

Newborn Screening for the Early Detection of Congenital Hypothyroidism: A Countrywide Comprehensive Program of Bangladesh Atomic Energy Commission

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ABSTRACT

The crucial practice of newborn screening allows for the early identification of curable medical issues in infants. Congenital hypothyroidism (CH), a disorder brought on by insufficient thyroid hormone production, is the subject of this study. Worldwide variations exist in CH prevalence, and early identification is essential for the best results. A thorough screening program was launched in Bangladesh from July 2018 to June 2022, gathering over 500,000 samples from infants throughout the nation. This program's goal was to recognize CH cases and offer prompt intervention in collaboration with 839 hospitals. TSH levels were found above the cut-off values in 274 of the samples, which corresponds to an incidence rate of about 1 in 1,825 births. TSH levels ranged from 20 to 75 mIU/L in the majority of positive cases, with the highest value reaching 506.05 mIU/L. The study discovered that infant girls were more likely than infant boys to have CH. The greater Mymensingh region showed a higher prevalence than other places, and regional variations in CH incidence were also noted. It was determined that iodine deficiency, which affects 38% of the population, may have an impact on the prevalence of CH. Low public knowledge and the unwillingness of the uneducated population to offer samples are obstacles to newborn screening in Bangladesh. To get beyond these obstacles and underline the value of early screening, public awareness campaigns and educational initiatives are required. The study emphasizes the necessity for focused interventions, especially for female newborns in areas where the prevalence of CH is higher. To effectively address iodine deficiency, access to comprehensive iodine supplementation

programs should be ensured. In conclusion, Bangladesh can successfully treat congenital hypothyroidism and enhance the health and wellbeing of babies across the country by addressing these issues, putting in place targeted interventions, and increasing access to screening programs. To improve outcomes for newborns with CH, the study underlines the relevance of early detection, timely intervention, and increasing public awareness.

Keywords: Congenital hypothyroidism, TSH, iodine deficiency, public awareness.

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INTRODUCTION

Newborn screening is a process by which a newborn is screened to detect usually treatable medical disorders at the time of birth. Newborn screening (NBS) is sometimes called “baby’s first test.” Blood, hearing, and heart tests are all part of the procedure (1). Newborn screening detects conditions that may have a long-term impact on a child's health or survival. Rapid detection, diagnosis, and medication can help youngsters attain their full potential and avoid death or handicap (2). NBS was developed on

the findings that the amino acid disorder phenylketonuria (PKU) could be remedied with diet modifications, but that early detection was necessary for optimum results. Robert Guthrie devised a simple approach in the 1960s that could reveal elevated amounts of phenylalanine in blood just after a baby was born using a bacterial inhibition assay (3, 4). Guthrie also pioneered the collecting of blood on filter paper that could be moved easily, realizing the need for a simple technique if large-scale screening was to be done. The second condition that was extensively included in the 1970s was congenital hypothyroidism (5). The development of enzyme immunoassays and HPLC enabled to add more diseases subsequently. These include galactosemia, maple syrup urine disease, homocystinuria, sickle cell disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, congenital adrenal hyperplasia, and neuroblastoma. The adoption of tandem mass spectrometry (MS/MS) screening in the early 1990s resulted in a significant increase in the number of potentially traceable congenital metabolic illnesses that can be recognized by specific amino acid patterns and acylcarnitines (6).

The neonatal screening process of the Asia Pacific region can be separated into four phases. Japan began newborn screening in the early 1960s, followed by a G6PD deficiency screening program in Singapore. Congenital hypothyroidism screening was introduced to the program in 1980, and it was launched in Taiwan, Hong Kong, China (Shanghai), India, and Malaysia. In 1990, based on their previous experience, Korea, Thailand, and the Philippines launched this initiative. Congenital hypothyroidism screening has been implemented in Indonesia, Mongolia, Sri Lanka, Myanmar, and Pakistan courtesy of financing from the International Atomic Energy Agency (IAEA) (7).

Congenital hypothyroidism is a medical condition that affects newborn babies and is marked by insufficient thyroid hormone production. Reduced amounts of thyroid hormones essential for healthy growth and development occur when the thyroid gland, which is located in the neck, fails to develop or operate as it should.

The biochemical imperfections in CH mean a shortage in moving T₄, which can result from the thyroid gland not

existing (thyroid aplasia), structural defects in the gland (thyroid dysplasia and hypoplasia), abnormal positioning of the gland (thyroid ectopic gland), or the thyroid gland's inability to produce thyroxine as a result of an inherited metabolic error (thyroid dyshormonogenesis). The prevalence of particular etiologies varies from country to country. The observed etiologies include ectopic thyroid (35-42%), thyroid agenesis (rates: 22-42%), and placement abnormalities of the gland (rates: 24-36%). Although a few cases of thyroid dysgenesis caused by gene mutations have been reported, the majority of these cases lack a consistent correlation to explain the underlying etiology.

The global prevalence of CH is reported to be between 1:2000 and 1:4000 neonates (8), and it varies by geographic location, with higher rates in coastal nations like Spain, Italy, and Greece than in landlocked countries like the Czech Republic and Bolivia (9,10,11,12). Within the same country, there were also regional differences in CH incidence. According to a study conducted in the United States, the southwest, the Great Lakes, and Hawaii had elevated levels (13).

Bangladesh started newborn screening by the Immunoradiometric assay (IRMA) in 1999 under a regional project of the International Atomic Energy Commission (IAEA). They found 16 affected babies from 31802 newborns (14). Due to a successful project of the Annual Development Program on newborn screening from July 2006 to June 2010. Then a time-resolved fluoroimmunoassay named Dissociation Enhanced Lanthanide Fluorescent Immunoassay (DELFLIA) was used because of its higher sensitivity, speed, and non-radioactive methodology. The Bangladesh government funded phase-2 of this project from July 2018 to June 2022. The objective of this project was to establish a well-decorated newborn screening laboratory and perform mass screening during this period. AutoDELFLIA 1235 automatic immunoassay system was introduced in 2019. A genetic Screening Processor (GSP) was installed in 2021.

MATERIALS AND METHODS

Reagents: The study used PerkinElmer Life and Analytical Sciences reagents to prepare standards and

anti-human alpha-fetoprotein tracer. The standards were calibrated against WHO international standards and were preserved in a wash concentrate and an enhancement solution. Known standards of 0.8, 10.3, 24.5, 49.3, 93.2, 239 μ U/mL were prepared by bovine serum albumin with Tris-HCl buffer solution which was preserved by < 0.1% sodium azide.

Instruments: Panthera PuncherTM, AutoDELFIA Plate processor 1235 automatic immunoassay system/ Genetic Screening Processor (GSP), and specimen gate software were paralleled for analysis. Panthera PuncherTM is a next-generation automatic punching machine capable of punching 9 plates simultaneously, detecting blood in filter paper, exporting punched information to AutoDELFIA manager 3.0, and generating analytical reports.

Blood collection: Umbilical cord blood was collected after the birth of babies on a specialized filter paper. Only a single drop of blood was collected in each position of filter paper and collected in three different positions. Blood spots were dried horizontally for hours, separated from other surfaces, and collected for analysis at the In-vitro division of National Institute of Nuclear Medicine and Allied Sciences (NINMAS).

METHODS

Dried blood spots were punched into an antibody-coated microtitration well by an automated Panthera PuncherTM. The Panthera puncher was used to punch plates, and all sample information was exported to AutoDELFIA software. AutoDELFIA manager 3.0 then analyzed the samples, adding reagents and liquids. The Genetic Screening Processor (GSP) was used for analysis, exporting samples information to the GSP workstation. The standard cut-off for TSH testing was 20 mIU/L, with higher values requiring urgent assessment. FT3, FT4, and TSH were diagnosed from serum blood, and higher TSH neonates were treated for follow-up.

RESULTS

In Bangladesh, a comprehensive screening program has been implemented to collect samples from newborns across the country, enabling early identification and management of CH cases. To ensure a comprehensive approach, the screening program has formed partnerships with 839 hospitals throughout Bangladesh. The program, which aimed to screen newborns for congenital hypothyroidism, collected approximately 500,000 samples from hospitals from July 2018 to June 2022, demonstrating its effectiveness in identifying and diagnosing the condition. This remarkable achievement signifies the program's effectiveness in screening a large number of newborns for congenital hypothyroidism.

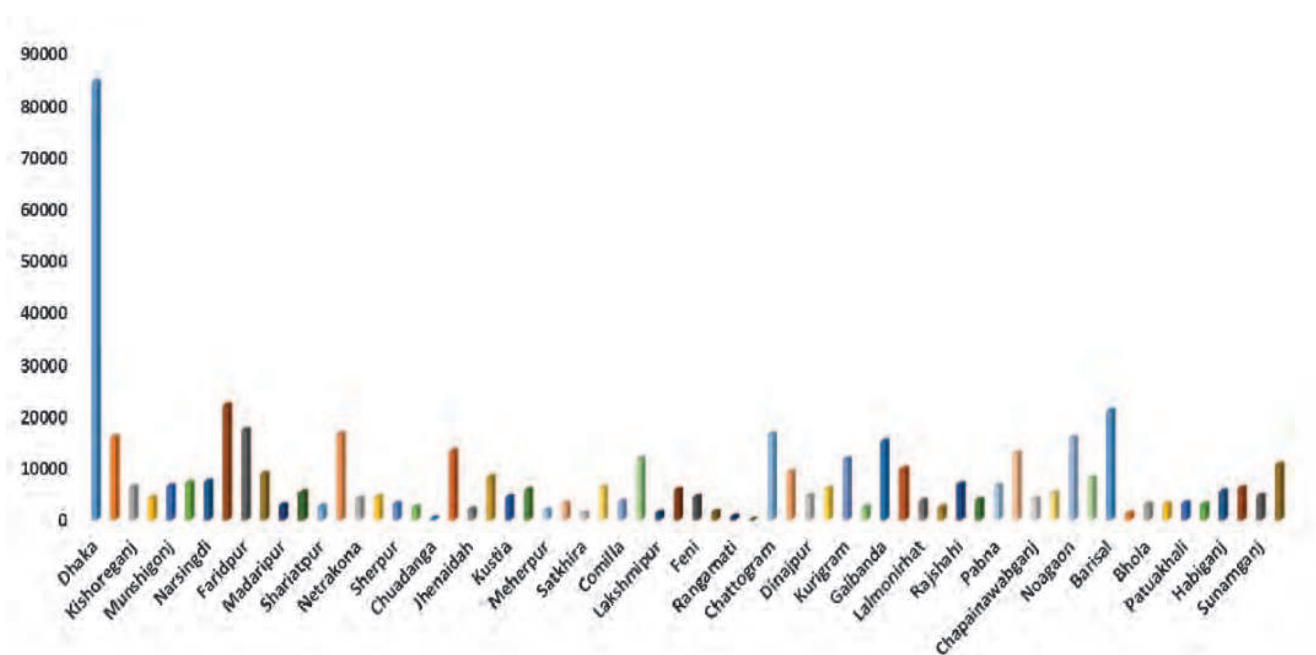


Figure 1: Distribution of Collected samples from Different Districts for Congenital Hypothyroidism Screening.

The distribution of sample collection for congenital hypothyroidism screening throughout several districts in Bangladesh is shown in this table chart. The biggest number of samples were taken in the districts of Dhaka, Gazipur, Tangail, Faridpur, Chattogram, Gaibandha, and

Naugaon. Compared to other areas of Bangladesh, these districts are renowned for having higher population densities. The major urban areas of Dhaka, Gazipur, and Chattogram have the highest concentrations of hospitals and clinics.

Table-1: Distribution of the hospitals in different divisions

DIVISION	AMOUNT OF HOSPITAL	PERCENTAGE
DHAKA	293	34.92
MYMENSINGH	25	2.98
KHULNA	99	11.80
CHATTOGRAM	115	13.71
RANGPUR	111	13.23
RAJSHAHI	98	11.68
BARISAL	52	6.20
SYLHET	46	5.48

There are 839 hospitals in total that are a part of the congenital hypothyroidism screening program, and impressively, 293 of them are in Dhaka, making up around 35% of the total hospital coverage. The concentration of hospitals in the Dhaka district in Bangladesh is a testament to the tremendous efforts put forth in this area with a high population density. The abundance of hospitals demonstrates the dedication to ensuring that new parents and their families have access to quality medical treatment.

An unsettling finding came to light among the 500,000 samples collected when it was found that 274 samples had TSH (thyroid-stimulating hormone) values higher than 20

U/mL. This finding leads to an incidence rate of roughly 1 in 1,825 births. The samples' TSH results showed a wide range, with the majority of readings lying between 20 and 75 U/mL, demonstrating how severe the thyroid dysfunction was in these instances. The most extreme TSH value ever found was an astounding 506.05 U/mL, highlighting the need for rapid medical care and intervention in these life-or-death circumstances. Even while the majority of infants with raised TSH levels can be successfully managed and treated, the tragic loss of 20 babies emphasizes the necessity and importance of early detection and treatment in situations of congenital hypothyroidism.

Table-2: Distribution of TSH values in different positive cases

Serial No.	Range of results	Amount
1	0-5	426791
2	6-10	50284
3	11-15	15653
4	16-20	6998
5	20 Above	274

A considerable deviation from the norm was seen in the average TSH level among positive cases, which was 64.01 U/mL. It's interesting that almost 80% of these positive cases had TSH levels below the limit of 90.00 U/mL, highlighting

the prevalence of milder instances. The 20% of positive cases that were left, however, were over this range, indicating a more serious thyroid dysfunction in a smaller but still significant subset.

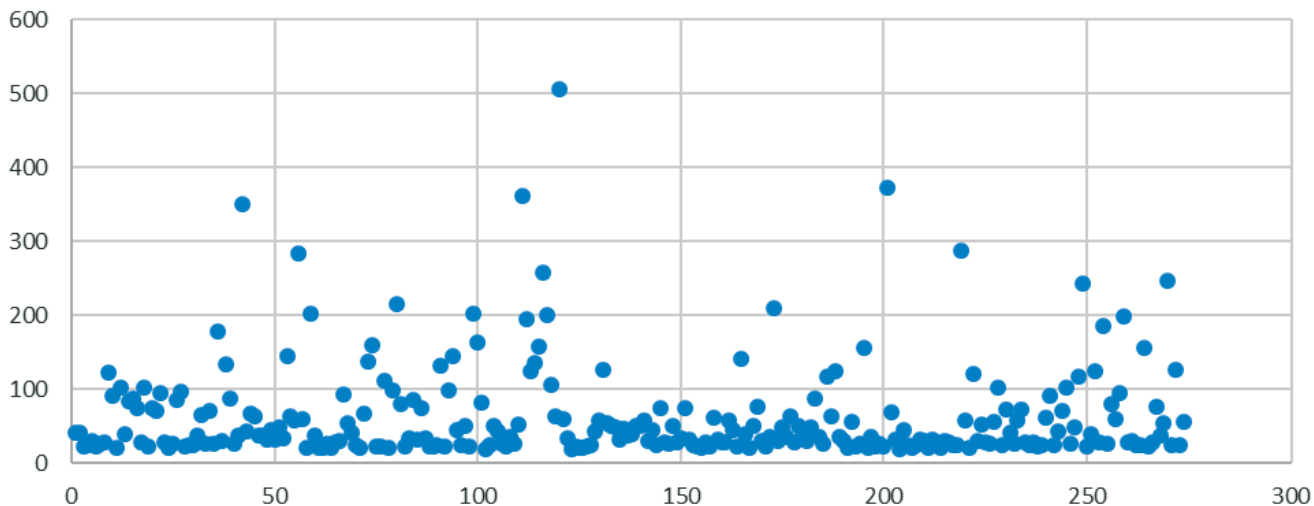


Figure 2: Variation of 20 Above TSH values of positive cases.

Male patients comprised 44.09% of the cohort who tested positive, while female patients made up the majority, 55.91%.

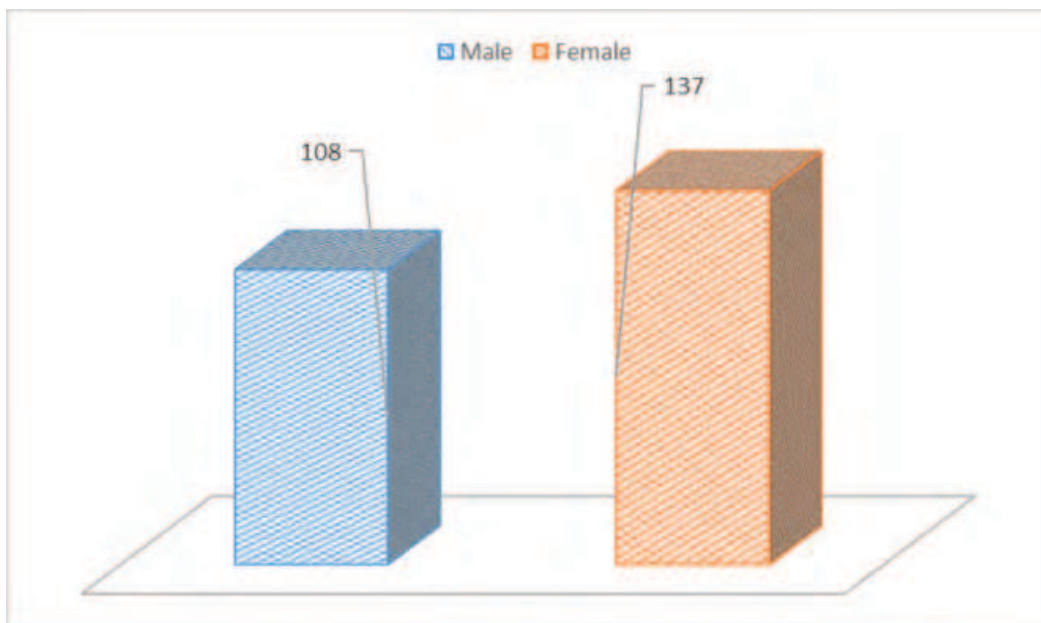


Figure 3: Number of High TSH patients (Gender wise)

It should be pointed out that females showed a higher vulnerability to congenital hypothyroidism, indicating a higher incidence within this gender. The majority of the samples, or about 87.5% of the total, came from infants who were delivered following a full-term gestation, according to

an analysis of the sample collection. On the other hand, 12.5% or so of the samples came from premature babies. Due to the prevalence of congenital hypothyroidism instances in both full-term and premature babies, independent of gestational age, it is crucial to screen for this condition.

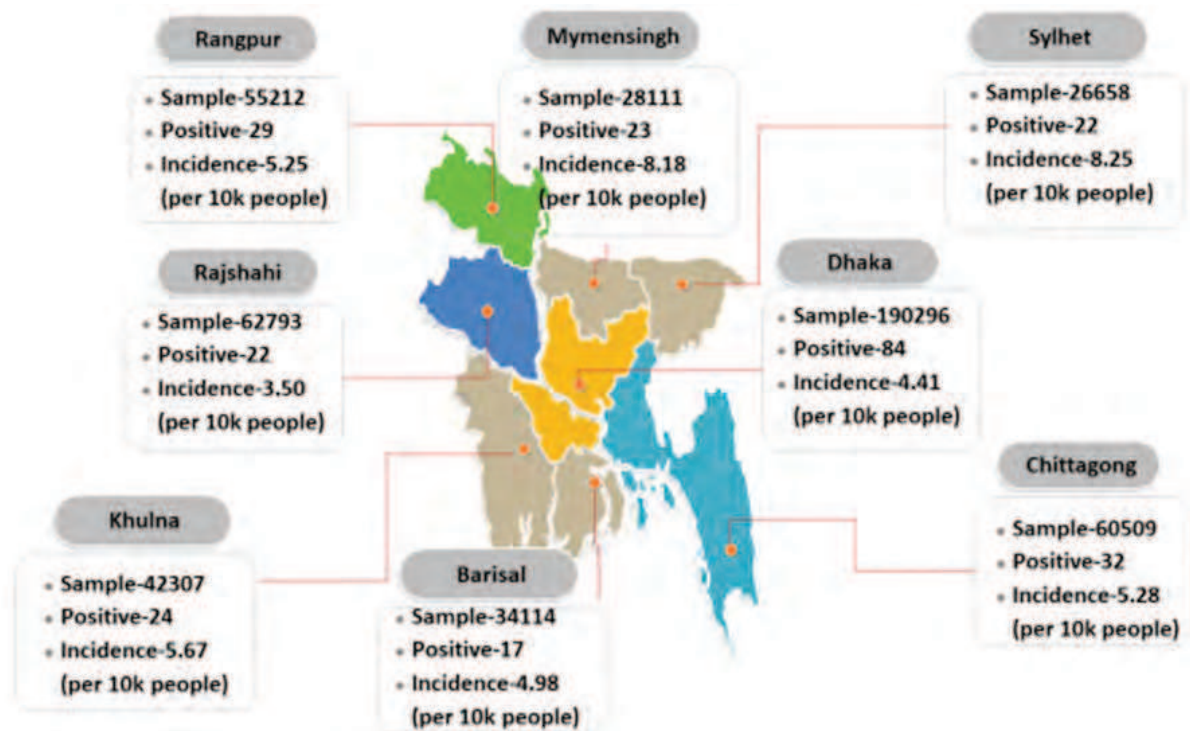


Figure 4: Incidence of CH in different divisions

Congenital hypothyroidism (CH) is prevalent in the Mymensingh division than any other division, although it is less common in the Rajshahi division.

DISCUSSION

Robert Guthrie (Father of newborn screening) started newborn screening in 1960 (16). Since then screening programs have been accepted by most of the developed countries. Screening for Congenital hypothyroidism is comprehensive to the developed countries (17). Because of the depressed economy of the developing countries, this is different in developing countries.

About 6,483 babies were born per day in Bangladesh. More than 85% of the delivery occurred at home. So, it is very challenging to bring all of the babies under the project. Lack of public awareness: many guardians are not interested in giving samples. For those meetings, seminars are organized and leaflets, banners, posters are distributed for public awareness. Efforts are given to make a separate institution for newborn screening.

Present study was done by DELFIA because of its higher sensitivity. Sensitivity is increased due to the Dissociation Enhancement principle. There is a big difference between

excitation and emission peaks that can decrease signal to noise ratio. Excitation occurs at 320 nm or 340 nm and fluorescence is measured at 615 nm (18). Standard cut off of cord blood samples was $20\mu\text{U/mL}$ (15).

A higher prevalence of CH was found in the samples, where about 274 instances had TSH values that were higher than the recommended cut-off levels. The incidence rate was 1:1825 which is greater than U.S. standards (1 in 2000 live births). Though African American babies have a reduced incidence of 1:10,000 live births (19). Bangladesh may have a greater frequency of CH due to a number of variables. Regional genetic variances, environmental influences, iodine intake levels, and discrepancies in healthcare access are a few of these issues. Gaining a deeper understanding of the variables influencing the elevated prevalence in Bangladesh requires a thorough analysis that takes these elements into account.

The incidence of CH is higher in girls than in boys, according to numerous research (20,21). The statistics gathered from the 274 positive cases show that there is a gender gap, with female newborns making up 55.91% of the total. The fact that

CH is more common in females highlights the necessity for specialized screening and intervention measures to guarantee early detection and effective care. Girls have a higher prevalence of CH, which is still under investigation. It is thought that genetic and hormonal variables may play a role in this discrepancy. A few elements that call for more investigation and study include the impact of sex hormones, changes in thyroid hormone metabolism pathways, and X-chromosome-related gene expressions (22).

It was discovered that the weights of the congenital hypothyroid neonates who tested positive were about typical. Neonatal infants who were born at full term often weighed little more than 3000g. Premature newborns, however, showed maximum weights between 1700g and 2100g. The fact that there is no correlation between weight and the development of CH is further highlighted by the fact that these weight ranges include a wide variety of newborn weights. It is important to take into account other risk factors when identifying neonates at risk because there is no association between baby weight and CH. The development of CH is greatly influenced by factors like genetic predisposition, family history, maternal thyroid health, and iodine intake during pregnancy.

CH is more common among newborns born in settings close to hilly terrain. Notably, the wider Mymensingh region exhibits a relatively higher prevalence of CH compared to locations further from these geographical factors, despite being situated close to hills and away from sea coastlines. Further research is needed to determine the root causes of this regional variance, including any potential variations in environmental influences and inherited traits. Iodine deficiency affects 38% of the nation's population, according to a report that The Financial Express published on April 17, 2019. This study, which looked at 60 million people, shows the scope of the issue in Bangladesh. Iodine deficiency was once common in highland districts like Rangpur and Mymensingh, where a sizable section of the population lived. Iodine insufficiency has returned despite the fact that things have improved since 1989 due to recent difficulties like the high cost of iodized salt. Congenital hypothyroidism can arise as a result of iodine shortage. Iodine deficiency during pregnancy can affect the mother's and the fetus's ability to

produce thyroid hormones, which raises the risk of CH. The higher frequency of CH that has been found in places like greater Mymensingh may be related to the prevalence of iodine shortage in such areas and its effects on thyroid function (23).

According to the report of the World Bank literacy rate of Bangladesh is 73.91%. About 63.37% of our population lives in rural areas (23). About 58% of urban and 74% of rural males above 60 years' male are literate, while only 24% of urban and 12% of rural females of this age group are literate. In the 10-14 years aged group, 74% of rural boys and 81% of rural girls are literate. This illiterate population is not interested in giving samples of newborn babies. They are not familiar with the demerits of CH. Their opinion was, their baby is healthy. Without any government policy or consciousness among mass people, it is very hard to collect the samples.

CONCLUSION

About 500,000 samples from neonates across Bangladesh were successfully gathered as part of this extensive screening effort, allowing for the early identification and treatment of congenital hypothyroidism (CH) cases. The program's success is attributed to its alliances with 839 institutions and skilled nurses. Data shows no link between newborn weight and CH development, emphasizing risk factors and female babies' higher prevalence. The study reveals regional variations in CH frequency, with higher frequency in Mymensingh region. Iodine supplementation programs are crucial due to iodine deficiency in Bangladesh, affecting 38% of the population. Raising awareness about congenital hypothyroidism and early screening is crucial for combating the condition and improving the health of babies in Bangladesh.

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