diagnosis and treatment	42
3. 4	Suspected cases of transitory hypothyroidism	43
3. 4. 1	Incidence of transitory hypothyroidism	43
3. 4. 2	Demographic characteristics of transitory hypothyroidism cases	44
3. 4. 3	Laboratory findings among transitory hypothyroidism cases	45
3. 4. 4	Further Evidence on transitory hypothyroidism	47
Chapter IV	DISCUSSION	48
Recommendations And Concluding Remarks		63
References		65
الملخص		75
Appendix (1)	Questionnaire Form	77
Appendix (2)	Growth Percentile Charts	82

LIST OF TABLES

Table	Page
Table 1. Worldwide Incidence of CH	6
Table 2. % of coverage for CH screened in the West Bank from 1990-1997	11
Table 3. Advantages and disadvantages of using thyroxine or thyrotropine hormone as a primary test for CH	13
Table 4. Coverage rate of newborn infants screened among districts during the period of study	27
Table 5. Screening coverage rate of live births in correlation with the number primary health care centers	28
Table 6. The recall rate for infants in the various districts during the study period	29
Table 7. Age of infants (days) at specimen collection and performance of Guthrie test	30
Table 8. Mean age (in days) among infants at specimen collection according to place of residence	30
Table 9. The incidence rate of PCH among the different districts in the West Bank (from October 1998 to May 2000)	31
Table 10. Number of suspected PCH cases according to place of residence	32
Table 11. Association between consanguinity and the occurrence of CH among the study and control cases	32
Table 12. Initial and follow-up thyroid function of infants with CH	34
Table 13. Clinical features of CH first noted by mothers among the 28 study cases	35
Table 14. The overall mean number of symptoms appeared postnataly per infant for the study and control cases	36
Table 15. Physical problems among suspected PCH cases based upon WHO criteria	36
Table 16 a. Association between age at treatment and height percentiles	37

Table 16 b. Association between age at treatment and weight percentiles	**37**
Table 16 c. Association between age at treatment, TSH values and growth criteria weight and height	**38**
Table 17. Clinical and historical findings among study cases	**38**
Table 18. Age in months at first identification of the study cases	**39**
Table 19. **Age of subject at the time of diagnosis and treatment**	**40**
Table 20. Incidence rate of transitory hypothyroidism among the different districts	**42**
Table 21. Association between transitory hypothyroidism and the place of residence	**42**
Table 22 a. Results of newborn screening for suspected transitory hypothyroidism according to regions	**43**
Table 22 b. Guthrie-TSH and T4 results for the severe suspected transitory hypothyroidism cases	**44**
Table 23. Frequency of neonatal with TSH values > 5 μIU/ml in whole blood according to districts	**45**

LIST OF FIGURES

LIST OF FIGURES	
Table	**Page**
Figure 1. Thyroid gland system	2
Figure 2. Chemical structures of T4 and T3	3
Figure 3. The adopted system for newborn screening in the West Bank	22
Figure 4. Flow chart for neonatal screening tests for the detection of CH in the West Bank	24

Abstract

Neonatal screening for congenital hypothyroidism (CH) was initiated in the West Bank in 1990. The aim of this study was to establish a base line data regarding CH incidence, and to determine possible risk factors.

This study show that the screening program system faced many inherited obstacles regarding sampling as well as handling of specimens, and also in the follow up of results and communicating results to concerned people. From October 1998 to May 2000, there were 85,149 live births. Around (69,957) neonates were screened using a primary measurement of TSH in capillary blood, using dried blood spots obtained by a heel prick. All samples were assayed by immunoassay method. Thirty-two cases were diagnosed as suspected permanent CH (incidence, 1:2186.15). This incidence is notably higher than reported in most other countries. The etiology of this high incidence is unknown, however, it seems to be of a multifactorial form. Although our result point that parental consanguinity may play a significant part on the frequency of CH in our population, environmental factors can not be excluded. Recall rate was found to be (0.78%). The incidence of transitory hypothyroidism remarkably high (1: 418.9). About 14.96 % of infants screened were with raised TSH level of 5 μIU/ml. Thus, neonatal screening seems to be highly affected by iodine deficiency leading to increased recall rates, transient and permanent cases of CH.

Although our screening program have benefited patients and families to some extent, it seems that it does not reached it's main objectives which are; early detection and therapy.

Screening and confirmatory thyroid function results revealed moderate to severe abnormalities, with unfortunate delay in screening (89 days), diagnosis (143 days) and treatment (152 days). Observations on severity of disease symptoms, growth and development problems were significantly correlated with delay in therapy. This fact supports the view that a comprehensive program has to be initiated. Thus, it seems reasonable to strive for early detection and management for effective prognosis. To achieve this goal, cooperation between all primary health care providers, to the infant from conception to birth, is definitely needed.

Chapter I

INTRODUCTION

1.1 Development and physiology of the thyroid system

Thyroid gland system consists of the thyroid gland and two specialized brain centers known as the hypothalamus and the pituitary gland (see figure 1). It forms and almost becomes mature during intrauterine fetal growth.

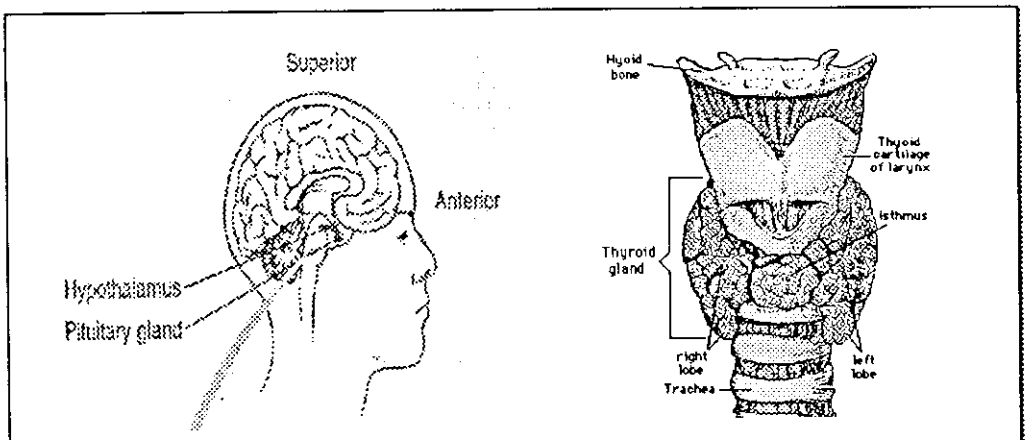


Figure 1. Thyroid gland system

Early in the first trimester, thyroid gland develops from endoderm of the pharyngeal duct. It descends to the anterior neck through a process of " differential migration", where half of the gland lies on each lobe of the trachea and unite to each other by an isthmus. This development is associated with the growth and development of the hypothalamus and pituitary gland. Through the second and the third trimesters, the fetal hypothalamic-pituitary-thyroid axis gradually mature [1].

Thyroid gland produces a set of hormones (see figure 2) that are vital in regulating the metabolism, growth and development of the fetus. They also play an important role in the growth of the CNS during fetal and childhood period.

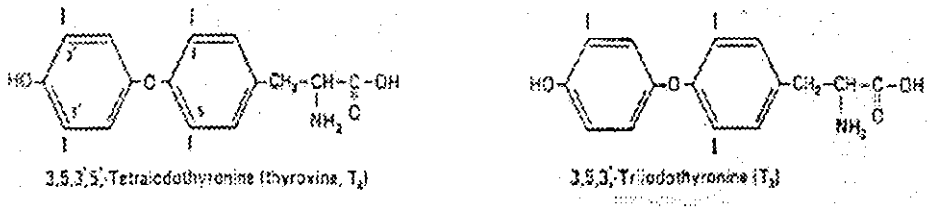


Figure 2. Chemical structures of Thyroxine (T4) and Triiodothyronine (T3)

Thyroid hormones are released under the influence of a thyroid–stimulating hormone (TSH) by a sensitive proteolytic process. Thyroxine is synthesized in the thyroid gland by a complex process involving the transport and oxidation of inorganic iodide, iodination of tyrosine (organification), and coupling of iodinated tyrosine residues within thyroglobulin.

Thyroxine (T4) binds to plasma thyroxine-binding globulin (TBG), where as tri-iodothyronine (T3) binds to both TBG and albumin. A small proportion is free (0.03% and 0.3% of free T4 and freeT3, respectively) representing the metabolically active parts [2].

Near full-term, fetal serum T3 levels increase moderately, with a further increase in T4-to-T3 conversion in newborn. Immediately after birth, there is a marked normal TSH surge, which reach the peaks between half and hour of life. TSH levels return to baseline by 48-72 hours of life. T4 is relatively low at birth, slowly increases to peak at 24 to 36 hours, and then slowly declines over weeks to months [2-4].

During the first and possibly the beginning of the second trimester of pregnancy, the human fetus is entirely dependent on the mother for it's thyroid hormone supply. Transfer of the maternal iodothyronines may take place either across the placenta or through the amniotic fluid swallowed by the fetus [5]. Under normal

circumstances, only small and limited amounts of maternal thyroid hormones cross the placenta [6-7]. The limited maternal supply is insufficient to compensate for most cases of severe congenital hypothyroidism (CH).

Other compensatory protective mechanisms are also involved in preventing brain damage in CH infants. An increased type II deiodinase activity in the fetal brain can maintain almost normal brain T3 levels despite low T4 concentration.

1. 2 Regulation of the thyroid hormones

Thyroid hormones are regulated by the interaction between the hypothalamus, pituitary, and thyroid gland. Thyroid function is essentially controlled by thyroid stimulating hormone (TSH), which is produced by the pituitary gland. The hypothalamus produces thyrotropin releasing hormone (TRH), which sets the base level of TSH production by the pituitary. The amounts of thyroid hormone T3 and T4 in the body are then balanced through a feedback mechanism. The pituitary constantly measures the amount of thyroid hormone in the body. If the level is too low, the hypothalamus secretes thyrotropin-releasing hormone (TRH), which in turn stimulates the pituitary to release TSH. The TSH directs the thyroid gland to produce more hormones until normal levels are reached.

1. 3 Congenital hypothyroidism

Hypothyroidism is a condition in which the thyroid gland does not make sufficient thyroid hormone to meet the body's requirement "under active thyroid gland". Congenital hypothyroidism is defined as hypothyroidism present in utero and persisting thereafter [8]. It is one of the most common diseases in pediatric endocrinology [9-11]. It is also considered as one of the most common preventable causes of mental retardation if treated early [9, 12-15].

1. 3. 1 Incidence of CH

Although the incidence of CH has been shown to vary among different parts of the world as shown in the table (1), it occurs in 1:3000 to 1:4000 newborns worldwide [11, 14, 16]. The incidence of CH varies with ethnic origin [16-20]. The possibility of seasonal variation in the incidence of CH also has been shown [21].

Most screening programs also report female preponderance, however, the significant of this sex ratio is unknown [17, 18].

Table 1. Worldwide Incidence of CH

Country	Period	Births, Total	Incidence, Mean	References
Europe	1985-1990	22,448,826	1:3,801	16
USA	1988-1990	12,429,086	1:4,119	16
Canada	1986-1988	1,126,778	1:3,884	16
Cuba	1987-1991	667,681	1:2,325	16
Australia	1985-1990	487,154	1:3,331	16
New Zealand	1987-1990	231,045	1:4,496	16
Japan	1990	1,218,535	1:3,856	16
Mexico*	1990-1991	30,429	1:1,480	16
Argentina* (Buenos Aires)	1985-1990	48,479	1:4,407	16
Brazil* (Porto Algero)	1987-1991	106,001	1:4,429	16
Israel	1985-1990	-	1:3,153	16
Saudi Arabia (Najran)	1990	30810	1:1400	19
Kuwait	1981-1987	-	1:3476	20
Oman	1991-1995	36,000	1:2200	21
Taiwan	1988-1990	991,132	1:5,788	22

- Represent a pilot study

1. 3. 2 Etiology

1. 3. 2. 1 Permanent CH

The permanent types of CH can be separated into the following:

A. Thyroidal abnormalities (primary hypothyroidism):

Including thyroid dysgenesis (TD), which generated as a result of agenesis (absent gland), hypoplasia (severely reduced in size), or an ectopic (mostly small and sub-lingual) thyroid gland. It is the most common etiology of CH accounting for about 85% of cases [13, 14, 26, 27]. The pathogenesis is largely unknown [9, 11]. Agenesis is the most severe form of TD and usually result in the lowest levels of thyroid hormone at birth [2, 8, 14]. Most cases of TD occur sporadically although, it can be a heritable [10].

Thyroid dyshormonogenisis represent another form of permanent of thyroid abnormalities as a result of in-borne errors of T4-biosynthesis, accounting for 10-15% of the cases of CH [11, 14, 27, 28].

A number of different defects have been characterized and include: 1) decreased TSH responsiveness, 2) failure to concentrate iodide, 3) defective organo-fication of iodide, 4) defective thyroglobulin (TG) synthesis or transport and 5) abnormal iodotyrosine deiodinase activity. All the inborn errors are autosomal recessive except for defects in thyroid hormone receptors (which are autosomal dominant) [10,11,14].

B. Extra thyroidal abnormalities

This includes the central (hypothalamic or pituitary) hypothyroidism. It is a rare disorder with an incidence rate that varies from 1:25,000 to 1:100,000 among newborn [14] and accounts for about 5% of the CH cases. Recently, it has been revealed that central CH can lead to severe symptoms during the neonatal period [10, 29, 30].

1. 3. 2. 2 Temporary or transient CH

Temporary or transient CH represents a condition that closely resembles mild hypothyroidism that can be detected at screening but disappear subsequently within a few days or weeks, either spontaneously or after a short period of therapy. No definitive data exist regarding its true incidence [25].

It can be classified into two categories:

Transient hypothyroxinemia:

This condition is common in premature infants and represents a transient state of hypothalamic (or tertiary) hypothyroidism. It is characterized by low total and free T4 concentrations with normal TSH levels.

Transient hypothyroidism and hyperthyrotropinemia:

This picture represents transient state of hypothyroidism principally due to iodine deficiency, occasionally to iodine overload

rare except in Europe (1:200 - 1:8000) resulting in abnormal thyroid function tests recovered in two to several weeks and the risk is increased with pre-maturity. Cases also have been reported as a result of prenatal or postnatal exposure to excess iodine [31-37]. Intrauterine exposure to anti-thyroid medication, given to pregnant women with Graves' disease, and transplacental passage of maternal TSH receptor blocking antibodies may result in this condition [38].

1. 4 Iodine deficiency disorders

Iodine is an essential micronutrient for thyroid function, necessary for the normal growth, development and functioning for the brain and body. Without a proper diet of iodine, the human body is susceptible to a number of problems identified as iodine deficiency disorders (IDD). Iodine deficiency disorder (IDD) is a serious global public health problem. It is the single most common cause of preventable mental retardation and brain damage [39, 40]. Lack of iodine in the diet is the main cause of IDD.

An estimated 1.6 billion people worldwide are threatened by iodine deficiency, representing nearly 30% of the world's population. Neonates and young infants constitute the target population for the effects of iodine deficiency. Iodine deficiency depends on the geophysical properties of the land, and therefore can affect rich and poor countries alike. Different regions appeared to be of various degrees of iodine deficiency including South East Asia, Hong Kong, Belgium [35].

Neighboring countries, Jordan and Lebanon, who have similar geographical characteristics, have conducted surveys that indicate the IDD does indeed constitute a public health problem. IDD is also appeared to be a severe public health problem in Upper Egypt [41].

appeared to be a severe public health problem in Upper Egypt [41]. Transient neonatal hypothyroidism is frequently observed in iodine-deficient areas in different parts of the world. Border line elevated neonatal serum TSH concentration frequently occur in newborns in iodine deficient areas and result in a higher recalling rate at the screening for CH [9, 36].

Neonates exhibit elevated serum TSH more frequently than adults for a similar degree of iodine deficiency [42].

1. 5 Clinical signs and symptoms

Symptoms of infants with CH may appear as early as 1-3 weeks or as late as 4-12 months. Initially, newborns with hypothyroidism present with hypothermia and cool skin, peripheral edema, abdominal distention and a posterior fontanel (> 5 mm in diameter), poor feeding and have prolonged jaundice (>3 days). During the first 4 weeks signs and symptoms include failure to thrive, respiratory difficulties, lethargy, decreased activity and constipation. Later on, during the third month of age, the picture appears more classical with myxedema, umbilical hernia, hypotonia, dry yellowish pale skin, hoarseness, loud breathing and constipation [11, 43]. In general, the extent of the clinical findings depends on the etiology, severity, and duration of the hypothyroidism. Infants with severe intra-uterine hypothyroidism tend to be the most symptomatic at birth.

1. 6 Newborn screening

Newborn screening is a preventive public health procedure that should be available to all neonates. It is a population based public health program applying preventive medicine in defined regions to reduce newborn morbidity and mortality from certain biochemical and genetic disorders at pre-symptomatic stage. Screening tests are designed to rapidly and inexpensively evaluate a large number of specimens, which are usually in the form of dried blood spots, in specifically designed filter paper blotters.

Over 300 gene disorders can be traced to specific biochemical defects referred to as in-born-errors of metabolism, and many of these disorders result in mental retardation. Because many disorders are extremely rare and screening all newborn is expensive, mass screening is currently being justified for only a few disorders.

Screening for congenital hypothyroidism was the third test implemented in an effort to prevent mental retardation as well as developmental disabilities during infancy. The first screening programs for this disease began in April 1974 in Quebec [44].

Currently, CH screening test is widely used as it allows earlier diagnosis and effective treatment. Approximately, 24 millions infants are screened worldwide, with 6,000-to-8,000 cases detected each year.

1. 6. 1 Newborn screening for CH in Palestine

Prior to the introduction of CH screening program in Palestine, many cases were commonly delayed, which resulted in brain, physical growth disabilities and other defects. A nationwide screening program in the West Bank was launched in June 1990. It was operated as part of the neonatal screening program in Israel in

the central CH laboratory at the Chaim Sheba Medical Center, Tel-Hashomer until 1995. At the beginning of 1997, the Palestinian Ministry of Health started re-conducting CH and phenylketonuria screening program independently.

Table 2. Estimated % of coverage for CH screened in the West Bank from 1990-1997

Year	% Coverage
1990	25.05
1991	27.00
1992	31.00
1993	35.00
1994	50.00
1995	60.00
1996	No screening
1997	70.00

Adopted from [45]

1. 6. 2 Socioeconomic impact

Newborn screening for congenital hypothyroidism entails substantial costs, some of which are inherent in the screening process. All abnormal test results trigger diagnostic and some times therapeutic cascades, with their associated economic costs. The costs for newborn screening for congenital hypothyroidism in the West Bank range from 1.5 US$ for normal case to 7.8 US$ for all inclusive program including follow-up confirmatory testing of repeated samples. In a developing country like Palestine, the question would be is newborn screening for CH is cost beneficial? Does the condition occur frequently enough to be a public health concern? The following reasons may justify that:

- Clinical and chemical indicators for IDD revealed that IDD problem is mild in the West Bank and Gaza Strip and is considered to a public health problem [46].

- Consequences due to the lack of proper diagnosis and treatment.
- The combination of neonatal screening program for CH and PKU disorders, same Guthrie cards, is expected to dramatically reduce cost risks because both screening use the same infra structure.

Beside the above facts, examination of blood-spotted filter paper for TSH concentration in the screening for CH is inexpensive, simple, and provides quick results.

The optimal coverage is 100,000 newborns/year and the number should not be less than 40,000 newborns/year to meat the economic and epidemiological need of population screening and to favor cost benefit ratio [47].

1. 7 Screening methodology

It is the objective of screening programs to detect infants with CH. Different screening strategies have evolved to detect them. The CH is a twofold screening process. Some centers have measured only T4, others only TSH, while still others have measure both hormones, either in all specimens or on a selective basis.

There are arguments in favor and against using either hormone as the preliminary screening [9, 12, 48-50].

1. 7. 1 T4 and sequential TSH measurement

Most North American programs use a T4-TSH laboratory approach, i.e., an initial filter paper blood spot T4 with a TSH measurement in specimens with low T4 values.

1. 7. 2 TSH and sequential T4 measurement

The majority of laboratory in Europe, Japan, Australia and part of North America are screening with primary TSH measurement supplemented by T4 determination in cases of high TSH values.

Table 3. Advantages and disadvantages of using thyroxine or thyrotropine hormone as a primary test for CH

Assay	Advantages	Disadvantages
T4 – TSH	1- Detect overt primary hypothyroidism. 2- Detect secondary-tertiary (1/50,000 – 1/100,000). 3- Hyperthyroxinemia.	1- Poor specificity (high recall rates). 2- Poor sensitivity (in patients with ectopic glands.
TSH - T4	1- Better in early detection of overt and subclinial primary hypothyroidism. 2- Sensitive index for early detection of transitory hypothyroidism. 3- Good index for iodine supply of the population.* 4- Higher specificity. 5- Better sensitivity.	Will miss: 1- Secondary-tertiary hypothyroidism missed. 2- Primary hypothyroidism with delayed TSH surge. 3- Hypothyroidism due to anomalies in T4-bindings globulin deficiency. 4- Hyperthyroxinemia.

- **Data collected from [9, 12, 37, 48-50]**
- **The World Health Organization (WHO), United Nations International Children's Emergency Fund (UICFF), and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) included neonatal TSH as one of the indicators for assessing IDD and their control [33].**

Both types of screening (T4, TSH) may miss a small number of affected infants [14,51].

Approximately 10% of programs in US collect two routine screening specimens, (for example, the first at age 2 to 5 days and a second at age 2 to 6 weeks of age). Results from these programs show that about 10% of infants are detected only as a result of the collection of the second specimen [12].

1. 7. 7 Follow-up

It is recommended that all newborns should have primary care providers designated before discharge to ensure prompt and appropriate follow-up of newborn screening results.

CH infants and children should be follow-up, including clinical examination, evaluation of growth including bone maturation, determination of serum total and free T4 and T3 and TSH, as well as an evaluation of psychomotor and intellectual development to be performed at regular intervals. In the developing countries, especially in the distant rural areas, follow-up and re-screening may be difficult in infants and may take time and add to the delay of fast treatment and managing.

1. 8 Imaging

Thyroid scintigraphy with 99m Tc-pertechnetate (TcPT) or radioactive iodine (^{123}I) is a useful assistant diagnostic procedure that allows the best evaluation of the cause of the syndrome at the neonatal age. It allows establishing a firm and final diagnosis of the cause of hypothyroidism [52].

Thyroid scintigraphy with TcPT is used in clinical practice for evaluating the anatomy and the function of the thyroid gland in adults and children. Thyroid sonography is useful in demonstrating enlarged or absent glands.

1. 9 Treatment

The main objective of early substitutive therapy is to prevent mental retardation. Every effort should be made to initiate therapy within the first days of life. Early diagnosis and treatment are highly effective, limits the duration of hypothyroidism, and it will decreases it's postnatal impact on cerebral development [5, 53].

Treatment for CH is available which are relatively simple, cheap, and extremely efficient, and the benefit-cost ratio of screening for CH is very elevated. L-thyroxine is the treatment of choice [12, 54].

The goals of treatment are to raise the serum T4 into the normal range as rapidly as possible, so as to minimize exposure of the neonatal brain to further hypothyroidism.

The duration of neonatal hypothyroidism that occur between delivery and the achievement of euthyroidism with therapy depends on both the ages at starting treatment and the initial dose of L-T4 [6, 8]. It is important to select the proper starting dose of Levothyroxine, which should be adjusted according to the weight of the neonate.

The adequate L-thyroxine dosage for the initial treatment of infants with CH is a subject of controversy. In the United States, higher doses (10-15µg/kg, per day) have used to treat CH than in Europe, and has been associated with a shorter time to achieve euthyroidism and an improvement in intelligence quotient (IQ) when tested at the age of 7 years [2, 6, 55]. The response of CH infants to the same dose of T4 is extremely variable, and careful biochemical and clinical monitoring is required during the initial phase of therapy.

It is recommended when adding treatment to maintain the serum T4 concentrations in the upper limit of normal serum values [9, 14, 48]. The American Academy of Pediatrics recommended to monitor frequently serum T4 or free T4 and TSH during the first

three years of life to ensure optimal therapy and after a change in a dose and any time there is a concern about treatment compliance [12].

Early TSH normalization should be the aim. Several publications have reported that, a raised plasma TSH is relatively common in children receiving treatment thyroxine for CH, particularly in early infancy, regardless the severity of hypothyroidism [56-59]. Plasma thyroxine must be maintained in the upper normal range to suppress TSH. Children with more severe hypothyroidism needed higher doses of thyroxine to keep TSH within the normal range [57].

At an early age, an optimal amount of thyroid hormones to the brain is the most important therapeutic aim. It is equally important to avoid overtreatment, which may result in some disturbances in children with CH [12, 14, 60].

1. 9 Prevention

Mental retardation in CH is prevented only when the diagnosis is made very early, ideally during the first days of life, with the help of fast and efficient screening.

1. 10 Outcomes of screening

Early diagnosis of CH in young infant depending on the clinical signs and symptoms is not easy because of the rarity and the lack of specificity of these clinical signs and symptoms within the first weeks of life [10, 11, 43]. So that only 5% are diagnosed by physical examination after birth [13, 14, 51].

Prior the advent of screening, diagnosis was usually delayed in the majority of infants resulted in poor neurodevelopmental outlook. Early treatment (before 3 months old) led to normal intelligence quotient (IQ) values in 85% of the neonates, where as delayed treatment was associated with subnormal IQ in more than 80% of the affected neonates [48].

With the advent of screening program based on filter paper methodology, the frequency of reported CH increased, and thyroid hormone replacement and normal mental development in most children has been achieved. Consequently, congenital hypothyroidism as a major cause of mental retardation has much reduced.

There is an inverse relationship between the age at which treatment is started and the intellectual quotation outcome of children [2, 8, 14, 44, 51]. Early treatment with L-thyroxine has probably reduced but failed to fully eliminate neurological impairment or damage [8, 58-61].

Several risk factors for the eventual mental outcome development in early treated CH, despite systematic neonatal screening were reported in many studies. These include; 1- pretreatment serum T4 concentration, 2- neonatal skeletal maturation, 3- aetiology of CH, 4- age at which treatment is started, 5- starting dose of L-T4, 6- adequacy of substitution treatment in the

first 2 years of life and even afterwards, and 7- socio-economic class of the family [2, 6, 7, 60, 61].

Aims of the study

Newborn screening for PKU was introduced in the West Bank of Palestine, since 1989, and was followed by CH in 1990. Until recently, no large-scale study neither on CH incidence nor its impact among the entire population. This was mainly due to several factors generated from the prevailing political situation of the area. Moreover, the only study in this respect was a preliminary report by Prof. Dr. Joseph Sack, in which a relatively high incidence was reported in the region. As a member of the working staff at the central laboratory, I was encouraged to look further to the problem aiming to:

1. Determining the incidence of congenital hypothyroidism, through the newborn screening program in the West Bank.
2. Conducting an appropriate follow-up and management for affected newborn with congenital hypothyroidism.
3. Assessing the extent and severity of CH in the West Bank, through measurements of n-TSH in the capillary and sera blood samples.
4. Determining the distribution of CH (permanent and transitory) in the West Bank in the different districts.
5. Searching for associated risk factors in connection with congenital hypothyroidism.

A long term purpose:

Try to delineate our future national policy on neonatal screening for congenital hypothyroidism.

Chapter II

MATERIALS and METHODS

Methodology

2. 1 Newborn screening program in the West Bank

In the (284) maternal and child health centers located in nine different regional centers throughout West Bank, and whenever possible, a heel prick blood samples collected, on dry filter papers, from each newborn infants on the 4-7 days postpartum. For those who released within the first day or borne at home, blood samples usually collected during their first visit to the maternal and child health centers, as they are usually referred for BCG vaccine during the 1st week. Blood samples were obtained in collaboration with the ongoing PKU screening program. The collected samples were then sent to regional clinics, which then arranged the transfer to a centrally located public health laboratory in the city of Ramallah as shown in figure 3.

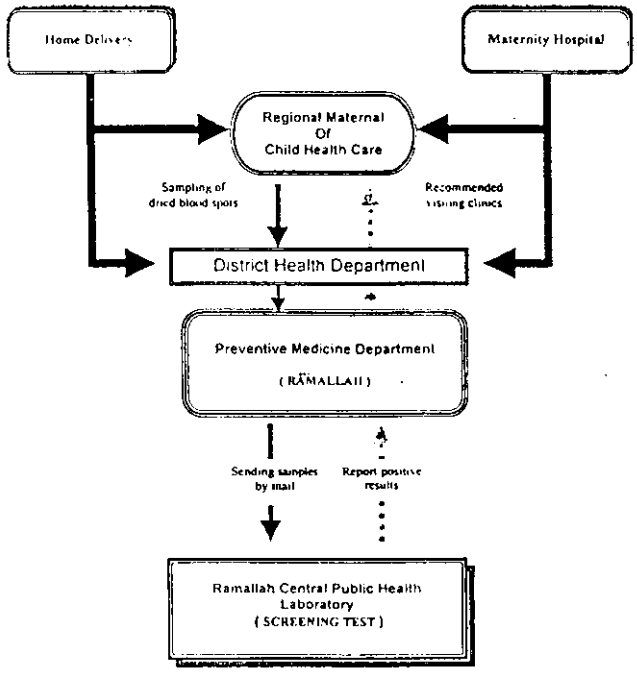


Figure (3). The adopted system for newborn screening in the West Bank

2. 2 Screened population

A total of 69,957 newborns were screened for CH during October 1998 through May 2000. Thyroid stimulating hormone (TSH) was determined quantitatively on specific filter paper by immunoradiometric assay (IRMA) using diagnostic product corporation (DPC) neonatal-TSH (Los Angeles, USA). The cutoff point used as criteria for recalling the infants under suspicion of CH is 40 μIU/ml of whole blood according to the manufacturer instructions.

When TSH concentrations were > 40 μIU/ml, the same samples were re-tested again in the following day and were considered as suspected of having CH. Samples with readings of 40 or more μIU/ml were then reported to the Preventive Medicine Department who in turn reported them to the maternal care centers where a second sample is usually obtained for a second test. For those with persistent readings above 40 μIU/ml, further confirmatory test is conducted through arrangements with the health care centers.

TSH levels ranging between 20 and 40 μIU/ml were considered at risk for CH, as recommended by the American Academy of Pediatrics, and were re-tested. Those with persistent levels above 40 μIU/ml were considered as suspected cases of having CH as shown in figure 4.

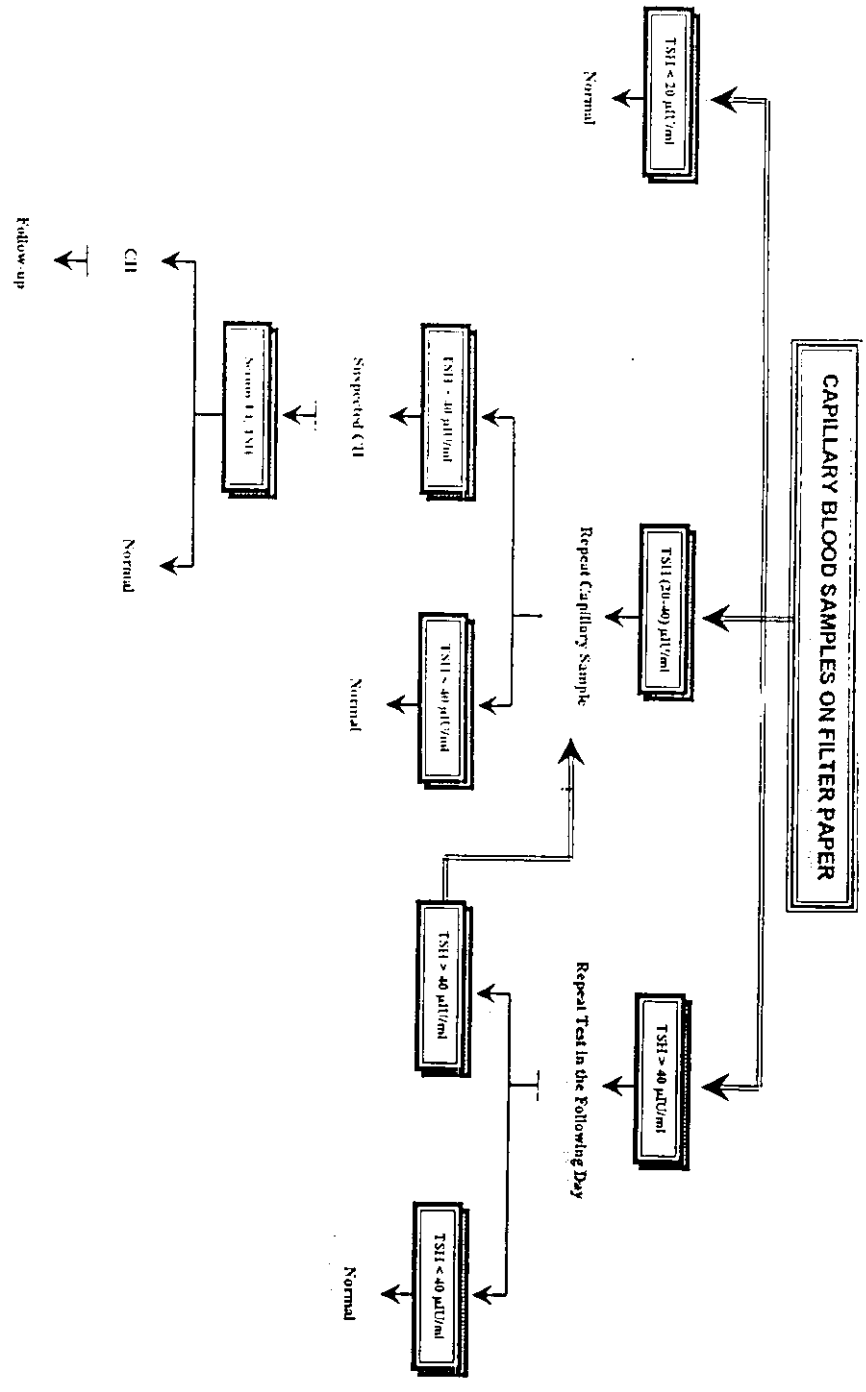


Figure (4). Flow chart for neonatal screening tests for the detection of CH in the West Bank.

2. 3 Neonatal TSH procedure (IRMA Assay)

IRMA is a two-site immunoradiometric assay utilizes a solid phase coupled monoclonal antibody and a second radiolabeled polyclonal antibody phase.

Blood sample spots were incubated simultaneously with the radiolabeled antibody in solution. During this incubation, TSH-antigen binds to the immobilized antibody while, at the same time, the radiolabeled antibody reacts with the same antigen complex. The tube was then decanted and washed, and the radioactivity of the labeled antibody bound to the antigen on the solid phase is measured (as a count per minute, CPM) using gamma counter. Calibrators of known TSH concentration were run concurrently with the samples being assayed and a standard curve is constructed. TSH concentration was then calculated using the standard curve.

2. 4 Neonatal T4 procedure

Is a solid-phase radioimmunoassay where ^{125}I –labeled T4 competes for a fixed time with T4 in the patient sample (the native antigen) for sites on T4-specific antibody immobilized to the wall of a polypropylene tube. After the completion of the required incubation period, the tube is aspirated or decanted. The activity of the radiolabel present in the precipitate is then counted for one minute in a gamma counter. The radioactivity in the antibody-bound fraction is inversely proportional to the native antigen concentration. The amount of T4 in the patient sample is then determined by comparing the counts to a standard curve.

2. 5 Evaluation of the newborn screening program

Evaluation of the screening program was one of the aims of this study. To achieve this aim, information regarding age at the time of specimen collection, age at the time of Guthrie test performance and the place of residence were collected, 960 randomly chosen infants from all districts, from the records of the central laboratory.

The coverage rate was calculated based upon the numbers of live births by each region during the period of study (Ministry of Interior, Department of Civil Affairs) and compared with the numbers of screened newborns.

2. 6 The incidence of permanent CH (PCH) in the West Bank

The incidence of CH was determined by dividing the numbers of suspected affected cases by the total number of the screened cards during the period of the study.

2. 7 Study cases

All infants with elevated filter paper-TSH (FP-TSH) (> 40 μIU/ml) at birth and with elevated confirmatory testing were recalled as suspected permanent CH cases. The initial number of cases was 32, of which only 28 were welling to participate in this study. Demographic data and details of clinical state, diagnostic investigations, treatment, pregnancy, neonatal history, and family back ground were collected in a specially designed questionnaire. Forty-eight infants, born in the same area, matching approximately the birth date intervals with patients, were selected as a control group.

Data were collected from subjects with parents permission and after the approval by the Ministry of Health / Primary Health Care.

2. 8 Transitory hypothyroidism

Demographic and clinical data concerning all transitory hypothyroidism cases were obtained either retrospectively or prospectively. Confirmatory FP-TSH measurement and T4 tests were performed blindly in an independent laboratory.

All the governmental hospitals in the West Bank were visited and the concerned persons were interviewed regarding the routine use of iodine-containing antiseptics in obstetrics and neonatology.

2. 9 Statistical analysis

Collected data were analyzed using SPSS (Statistical Package for Social Sciences). Data analysis procedures included both descriptive and inferential statistics.

Chapter III

RESULTS

3. 1 Newborn screening program for CH in the West Bank

3. 1. 1 Coverage rate

Data presented in Table 4 shows the coverage rate of newborn infants screened among the various districts of the West Bank – Palestine (from October 1998 to May 2000). The coverage rates ranged between 58.8% to 94.4%. The following percentages 85.8, 78.4, 74.9, 75.9, 82.1, 58.8, 72.2 and 94.4 were observed in Jenin, (Tulkarm and Salfeet), Qalqilia, Nablus, Ramallah, Jericho, Bethlehem and Hebron, respectively. During the period of the study, a total of 85,149 live infants were born of which 69957 were screened. The overall screening coverage rate was 82.15 %.

Table 4. Coverage rate of newborn infants screened among districts during the period of study

District	From October 1998 – May 2000		
	No. of live births	No. of infants screened	% of coverage
Jenin	13274	11399	85.8
Tulkarm and Salfeet	10217	8015	78.4
Qalqilia	3944	2954	74.9
Nablus	14546	11049	75.9
Ramallah	12616	10364	82.1
Jericho	2078	1223	58.8
Bethlehem	8675	6264	72.2
Hebron	19799	18689	94.4
Total	**85149**	**69957**	**82.15**

A network of approximately (284) primary health care centers located throughout the various districts and provides several services including collection of blood samples for Guthrie test. The distribution of these centers is shown in table 5. A positive correlation between the coverage rates and the number of heath care centers was observed. This correlation is statically significant (*P=0.012, r=0.714*) with the exclusion of Jericho district as shown in table 5.

Table 5. Screening coverage rate of live births in correlation with the number primary health care centers

Districts	Primary health care centers	Primary health care centers/ births	% of coverage
Jenin	44	1:301.7	85.8
Tulkarm and Salfeet	35	1:464.4	78.4
Qalqilia	13	1:303.4	74.9
Nablus	31	1:469.2	75.9
Ramallah	35	1:360.4	82.1
Jericho	12	1:173.1	58.8
Bethlehem	15	1:578.3	72.2
Hebron	99	1:199.9	94.4
Total	**284**	**1:299.8**	**82.15**

3. 1. 2 Recall rate

Table 6 represents the recall rate in various districts. All infants (545) with capillary blood TSH level > 20 µIU/ml were recalled for retesting. The overall recall rate was 0.78 %. Capillary blood TSH levels ranged between 20- 40 µIU/ml were represented by 346 (63.6%) of the recalled infants while of the rest of the recalled infants 198 (36.4 %) were with TSH levels > 40 µIU/ml.

Slight variations in the recall rates were observed between the various districts (0.45 – 0.76), however, Jenin district showed the highest recall rate (2.03).

Table 6. The recall rate for infants in the various districts during the study period

District	20 – 40	> 40	> 20	Recall rate
Jenin	163	69	232	2.03
Tulkarm	17	8	25	0.45
Qalqilia	8	8	16	0.54
Nablus	34	26	60	0.54
Salfeet	9	10	19	0.76
Ramallah	32	15	47	0.45
Jericho	4	3	7	0.57
Bethlehem	29	17	46	0.73
Hebron	50	42	92	0.49
Total	**346**	**198**	**544**	**0.78**

3. 1. 3 Sample collection and testing

Data presented in table 7 shows that the mean age of infants at filter-paper blood samples, in the adopted screening program in the West Bank, were 13.04 days. On the other hand, the mean age at which the test done was 54.19 days. The percentages of 0.0%, 0.52%, 11.8% and 87.6% represent the performance of Guthrie test at age groups (1-7, 8-15, 16-30, >30 days), respectively. This reflects an elapsed interval between collecting samples and the screening tests. About 11% of FP-blood samples were obtained on the age of more than one month. It also shows that the majority of the performed tests were carried out at a very late state.

Variations in the time of specimen collection and the newborn-screening test performance were observed between the studied regions (ranged from 9.52, 40.00 days in Jenin to 19.35, 68.00 days in Hebron, respectively). There was no statistically significant

correlation between age at specimen collection and the number of primary health care centers among regions.

Table 7. Age of infants (days) at specimen collection and performance of Guthrie test

District	(n)	Age of infants at specimen collection		Age group percentage of infants at Guthrie test done			
		Mean	(Range.)	1-7	8-15	16-30	> than 30
Jenin	125	9.52	(1.0 - 60.00)	-	1	26	98
Tulkarm	100	10.01	(2.0 - 39.00)	-	-	18	82
Qalqilia	90	10.31	(2.0 - 74.00)	-	-	9	81
Nablus	99	14.44	(2.0 - 65.00)	-	-	18	81
Salfeet	82	12.87	(2.0 - 40.00)	-	-	6	76
Ramallah	104	15.95	(2.0 - 80.00)	-	-	3	101
Jericho	115	12.31	(2.0 - 39.00)	-	1	17	97
Bethlehem	103	10.61	(1.0 - 128.0)	-	3	9	91
Hebron	142	19.35	(1.0 - 124.0)	-	-	8	134
Total	**960**	**13.04**	**(1.00 - 128.0)**	-	**5 (0.52%)**	**114 (11.8%)**	**841 (87.6%)**

The mean age at the time of blood specimen collected was relatively better in camps than in urban and rural areas. Analysis of variance test (ANOVA) indicate that residency has no effect on the time at which specimen collected, which indicate that there are other local specific factors that could play a role in the delay.

Table 8. Mean age (in days) among infants at specimen collection according to place of residence

Residency	(n)	Mean	Median
Urban	335	12.17	8.00
Rural	603	13.67	8.00
Camp	22	8.90	7.00
Total	**960**	**13.04**	**8.00**

3. 2 Incidence of CH in West Bank

The screening disclosed (198) newborns that were initially diagnosed as having CH. However, only 32 cases were confirmed to be as suspected permanent CH cases. Based on the numbers of live births screened during the period of the study, the overall incidence rate of suspected permanent CH among the tested population in the West Bank was 1: 2186.15 (32: 69957) as shown in table 9. The highest incidence rate was observed in Salfeet district followed by Jenin and Qalqilia, while relatively low incidence was observed in Tulkarem and Ramallah districts. Fifty percent of the cases came from the districts of Jenin and Hebron (28.1% and 21.9, respectively).

All of the cases were with elevated filter paper TSH values > 40 μIU/ml on follow-up.

Table 9 the incidence rate of PCH among the different districts in the West Bank (October 1998 to May 2000)

District	No. of infants screened	No. of suspected neonates with PCH	Incidence	Percentage
Jenin	11399	9	1:1266.55	28.1
Tulkarm	5521	0	-	-
Qalqilia	2954	2	1:1477.00	6.3
Nablus	11049	5	1:2209.80	15.6
Salfeet	2494	3	1:831.33	9.4
Ramallah	10364	3	1:3454.66	9.4
Jericho	1223	0	-	-
Bethlehem	6264	3	1:2088.00	9.4
Hebron	18689	7	1:2669.85	21.9
Total	**69957**	**32**	**1:2186.15**	**100**

3. 3 Follow up of suspected permanent CH cases

Small percentage of the suspected cases was excluded (4 out of 32) and this was due to the fact that some were lost on follow-up or refused to participate.

3. 3. 1 Demographic characteristics of CH cases

Data presented in table 10 shows that 82.1% of studied cases were living in rural regions, while the rest of cases 17.9% were living in urban areas.

Table 10. Number of suspected PCH cases according to place of residence

Place of Living	Frequency	Percentage
Urban	5	17.9
Rural	23	82.1
Total	**28**	**100**

Data presented in table 11 shows that (18) 66.6% of the study cases were infants of consanguineous mating, (12) 44.4% of which had been resulted from first cousins. Test of consanguinity, for the effect of consanguinity on PCH, indicates a statistically significant correlation $P = 0.0233$ (data not shown).

Table 11. Association between consanguinity and the occurrence of CH among the study and control cases

Degree of consanguinity	Percentages for parents of CH infants (n = 27)*	Percentages for Controls (n = 4295)†
First Cousins	(12) 44.4	26.4
Other relatives	(6) 22.2	19.4
None	(9) 33.3	54.2
Total	**(27) 100**	**100**

* 1 missing case

† Source: Palestinian Central Bureau of Statistics. The demographic survey in the West Bank, 2000, table 22; page 88.

3. 3. 2 Laboratory findings of CH cases

Table 12 summarizes the thyroidal functional abnormalities observed among PCH suspected infants. The mean filter paper TSH value was 359.24 μIU/ml (range 31 to 898.0 μIU/ml). More than two third of cases showed a marked elevation on both FP-TSH (≥ 200μIU/ml) and confirmatory serum test (≥ 100 μIU/ml).

Subject 17, had initially capillary blood TSH value within the intermediate zone (31 μIU/ml). However, the recall value showed a marked increase in TSH level (204 μIU/ml). His serum TSH and T4 values were with abnormal ranges during the first few weeks of life.

Of the hypothyroid infants, the ratio of females to males was 16:16 (1:1).

Table 12 Initial and follow-up thyroid function of infants with CH

Subject	Sex	Newborn Screening -Filter Paper † TSH (< 40 µIU/ml)	Confirmatory Serum TSH (0.47 – 5.01 µIU/ml)	Total-T4 (4.50–12.00 µg/dl)	Free-T4 (0.7- 2.0 µg/dl)	Age at treatment started (days)
1	M	403.5	100.00	.00	-	84
2	M	240.0	More than 100	-	.540	82
3	M	-	More than 100	-	.200	395
4	F	538.4	More than 100	-	.460	103
5	F	62.5	34	3.2	-	88
6	F	898.0	More than 100	-	.330	261
7	F	231.3	More than 100	.90	-	77
8	F	200.0	More than 100	-	.600	334
9	F	44.8	20.00	-	.560	79
10	M	314.2	More than 100	2.30	-	125
11	F	860.0	More than 100	1.00	-	200
12	F	880.0	More than 100	.90	-	176
13	F	180.0	More than 100	-	.400	130
14	F	650.0	More than 100	.50	-	425
15	M	45.9	15.00	-	.600	107
16	F	395.0	190.00	-	.400	47
17	M	31.0	300.00	-	.400	-
18	M	44.3	22.40	-	.600	216
19	M	320.0	More than 100	-	-	146
20	M	323.0	130.00	-	.008	58
21	F	548.0	More than 100	-	.560	167
22	M	539.0	More than 100	-	.400	87
23	F	420.0	More than 100	-	.450	136
24	M	460.9	More than 150	-	.300	179
25	M	373.9	More than 150	-	.070	97
26	M	78.5	50.00	-	.600	185
27	F	373.5	More than 100	1.11	-	52
28	M	295.0	418.00	-	.330	74
29	F	535.0	More than 150	-	.100	68
30	M	107	65	-	.400	-
31	F	692.5	100	-	-	-
32	M	46.2	49.3	-	-	-

* F:M ratio = 1:1 (16:16)

† Median = 323.00 µIU/ml Min. value = 31 µIU/ml Max. value = 898.0 µIU/ml

Mean value = 359.24 µIU/ml Standard deviation = 253.178

3. 3. 3 Clinical findings of CH

Table 13 lists the clinical findings noted by mothers at cases first examination. Prolonged jaundice, inactivity, constipation, sleepiness, and edema were the most striking features could be noted by mothers as well as by physician. Three (10.7%) out of 28 neonates diagnosed by screening did not revealed any clinical signs suggestive of hypothyroidism.

There was statistically significant correlation between the number of symptoms per each case and both Guthrie TSH value (direct correlation with P value = 0.042, r = 0.247), and serum free-T4 (inverse correlation with P value = 0.02, r = -0.372), indicating that such symptoms were directly related to intensity of the hormonal deficiency. Significant direct correlation was also observed between the number of symptoms with the age when diagnosis done (P value = 0.048, r = 0.327).

Table 13 Clinical features of CH first noted by mothers among the 27* study cases

Signs and Symptoms	Frequency	Percentage
Inactivity	17	63.0
Prolonged Jaundice	17	63.0
Sleepiness	16	59.3
Decrease Crying	12	44.4
Edema	16	59.3
Enlarged Tongue	13	48.1
Feeding Difficulty	11	40.7
Hoarse Cry	6	22.2
Constipation	17	63.0
Mottled Skin	11	40.7
Umbilical Hernia	6	22.2
Abdominal Distention	10	37.0

* 1 missing case

Data presented in table 14 represent the mean number of symptoms per case. Analysis of variance (ANOVA) test indicate a significant *P* value (*P*= 0.000) between the difference means of both study and control cases.

Table 14. The overall mean number of symptoms appeared post-nataly per infant for the study and control cases

	Cases (n = 28)	Controls (n = 48)
Mean number of symptoms per infant	4.84	0.757

3. 3. 4 Growth and development

To evaluate physical development of the cases, growth percentile charts (WHO) were used. The study included 23 subjects out of a total of 32 suspected cases. Out of this group, 11 subjects (47.82%) were with retarded growth (under weight, short stature or both). Data presented in table 15 showed that 5 (21.7%) of the study cases were with short stature, 2 (8.69%) were underweight and 4 (17.39%) were with under weight and height at time of evaluation. All 11 cases seem to suffer from delayed speech and 5 cases were reported to have teeth deformation and or delayed walk (data not shown).

Table 15. Physical problems among suspected PCH cases based upon WHO criteria

Physical Problem	Number	Percentage
Under weight	2	8.69
Short stature	5	21.7
Combination (under weight and short stature)	4	17.39

Tables 16 a-c shows the physical criteria among treated PCH subjects. The data clearly shows that these cases were within the acceptable range with respect to both height and weight percentiles

especially for those who had early treatment. It is worth noting that the majority of the previously mentioned subjects (11), with growth retardation, were among those who started late treatment (3 months or more). In addition most of them have TSH levels above 200 μIU/ml as shown in table 16c.

Statistically significant indirect correlation was observed between age at which treatment started with height (P= 0.021, r= - 0.426) and with weight (P= 0.034, r= - 0.386) percentiles. No statistically significant correlation observed with respect to Guthrie-TSH values.

Table 16 a. Association between age at treatment and height percentiles

Height percentiles	Age at treatment started				Total
	< 1 month	(1 – 3) month	(> 3 – 12) month	> 12 month	
≤ 3rd percentile	-	1	6	2	9
> 3rd – 10th percentile	-	1	3	-	4
> 10th – 25th percentile	-	2	1	-	3
> 25 – 50th percentile	-	2	2	-	4
> 50th percentile	-	2	1	-	3
Total	**-**	**8**	**13**	**2**	**23**

Table 16 b. Association between age at treatment and weight percentiles

Weight percentiles	Age at treatment started				Total
	< 1 month	(1 – 3) month	(> 3 – 12) month	> 12 month	
≤ 3rd percentile	-	0	6	-	6
> 3rd – 10th percentile	-	1	2	2	5
> 10th – 25th percentile	-	4	3	-	7
> 25 – 50th percentile	-	3	1	-	4
> 50th percentile	-	-	1	-	1
Total	**-**	**8**	**13**	**2**	**23**

Table 16 c. Association between age at treatment, TSH values and growth criteria weight and height.

Cases	Guthrie-TSH value	Age at treatment started
3	*	395
4	538.4	103
6	898	261
8	200	334
10	314.2	130
12	880	176
14	650	425
21	548	167
22	539	87
24	460.9	179
25	373.9	97

* Was not done at that time

Data presented in table 17 shows that 53.6 % of PCH cases (28) came from families with previous history of thyroid problems. The mean birth weight for this group was 3.511Kg. This value is slightly higher than that of the controls. All were delivered from normal full term pregnancies. The mean gestation time was 40.21 (ranged from 38 to 42 weeks) without any reported perinatal problems. Gestational age was similar to that of the controls. None of the cases were reported to have any congenital anomalies other than hypothyroidism.

None of the mothers was reported to be on propylthiouracil or iodine medication during pregnancy.

Table 17. Clinical and historical findings among study cases

History	CH infants (n = 28)	Controls (n = 48)
% with family history of thyroid problems	53.6	0
Mean of Gestational length / week	40.21	38.94
Mean of Birth weight /gr.	3511.1	3277.7 *

* Data adopted from Palestinian Central Bureau of Statistics. The demographic survey in the West Bank, 1998. The number of controls was 2350 infants.

3. 3. 5 Health services for CH cases

3. 3. 5. 1 Identification of cases

Out of the 28 suspected infants with permanent CH, (24) 85.7% were identified through the screening program and the rest (4) 14.3% cases were clinically identified. The majority of the cases (≈ 92.8%) were first identified at age above one-month (with a mean time 89.22 days), as shown in table 18.

Table 18. Age in months at first identification of the study cases (n=28)

Method of Detection	Age at which Cases First Identified				Total
	< 1	1-3	> 3 –12	> 12	
Routine screening	1(3.5%)	17(60.7%)	6(21.4)	-	24(85.7%)
Clinical identification	1(3.5%)	1(3.5%)	1(3.5%)	1(3.5%)	4 (14.3%)
Total	2(7.0%)	18(64.2%)	7(24.9%)	1(3.5%)	28(100%)

3. 3. 5. 2 Diagnosis and treatment

Data presented in table 19 shows that all PCH cases were diagnosed after 1 month (with a mean time of 143.18 days). This clearly indicates an elapsed interval between the screening test and the diagnostic investigations. The infants' average age at the starting date of treatment was 152.22 days. In all infants treatment was delayed until after the fourth week of age. Delayed treatment beyond 3 months of age was observed among (62.9 %) of the cases. Thyroid scan was not performed on any of the study cases, thus no classification of cases was done.

Table 19. Age of subject at the time of diagnosis and treatment

Age of subject started taking L-T4 (month)	Age of subject diagnosed (month)				Total
	< 1	1-3	> 3 –12	> 12	
< 1	-	-	-	-	-
1-3	-	9 (33.3%)	1 (3.7%)	-	10 (37.0%)
>3 –12	-	-	15 (55.5%)	-	15 (55.5%)
> 12	-	-	1 (3.7%)	1(3.7%)	2 (7.4%)
Total	-	9 (33.3%)	17 (62.9%)	1(3.7%)	27* (100%)

* 1 missing case

3. 4 Suspected cases of transitory hypothyroidism

In addition to the suspected permanent cases with CH (32), another 167 cases with capillary neonatal TSH value above 40 μIU/ml were detected. First repeat examination of these additional cases was performed at an age range between 30 and 90 days and this was mainly due to recall difficulties. At recall, all 167 cases showed normal capillary TSH levels, thus, the observed elevated TSH levels (hyperthyrotropinemia) were transient. Duration of hypothyroidism among this group is undetermined, however, it seems to be short based on the results of the second sampling. None of the cases among this group reveal any of the symptoms or signs of hypothyroidism as recalled by their physicians.

3. 4. 1 Incidence of transitory hypothyroidism

Data presented in table 20 shows the incidence rates of transitory hypothyroidism in the various districts. The overall incidence of was 1:418.9 births with a percentage of approximately (0.24%). Incidence rates seems to show a marked variation between the various districts and highest was found in the district of Jenin (around 1:190).

When comparing the incidence rate of transitory hypothyroidism among regions with the recall rate (table 6), a statistically significant correlation ($P = 0.001$) was observed.

Table 20. Incidence rate of transitory hypothyroidism among the different districts

Districts	No. of suspected transitory cases	Incidence	Percentage
Jenin	60	1:189.98	35.9
Tulkarm	8	1:690.12	4.8
Qalqilia	6	1:415.66	3.6
Nablus	22	1:502.22	13.2
Salfeet	7	1:356.28	4.2
Ramallah	12	1:863.66	7.2
Jericho	3	1:407.66	1.8
Bethlehem	14	1:447.42	8.4
Hebron	35	1:533.97	21.0
Total	**167**	**1:418.90**	**100**

3. 4. 2. Demographic characteristics of transitory hypothyroidism cases

Data presented in table 21 shows the association between transitory hypothyroidism and place of living. As in the suspected permanent CH, the majority of transitory cases (79.0%) were found among those living in rural areas.

Table 21. Association between transitory hypothyroidism and the place of residence

Place of Residence	Frequency	Percentage
Urban	32	19.2
Rural	132	79.0
Camp	3	1.8
Total	**167**	**100**

3. 4. 3 Laboratory findings among transitory hypothyroidism cases

Data presented in table 22-a shows the laboratory biochemical results among transitory hypothyroidism cases. The overall mean TSH value was 75.67μIU/ml, while the overall mean T4 value was 7.29μg/dl. The cases were split between either high TSH with T4 value below normal range (65.5%) indicating transient hypothyroidism and high TSH value with sub-normal T4 value of (34.5%) indicating transient hyperthyrotropinemia. A severe state was observed, table 22-b, among eight cases (4.8%) as indicated from their high TSH (range 80.3 - 616.8 μIU/ml) and low total T4 (range 0.0 - 3.2 μg/dl) profiles.

There was a statistically significant correlation between age at specimen collection and both capillary screening TSH and total T4 values ($P = 0.000$ and $P = 0.008$ respectively).

Table 22 a. Results of newborn screening for suspected transitory hypothyroidism according to regions

Districts	(n)	TSH (< 40 μIU/ml) Mean	(Range) *	Total-T4 (> 8 μg/dl) † Mean	(Range)
Jenin	60	72.97	(40.0 - 430.0)	7.48	(0.0-12.6)
Tulkarm	8	61.75	(40.6 - 98.00)	6.66	(3.2-10.9)
Qalqilia	6	71.78	(44.0 - 91.70)	8.96	(7.2-12.3)
Nablus	22	83.19	(40.4 - 430.0)	6.45	(1.5-9.0)
Salfeet	7	66.47	(40.5 - 121.8)	-	-
Ramallah	12	71.10	(42.0 - 121.0)	-	-
Jericho	3	54.70	(44.2 - 66.90)	10.5	(10.5)
Bethlehem	14	68.55	(45.6 - 164.7)	-	-
Hebron	35	87.48	(40.0 - 616.8)	6.87	(1.7-13.0)
Total	**167**	**75.67**	**(40.0 - 616.8)**	**7.29**	**(0.0-13.0)**

† Only 111 samples were analyzed for the total T4 test

- Test was not performed

Table 22 b. Guthrie-TSH and T4 results for the severe suspected transitory hypothyroidism cases

Case	Time of specimen collected (days)	TSH (μIU/ml)	T4 (μg/dl)
1	16	430	0.0
2	10	209.5	3.1
3	12	160	3.2
4	20	111.1	5.0
5	22	616.8	2.0
6	16	87.2	3.0
7	41	165	1.5
8	24	430	1.5

3. 4. 4 Further evidence on transitory hypothyroidism

Transitory hypothyroidism further confirmed using the calculated frequency of neonatal TSH > 5 μIU/ml. Table 23 represents the calculated TSH values among newborn in the various districts. In comparison with data on the incidence of transitory hypothyroidism presented in table 20, data presented in table 23 shows a statistically significant correlation (*P value* = 0.024) between the two sets of results (transitory and TSH > 5 μIU/ml). This is clear from the findings among the cases in all studied districts. Jenin district has the highest frequency of TSH values above 5 μIU/ml as was the case for transitory hypothyroidism in table 20. Findings on recall rates presented in table 6 also provide evidence in support of this association (*P* = 0.000).

able 23. Frequency of neonatal with TSH values > 5 μIU/ml in whole blood according to districts

District	(n)	Frequency of TSH > 5 μIU/ml whole blood (%)
Jenin	11,399	24.12
Tulkarm	5,521	11.84
Qalqilia	2,954	14.10
Nablus	11,049	15.68
Salfeet	2,494	15.03
Ramallah	10,364	12.67
Jericho	1,223	14.50
Bethlehem	6,264	15.11
Hebron	18,689	11.62
Total	**69,957**	**14.96**

Chapter IV
DISCUSSION

Discussion

Screening program

The current study represents a base line data on the status of CH among Palestinian newborn of the West Bank. Newborn screening program has been conducted since 1990, in the whole districts of the West Bank, to facilitate detection of children with CH. The strategy employed in our country has been illustrated in figure (3). In the West Bank, it is estimated that about 50 thousand infants are born each year and although the screening for CH ongoing with PKU in Palestine is mandatory and free of cost, the coverage rate was and still relatively at low levels (see table 1and 5). Out of an estimated 85,149 infants born in the West Bank during the study period (from October 1998 to May 2000), only 69,957 infants were screened. Thus, representing a coverage rate of about 82.15% (see table 4). The coverage rates of 98 - 99% or above was reported for live births in developed countries [17, 62, 63]. A possible explanation for the observed low coverage could be due to the followings: prevailing political situation; home - deliveries; inadequate primary health care centers and poor awareness on the importance of screening program. With the exclusion of Jericho, as a local specific problem, statistically significant correlation (P= 0.012) was found between the availability of health care centers and the coverage rate among the various districts as shown in table 5. A good number (10%) of infants are still delivered at home, by midwives, and this would definitely reflected on the coverage rate. One thus can conclude that with increasing the number of primary health care centers and dissemination of information on the benefits of the screening program are most likely to improve the coverage rate.

Although, it is highly desirable by the American Academy of Pediatrics, that filter paper heel blood to be taken between 2 and 6 days of age [12], none of the screened newborns in our study was sampled at that time. The estimated mean time of 13.04 days, after birth, was observed in our study (see table 7). A clear delay in blood sample collection is evident from the findings of 11.1% of the samples were collected at the age of one month. Data presented in table 8 revealed that place of residence has a slight effect on the time of specimen collection as no significant differences were observed among the inhabitance of urban, rural and camp population. Delay in specimen collection could be attributed to home deliveries; poor health education and awareness of both the public and health care providers regarding the importance of early specimen collection for effective screening and others such low quality of collection and handling of specimens. An evidence which support above assumptions is that Ramallah district still shows a delay in the sampling time even though the central public health laboratory is located in it's vicinity, see table 7.

Our findings in this respect show an estimated high percentage (87.6%) of infants screened by the age of ≥ 1 month. The mean time of age at screening was 54.19 days. The elapsed interval between sample collection and screening tests could be mainly due to mailing time and availability of test kits and both factors are influenced by the prevailing political situation.

The findings of an overall recall rate of 0.78 %, based on a cut-off point of TSH (> 20 μIU/ml), is higher than the usual estimation with the primary TSH approach (< 0.1%) [12, 13, 37]. Our recall rate (0.28%) of neonates based on a cut-off point of a capillary TSH of 40 μIU/ml was similar to that reported by Delange [37]. A much

higher recall rate of (2.3%) was reported by Yordan *et al.*, [64]. Iodine deficiency was reported as a major factor contributing to such high recall rate [37].

Suspected permanent CH cases

The screening disclosed 198 newborns that were initially diagnosed as having CH however, 32 of them were suspected to have permanent CH. In our study, the incidence was estimated by identifying all living positive cases that were confirmed by serum test during the period from October 1998 to May 2000. The overall incidence rate of 1:2186.15 was found (see table 9). This finding is comparable to that reported among the infants of Najran province in Saudi Arabia and Oman and among infants of Northern Israel [19, 21, 65]. It is also in good accordance with the preliminary reported incidence, in our area, by Sack *et al.*, [66]. However, the observed overall incidence is higher than that reported from industrialized countries including Israel [16, 62].

In general, around 85% of CH cases were sporadic due to thyroid dysgenisis and only 10-15% of cases was reported to result from thyroid hormone dyshormonogenisis [11, 14, 27]. Our study revealed that parental consanguineous marriages are fairly high (66.6%), and might account for the observed increased incidence of CH among the Palestinian population. A positive correlation (P=0.0233) was observed between consanguineous marriages, first cousins, and CH in comparison with affected cases among total unrelated population (see table 11). In addition, the finding of a high incidence of autosomal recessive inherited disease (PKU) in the West Bank [45] is further evidence in support of our previous assumption regarding CH incidence and consanguinity. Therefore, dys-hormonogenisis, a recessively transmitted autosomal trait, could

contribute to this high incidence in our area. They result from inheritable enzymatic deficiencies in the secretion and synthesis of thyroid hormones [11, 14, 27]. Furthermore, 53.6% of our subjects came from families with a previous history of thyroid disorders, as shown in table 17, thus confirming a hereditary role. The findings of J. Sack *et al.*, [62] on dyshormonogenisis among Arab population in Israel, in association with a high rate of consanguinity, is another supporting evidence in this respect. A high incidence CH in association with dyshormonogenisis was also reported among Asian population [17, 64].

Although, hereditary seems to play a role in occurrence of CH, other factors can not be ruled out such as environmental factors. Iodine is essential for the normal development of the fetus to prevent CH. There is also a close link between the iodine contents of water and soil, and the daily iodine intake, especially in rural areas, where people are less exposed to food from external sources [65, 66]. Thus, nutritional iodine deficiency could be another factor contributing to the observed high incidence of CH in the West Bank.

In general we can concluded that internal factors (including thyroid dysgenisis, dyshormonogenisis) and/or environmental external factors are accused in the observed high incidence of CH in the West Bank.

Geographic distribution of the disease is of high importance for health care administrators in order to plan for the personnel and services necessary to cover for follow-up of affected individuals. It also helps in determining where to locate regional specialized care centers for such cases. The distribution of disease cases among the various districts was; 28.1% in Jenin; 21.9% in Hebron; 15.6% in

Nablus; 9.4% in (Salfeet; Ramallah; and Bethlehem) and 6.3% in Qalqilia district, (see table 9).

A clear difference in the incidence of CH was observed among the different districts of the West Bank. These differences may affected by the small number of infants screened in each region or may represent an actual difference inherent in each district. The incidence of CH was notably high (1:1266) in Jenin district. The reason behind the finding of high incidence in Jenin district as an example is not clear, however, data on high consanguineous rate in this district (Palestinian Central Bureau of Statistics) may partially explain this observation.

High percentages 82.1% of CH affected cases were derived from rural society where consanguineous marriages are a spreading phenomenon, see table 10. This finding is consistent with PKU disease distribution [41]. Furthermore, the previously proposal role of iodine insufficiency could contribute to this high incidence in rural areas.

Biochemical and clinical findings of the study cases

Newborn screening and confirmatory thyroid function results revealed moderate to severe abnormalities in most of cases (see table 12). Severity of CH in our study cases was assessed from the first quantitative FP-TSH measurement and after both serum TSH and T4 confirmation. The mean FP-TSH value was clearly high (359.24 μIU/ml) with a mean time of specimen collection (42.37) days. More than two third of cases had a marked elevation on FP-TSH (≥ 200 μIU/ml) as well as on confirmatory serum test (≥ 100 μIU/ml). These high values could be attributed, in one part, to the severity of the disease and on the other, to the delay of screening and diagnosis.

All studied cases (32) were with elevated serum TSH and were below the normal range of either total T4 or free-T4 and accordingly they were suspected to have primary CH based on the recommended AAP values [12, 13]. All cases were considered to be of suspected permanent hypothyroidism until they proven otherwise, on later time, as confirmatory permanence of thyroid disease have to be re-evaluated at the age of three years [12, 49]. Unfortunately, thyroid scan is not available and hence, the etiology remained undiagnosed and the types of CH were not categorized in all patients at the evaluation. This point deserves further investigation.

The finding of one case (case number 17, see table 12) with an initial FP-TSH value in the intermediate zone (20 – 40 μ IU/ml) who developed hypothyroidism on a later date represents a delay raise in the TSH. Suggestion was stated that the cause of such case may be immaturity of the hypothalamic-pituitary-thyroid axis or abnormality of pituitary-thyroid feedback regulation [12, 61, 63, 67]. Although, considerations the importance of the intermediate zone may increase the number of recall rates, it may allow diagnosis of some new cases of hypothyroidism with various defects [68].

Most studies report a female preponderance for CH [17, 18, 22, 24], our study revealed an evenly split of CH cases between males and females. This contradictory is most likely to be affected by the small number of the study cases.

It is note worthy, that all study cases were products of normal term pregnancies with normal average weight (see table 17).

Though, most of infants with CH appear normal at birth, and that many clinical signs and symptoms are non-specific for congenital hypothyroid infants [2, 10-12, 43], most of our cases as revealed from the questionnaire had overt and several of these

features. The most prevalent clinical features were prolonged jaundice (63%), inactivity (63%), constipation (63%), sleepiness (59.3%), and edema (59.3%), as shown in table 13. Out of 28 cases that participated on follow up, symptoms suggestive of hypothyroidism were observed among 25 children. The number of features per infant noted varied from (0-11) with an average of 4.84 signs.

A statistically significant differences ($P = 0.000$) were observed between hypothyroid cases and the control group (48 normal health infants) for the mean number of clinical features, (see table 14). The appearance and persistence of such symptoms in parallel with abnormal TSH screening result, could be used as an indicator for the presence of hypothyroidism, and thus provoke an immediate and comprehensive thyroid tests to be initiated. The frequency of symptoms and signs of hypothyroidism among our cases study were higher than that reported in Israel [57]. Findings on frequency of signs and symptoms in our study could be, in part, due to the following possibilities:

1- Severity of the disease among our cases as revealed from their thyroid function test profile (more than two-third of cases was with FP-TSH value (≥ 200 μIU/ml). A strong association between severity and number of symptoms per infants was observed ($P = 0.042$).

2- Delay in diagnosis, where signs and symptoms are incrementally appeared ($P = 0.02$).

3- Disease onset, which varies depending on disease etiology and can appear as early as the third trimester to some time after birth.

4- Human errors of judgments (overestimation by mothers).

Out of 28 positive cases, (24) 85.7% were first identified through the screening program, however, the remaining (4) 14.3% were identified clinically after they were presented with symptoms before the abnormal screening became known. It is important to point out that FP-blood samples for some of these 4 cases arrived at the central laboratory very late and others were due to inter-laboratory delay. Such findings emphasize the importance of biochemical screening in early detection and diagnosis of hypothyroid infants. On the other hand, most of the study cases (92.8%) were first identified at age above one month. The mean age at the time of screening were (89.22) days, thus, representing an unfortunate delay in screening (see table 18).

All study cases were diagnosed after one month of age with a mean time of (143.18) days, see table 19. This unjustified delay resulted from incapacity in the retrieval and follow-up of subjects with abnormal screening results in one side and to internal limitation of the screening program policy in dealing with the positive results.

Hormone therapy was administered in almost all cases. The average age for initiation of treatment was (21.74) weeks. This indicates a clear delay in treatment compared to reports from various screening programs where implementation of hormone therapy instituted as early as 20 days [6, 17, 56, 64, 69]. In Israel, initial studies reported a treatment age of 4.8 weeks [62], which was dropped into (14) days nowadays (personal communication). Unsatisfied delay in our screening program related to sample collection, handling, transportation, analysis, reporting, and follow-up contributes to needless delay in diagnosis and treatment of a newborn with hypothyroidism. Every effort should be made to initiate therapy within the first days of life, and that substitution therapy for CH

respect are in good correlation with previous reports where infancy and childhood growth is a thyroid dependant process and the onset of growth is in part related to the age of treatment started [48, 61]. Also linear growth is supposed to become thyroid dependant postnatal [71, 72], and a delay in treatment was reported as a risk factor in relation to longitudinal growth [71].

Thus, one can conclude that the observed reverse outcomes on growth were mainly the results of treatment delay and in part by the degree of severity.

Available data regarding pretreatment L-T4 dose is limited. Thus, further detailed study on treatment quality and it's impact on the health and development of CH is essential at this stage.

Our findings on teeth development and walk delay (5 out of 11 with either height or weight problems) provide further evidence on the reverse outcomes due to the delay in treatment. It is important to note that we found three CH cases with late diagnosis and lack of proper regular treatment represented with severe growth and development, there cases were below the minimal range for growth (height and weight). Thus reflecting the importance of early diagnosis and treatment on the health and development of permanent CH cases. Various studies have shown that CH may be associated speech delay that may be worsened with the delay of therapy [68, 73]. All cases with either weight or height problems had speech delay as complained by their mothers. Five of these cases who started treatment above three months had teeth deformation and walk delay.

There is a prevailing view that CH is associated with an increase prevalence of non-thyroidal congenital abnormalities [63, 74-77]. The prevalence rate of congenital malformations varied among different studies [74]. In contrast, none of our study cases was

represented with any extra thyroidal anomalies. This could be due to the small number of the sample in one hand or on the other hand due to the fact that such infants are usually undergone special treatment in hospitals and thus escaped follow-up.

Transient hypothyroidism

In addition to the previously found permanent CH cases, our findings on transient hypothyroidism rate seems fairly high (1: 418.9) as shown in table 20. It also seems to be common among full term infants. Such rate is consistent with reports from Europe (1:200-1:8000) [12].

All studied (167) transitory hypothyroidism cases showed normal values with respect to both capillary-TSH and/or T4 were normal, at the time of recall examination, with an estimated mean time of (75.57) days. Around sixty five percent of the cases were with high TSH values and with a T4 value below the normal range. On the other hand, around thirty four percent cases were with high TSH values and with a sub-normal T4 value, suggesting short-term of the transient hypothyroidism or transient hyperthyrotopenemia respectively (see table 22.a).

Relatively marked regional differences in the incidence of transitory hypothyroidism were observed. While the incidence in Ramallah was low, it was higher in Jenin, Salfeet and Qalqilia (see table 20).

Iodine deficiency, postnatal exposure to excess iodine, drug-induced fetal hypothyroidism and delay at which the first heel pricks blood is obtained were some of the possible explanations for the occurrence of high transitory hypothyroiisiam rate.

Iodine deficiency or excess seems to influence the frequency transient hypothyroidism [18]. Transient hypothyroidism, with raised

TSH levels, secondary to the use of iodine containing solutions (povidone iodine) has been observed [27, 28]. Routine skin cleansing with iodine for infants is not a common practice in our health system (obstetrics and neonatology) as revealed from most of the visited hospitals during the study work. Thus, one can concluded that transitory hypothyroidism is not a common sequel of routine skin cleansing with iodine.

On the other hand, the finding of overall transient hyperthyrotropinemia with a raised TSH level of (5 μIU/ml) among 14.96 % of the studied infants, not associated with low birth weight and low gestational age. Based on WHO criteria, such condition corresponds to mild iodine deficiency [78]. This finding is in agreement with the previously reported median urinary iodine content of 9.48μg/dl among the Palestinian school-aged children of the West Bank [46]. The frequency of regional neonatal-TSH (> 5 μIU/ml, whole blood) as revealed in table (23) indicate mild to moderate iodine deficiency disorders. Thus, nutritional iodine deficiencies are more likely to play a major role in the occurrence of transitory hypothyroidism in our districts. Further evidenced in this respect can be deduced from the finding on rural population where the majority of transitory cases (79.0%) found (see table 21). In Europe, transient hypothyroidism and transient hyperthyrotropinemia in the neonate [9] frequently accompany a mild degree of iodine deficiency.

In our study, recall rates for suspicion of congenital hypothyroidism (0.78%) correlates well with the findings on transitory hypothyroidism among the various districts (P=0.000). This provides further evidence in support of our previous assumption on the role of iodine deficiency.

The role of goiterogenic agents of food substances has been implemented [78]. Bacterial and chemical pollution of water supplies could be one of the reasons for iodine deficiency. Our study implies that the etiology of IDD could be due to goiterogenic factors in the diet or environment other than iodine deficiency. This evidence came from the fact that districts like Jenin and Salfeet which has been proposed to be of a normal estimation of iodine deficiency by previous studies [46, 65], was found to be with a high incidence rate of transitory hypothyroidism (see table 20). Furthermore, these districts show high recall rates and the raised TSH level of (> 5 μIU/ml) occurred in 24.12% and 15.03% of infants, respectively (see tables 6 and 25). Our results together with previous reports on iodine deficiency indicate that other environmental factors seems to be involved in the occurrence of transitory hypothyroidism in this district and the situation might be applicable to other districts. Further investigations are required to clarify this point.

Mothers with sub-clinical auto-immune thyroid disease or previously treated for Graves' disease, their infants are more prone to fetal and neonatal transient hypothyroidism [11]. None of the mothers of the infants involved was reported to be on propylthiouracil or iodine medication during pregnancy.

Delay in sample collection of Guthrie cards inherited in our program system could add a further complication for the occurrence of high frequencies of transitory hypothyroidism cases [12-14].

Study by Calciura *et al.*, showed that hypothyroidism at birth, even short-term transitory, can adversely affect long-term intellectual development [69]. Thyroid insufficiency in mothers, at least in areas of endemic goiter, is a reliable indicator of increased risk of CH in newborn [18]. The fetus and the newborn are more

sensitive than adults to reduced environmental iodine supply [34,35,42,78]. The hypersensitivity of the neonates to the effects of iodine deficiency is explained by their limited intrathyroidal iodine pool, which requires increased TSH stimulation and a fast turnover rate in order to maintain normal secretion of thyroid hormones [78].

It is important to note that screening programs do not simply consider transient hypothyroidism, especially for those with high FP-TSH, as an end point of diagnosis, however, they are aware of the fact that such situations may reflect a severe condition. In our study, 8 of 167 transitory hypothyroidism were represented with severe form, as revealed from their TSH and T4 results, a situation may necessitate reinstitution of L- thyroxine at early stage (see table 22 a and b). In general, the issue is that benefit of levothyroxine treatment outweighs the risks of having a child with abnormal function of the central nervous system [73].

The finding of statistically significant correlation between age at specimen collection and both capillary screening TSH and total T4 values (P= 0.000 and P = 0.008, respectively) among these patients in particular (see table 22 b), indicate the immediate need for medical intervention.

Recommendations and Concluding Remarks

1. An effective mechanism should be established at all facilities levels to strengthen the coverage rate and this can be achieved through increasing primary health care centers and increase awareness of people towards screening tests and their advantages.

2. Specially designed programs are required to health care providers and public with special emphasis on the importance of early blood specimen collection not later than 7 days of life, as recommended by the American Academy of Pediatrics (AAP).

3. It would seem reasonable to strive for an appropriate follow up and management for effective prognosis.

4. A thorough maternal and family history in conjugation with clinical signs and symptoms of hypothyroidism, biochemical tests, for every suspected neonate, should be used to rapidly establish the diagnosis.

5. Due to the various complications in treatment and follow up of affected cases, it is essential to establish a specialized CH referral center in the region.

6. Further follow up studies are needed to determine intellectual quotient of affected cases.

7. Scintigraphy of the thyroid in all recalled infants should be implemented in order to establish a firm and final diagnosis of the cause of hypothyroidism.

8. Comprehensive studies on birth defects that associated with CH are still needed.

9. Routine monitoring of thyroid hormone during pregnancy for women with affected children.

10. Genetic counseling is of utmost importance to alert mothers, of the high risk of recurrence and to ensure prompt evaluation of all subsequent offsprings.

1- W. Stubbs (2000) Brief review of thyroid hormone regulation, biological effects of thyroid hormone, and good of treatment. *www.doh.wa.gov/phl/newborn/review97.htm.*

2- Dattani M., and Brook C. G. D. (1996) Outcomes of neonatal screening for congenital hypothyroidism. *Current Opinion in Pediatrics*, 8: 389-395.

3- Novogroder M. (1980) Neonatal screening for congenital hypothyroidism. *Pediatric Clinics of North America,* 27(4).

4- Saslow J. G., Post E. P., and Southard C. A. (1996) Thyroid screening for early discharged infants. *Pediatric*, 98(1): 41-44.

5- Klein A. H., Foley T. P., Larsen P. R., Agustin A. V., and Hopwood N. J. (1976) Neonatal thyroid function in congenital hypothyroidism. *The Journal of Pediatrics*, 89(4): 545-549.

6- Chiovato L. and Bargagna S. (1999) Congenital hypothyroidism: treat but don't forget their parents. *European Journal of Endocrinology*, 141: 101-104.

7- Siragusa V., Boffelli S., Weber G., Triuzi F., Orizzi S., Scotti G., and Chiumello G. (1997) Brain magnetic resonance imaging in congenital hypothyroid infants at diagnosis. *Thyroid*, 7(5): 761-763.

8- Rovet J. F. (1999) Congenital hypothyroidism: long-term outcome. *Thyroid*, 9(7): 741-748.

9- Delange F. (1997) Neonatal screening for congenital hypothyroidism: results and perspectives. *Hormone Research*, 48: 51-61.

10- Grütters A., Krude H., Biebermann H., Liesenkötter K. P., Schönberg T., and Gudermann T. (1999) Alterations of neonatal thyroid function. *Acta Paediatrica Supplement*, 428: 17-22.

11- Orgiazzi J. (2000) Hypothyroidism: causes, mechanisms, clinical presentation, diagnosis and treatment. *www.osiris.sanderland.ac.uk./autism/thyroid.htm.*

12- American Academy of Pediatrics (1993) Newborn screening for congenital hypothyroidism: recommended guidelines. *Pediatrics*, 91(6): 1203-1209.

13- Allen D. B., Farrell P. M. (1996) Newborn Screening: Principles and Practice. *Advances in Pediatrics*, 43: 85-93

14- LaFranchi S. (1999) Congenital hypothyroidism: etiologies, diagnosis, and management. *Thyroid*, 9(7): 735-740.

15- Tsai W. Y., Lee J. S., Wary T. R., Chen J. S., Chuange S. M. (1993) Clinical characteristics of CH detected by neonatal screening. *Journal of Formos Medical Associations*, 92(1): 20-23.

16- Toublance J. E. (1992) Comparison of epidemiological data on congenital hypothyroidism in Europe with those of other parts in the world. *Hormone Research*, 38: 230-235.

17- Grant D. B. and Smith I. (1988) Survey of neonatal screening for primary hypothyroidism in England, Wales, and Northern Ireland 1982-4. *British Medical Journal*, 296: 1355-1359.

18- Lorey F. W. and Cunningham G. C. (1992) Birth prevalence of primary congenital hypothyroidism by sex and ethnicity. *Human Biology*, 64(4): 531-538.

19- Al-Jurayyan N. A., Shaheen F. I., Al-Nuaim A. A., El-Desoki M. I., Faiz A., Al-Herbish A. S., Bakr A. M., Al-Swailem A. A., Al-Mazrou Y. Y. (1996) Congenital hypothyroidism: increased incidence in Najran province, Saudi Arabia. *Journal of Tropical Pediatrics*, 42(6): 348-351.

20- Daoud A. S., Zaki M., Al-Saleh Q. A., Teebi A. S., Al-Awadi S. A. (1989) Congenital hypothyroidism in Kuwait. *Journal of Tropical Pediatrics*, 35(6): 312-314.

21- Elbualy M., Bold A., Gibbons U. (1998) Congenital hypothyroid screening: the Oman experience. *Journal of Tropical Pediatrics*, 44(2): 81-83.

22- Tsai W. Y., Lee J. S., Chao M. C., Chen L. Y., Lin S. J., W. U. K. H., Wang T. R., Chen J. S., Chuang S. M. (1995) Prevalence of permanent primary congenital hypothyroidism in Taiwan. *Journal of Formos Medical Associations*, 94(5): 271-273.

23- Brown A. L., Fernhoff P. M., Milner J., McEwen C., and Elsas L. S. (1981) Racial differences in the incidence of congenital hypothyroidism. *The Journal of Pediatrics*, 99(6): 934-936.

24- Waller DK, Anderson JL, Lorey F., Cunningham GC (2000) Risk factors for CH: an investigation of infants birth weight, ethnicity, and gender in California, 1990-1998. *Teratogy*, 62(1): 36-41.

25- Hall S. K., Hutchesson A. C. J. and Kirk J. M. (1999) Congenital Hypothyroidism, Seasonality and Consanguinity in the West Midlands, England. *Acta Paediatrica*, 88: 212-215.

26- Dallas J. S. (2000) Congenital hypothyroidism. *www.the-thyroid-society.org/med_letter2.htm.*

27- Macchia P. E., Felice M. D., and Lauro R. D. (1999) Molecular genetics of congenital hypothyroidism, current opinion in genetics and development. *Journal of BioMed*, 9(3): 289-294.

28- Rotenstein D. (2000) Congenital hypothyroidism. *URL: http:// www.mc.vaderbilt.edu/peds/pidl/endocr/hypothyroidism.htm.*

29- Biebermann H., Leisenkötter KP, Emeis M., Obladen M. and Grüters A. (1999) Severe congenital hypothyroidism due to a homozygous mutation of the ß-TSH gene. *Pediatric Research*, 46(2): 170-173.

30- Doeker B. M., Pfaffle R. W., Pohlenz J. and Andler W. (1998) Congenital central hypothyroidism due to a homozygous mutation in the thyrotropin ß-TSH subunit gene follows an autosomal recessive inheritance. *Journal of Clinical Endocrinology and Metabolism*, 83(5): 1762-1765.

31- Oliver L. F., Azpeitia P. A., Alfonso S. L., Gonzalez L. G., Gutierrez V. C., Rodriguez A. J., Yanez A. JM (1989) Neonatal hypothyroidism secondary to the use of povidone iodine. *Circulation Paediatrica*, 2(4): 168-171.

32- Lin C. P., Chen W., W. U. K. W. (1994) Povidone-iodine in umbilical cord care interferes with neonatal screening for hypothyroidism. *European Journal of Pediatrics*, 153(10): 756-758.

33- Delange F. (1998) Screening for congenital hypothyroidism used as an indicator of the degree of iodine deficiency and of its control. *Thyroid*, 8(12): 1185-1192.

34- Delange F. (1998) Risks and benefits of iodine supplementation. *The Lancet*, 251: 923-924.

35- Kung A. W. C., Lao T. T., Low L. C. K., Pang R. W. C. and Robinson J. D. (1997) Iodine insufficiency and neonatal hyperthyrotropinaemia in Hong Kong. *Clinical Endocrinology*, 46: 315-319.

36- Montanelli L., Pinchera A., Santini F., Cavaliere R., Vitti P., Chiovato L. (1998) Transient congenital hypothyroidism: physiopathology and clinical. *Annual First Sanita*, 34(3): 321-329.

37- Delange F. (1998) Screening for congenital hypothyroidism used as an indicator of the degree of iodine deficiency and of its control. *Thyroid*, 8(12): 1185-1192.

38- Dussault J. H. and Fisher D. A. (1999) Thyroid function in mothers of hypothyroid newborns. *Obstetrics Gynecology*, 93: 15-20.

39- International Council for Control of Iodine Deficiency Disorders (ICCIDD) (1999) IDD control in some African countries. *IDD newsletter*, 15(1): 1-16.

40- WHO (1995) Iodine deficiency: what it is and how to prevent it. *Regional office for the Eastern Mediterranean, Alexandria.* pp: 1-14.

58- Salerno M., Militerni R., Maio S. D., Bravaccio C., Gasparini N. and Tenore A. (1999) Intellectual outcome at 12 years of age in congenital hypothyroidism. *European Journal of Endocrinology*, 141: 105-110.

59- Peran S., Garriga M. J., Escobar G. M., Asuncion M., and Peran. (1997) Increase in plasma thyrotropin levels in hypothyroid patients during treatment due to a defect in the commercial preparation. *Journal of Clinical Endocrinology and Metabolism*, 82(10): 3192-3195.

60- Glorieux J., Dussault J., and Vlient G. V. (1992) Intellectual development at age 12 years of children with congenital hypothyroidism diagnosed by neonatal screening. *The Journal of Pediatrics*, 121(4): 581-584.

61- Fuggle P. W., Grant D. B., Smith I., and Muphy G. (1991) Intelligence, motor skills, and behavior at 5 years in early-treated congenital hypothyroidism. *European Journal of Pediatrics*, 150: 570-574.

62- Sack J., Kletter G., Amado O., and Aksein E. (1985) Screening for hypothyroidism in Israel during a 4-year period. *Israel Journal of Medical Science*, 21(6): 485-489.

63- Law WY, Bradley DM, Lazarus JH, John R, Gregory JW (1998) Congenital hypothyroidism in Wales (1982-1993): demographic features, clinical presentation and effects on early neurodevelopment. *Clinical Endocrinology*, 48(2): 201-207.

64- Yordam N., Calikoglu A. S., Hatun S., Kandemir N., Oguz H., Tezic T., and Ozalp I. (1995) Screening for congenital hypothyroidism in Turkey. *European Journal of Pediatrics*, 154: 615-616.

65- Sack J., Kaiserman I., Tulchinsky T., Harel G. and Gutekunst R. (2000) Geographic variation in groundwater iodine and iodine deficiency in Israel, the West Bank and Gaza. *Journal of Pediatric Endocrinology and Metaboloism*, 13(2): 185-190.

66- Sack J., Feldman I., and Kaiserman I. (1998) Congenital hypothyroidism screening in the West Bank: a test case for screening in developing regions. *Hormone Research*, 58: 151-154.

67- Grant G. A., Carson D. J., Reid M. M., and Hutchinson J. M. (1986) Congenital hypothyroidism missed in screening. *Archives of Disease in Childhood*, 61, 189-197.

68- Leger J., Lemerrer M., Briard M. L. and Czernichow P. (1987) Hypothyroidism in children with filter paper TSH of 30 to 50 μU/ml at initial screening. *Acta Paediatrica Scandinava.* 76: 599-602.

69- Calciura F., Mendoria G., Distefano M., Castornia S., Fazio T., Motta R., Sava L., Delange F. and Vigneri R. (1995) Childhood IQ measurements in infants with transient congenital hypothyroidism. *Clinical Endocrinology*, 43: 473-477.

70- Tillotson S. L., Fuggle P. W., Smith I., Ades A. E., Grant D. B. (1994) Relation between biochemical severity and intelligence in early treated congenital hypothyroidism: a threshold effect. *British Medical Journal*, 309: 440-445.

71- Heyerdahl S., Ilicki A., Karlberg J., Kase BF and Larsson A. (1997) Linear growth in early treated children with congenital hypothyroidism. *Acta Paediatrica*, 6: 479-483.

72- Vogiatzi M. G. and Copeland K. C. (1998) The short child. *Pediatrics in Review*, 19(3): 92-99.

73- Dalivia A. L., Lider B., Dimartino-Nardia J. and Saenger P. (2000) Three-year follow-up of borderline congenital hypothyroidism. *The Journal of Pediatric*, 136(1): 53-56.

74- Oakley G. A., Muir T., Ray M., Girdwood R. W. A., Kennedy R. and Donaldson M. D. C. (1998) Increased incidence of congenital malformations in children with transient-thyroid stimulating hormone elevation on neonatal screening. *Journal of Pediatrics*, 132: 726-730.

75- Al-Jurayyan N. A. M., Al-Herbish A. S., El-Desouki M. I., Al-Nuaimj A. A., Abo-Bakr A. M. and Al-Husain M. A. (1997) Congenital anomalies in infants with congenital hypothyroidism: is it a coincidental or an associated finding?. *Human Hereditary*, 47: 33-37.

76- Devos H., Rodd C., Gagne N., Laframboise R. and Vliet G. V. (1999) A search for the possible molecular mechanisms of thryoid dysgensis: sex ratio and associated malformations. *The Journal of Clinical Endocrinology and Metabolism*, 84(7): 2502-2506.

77- Rapaport R., Barnabas S. (2000) Congenital hypothyroidism: expanding the spectrum. *Journal of Pediatrics*, 136(1): 10-11.

78- Delange F. (1994) The disorders induced by iodine deficiency. *Thyroid*, 4(1): 107-123.

الملخص

لقد بدأ برنامج التشخيص المبكر لقصور عمل الغدة الدرقية في منطقة الضفة الغربية في العام 1990, ونظرا لعدم وجود دراسات سابقة حول هذا الموضوع فقد هدفت هذه الدراسة لتأسيس قاعدة بيانية صحية حول هذا المرض من حيث انتشاره في الضفة الغربية, و تحديد عوامل الخطورة المتعلقة بذلك.

لقد تبين من خلال هذه الدراسة أن هذا البرنامج في المنطقة يواجه عدة معوقات فيما يتعلق بالية جمع العينات و متابعة حالات الإصابة فيما بعد. فقد بلغت عدد حالات الولادة المسجلة في الضفة الغربية خلال فترة الدراسة (منذ الفترة ما بين شهر تشرين أول 1998 و نيسان 2000) حوالي 85,149 حالة, وقد تم عمل هذا الفحص لحوالي 69,957 مولود من خلال قياس مستوى الهرمون المنشط للغدة الدرقية عند حديثي الولادة (n-TSH). و بينت النتائج وجود 32 حالة من الحالات المشكوك فيها بالإصابة بالقصور الدائم لعمل الغدة الدرقية و بنسبة تعادل واحد لكل 2,186 حالة تقريبا. و تعتبر هذه النسبة من النسب المرتفعة عالميا بالمقارنة مع كثير من دول العالم. 547646

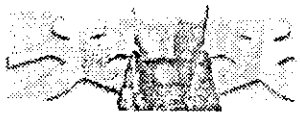
فيما يتعلق بمسببات هذا المرض فلا زالت غير محددة و غير واضحة, و قد تكون نتيجة لأسباب عديدة متداخلة, و تشير النتائج الأولية بأن زواج الأقارب يلعب دورا هاما في ارتفاع نسبة الإصابة بهذا المرض في مجتمع الضفة الغربية, و لا بد من الإشارة إلى انه لا يمكن استبعاد الدور الذي تلعبه العوامل البيئية في ذلك.

ولقد بينت النتائج أن ما يعادل(0.78%) من الأطفال تم استدعائهم لإعادة الفحص و هذا ما يعكس نتائج هذه الدراسة من أن هناك قصور مرحلي أو مؤقت لعمل الغدة الدرقية و بنسبة تعادل حوالي واحد لكل 419 حالة. و كذلك تبين الدراسة زيادة في ارتفاع الهرمون المنشط للغدة الدرقية (اكبر من 5 µIU/ml) بما نسبته 15% من الأطفال الذين شملهم الفحص خلال فترة الدراسة مما يعكس و بصورة واضحة بأن نتائج المسح الخاص بهذا الخلل لحديثي الولادة يتأثر بنقص عنصر اليود مما يؤدي بالتالي إلى ارتفاع نسبة إعادة الطلب لإجراء الفحص مرة أخرى لهؤلاء الأطفال.

على الرغم من إيجابيات برنامج المسح المذكور لكل من الأطفال المصابين و عائلاتهم إلا أنه و لأسباب معينة يبدو أن هذا البرنامج لم يتمكن من الوصول إلى كامل أهدافه المرجوة بالشكل الصحيح و التي تتمثل في التشخيص و العلاج المبكر للحالات الإيجابية. فقد أظهرت نتائج المسح و كذلك الفحوصات الأخرى الداعمة لهذه النتائج وجود حالات مرضية متزامنة مع أعراض ما بين متوسطة إلى شديدة الحدة , مع وجود تأخير واضح في العمر الزمني لإجراء الفحص (89 يوم) و كذلك في التشخيص (143 يوم) و البدء في العلاج (152 يوم) . و تجدر الإشارة بأن حدة الأعراض المرضية و كذلك مشكلات النمو و التطور قد تزامنت و بشكل واضح مع التأخير في العلاج, مما يستدعي ضرورة وجود برنامج شامل للحد من هذه المشكلة بحيث يهدف هذا البرنامج إلى البحث عن افضل الوسائل للفحص المبكر و الأداء الفعال في التشخيص و العلاج. و لتحقيق هذا الهدف لا بد من التعاون فيما بين جميع الجهات المعنية في المؤسسات الصحية للرعاية الأولية للأطفال منذ لحظة الحمل و حتى مرحلة الولادة و ما بعد الولادة.

بسم الله الرحمن الرحيم

- QUESTIONNAIRE -



EARLY DETECTION OF CONGENITAL HYPOTHYROIDISM IN PALESTINE

Infant's Name : _____

Case No. : Guthrie Card No.:

ADDRESS :

Place of living : a. Village ☐ b. City ☐ c. Camp ☐

Telephone No. :

Father's Name : _____

Level of education :a. None ☐ b. High school ☐ c. High diploma ☐ d. University studies ☐

Occupation :

Mother's Name : _____

Level of education :a. None ☐ b. High school ☐ c. High diploma ☐ d. University studies ☐

Occupation :a. Yes ☐ (type) _____ b. No. ☐

Ethnic Group :
- Muslim ☐
- Christian ☐

Consanguinity :
- None. ☐
- First cousins. ☐
- Second cousins. ☐
- Distant cousins. ☐

E-2000 1

tient's Name

Birth Date

Serono