



Cross-sectional Study

Prevalence of transient congenital hypothyroidism among neonates[☆]Ezatollah Rafiei Alavi^{a,*}, Niloofar Rafiei^b, Romina Rafiei^c, Ermia Farokhi^d^a Department of Pathology, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran^b Student Research Committee, Iran University of Medical Sciences, Tehran, Iran^c Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran^d Liver Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
 Congenital
 Hypothyroidism
 Thyroid hormone
 Maternal
 Neonates
 Transient

ABSTRACT

Objective: Persistence of low levels of thyroid hormone from the time of birth is one of the significant causes of the mental retardation. The aim of this study was to determine the prevalence of transient congenital hypothyroidism among neonates in (XXX).

Methods: This cross-sectional study, neonates aged 3–5 days who were referred to our center for checkup were screened for thyroid stimulating hormone. Those with TSH < 5mIU/l were, infants were subjected to retesting after one week for TSH and T4 levels. A questionnaire consisting of test results, demographic characteristics, place of sampling, gender, need for re-sampling after the second week for TSH level, birth weight, type of hypothyroidism and prematurity was filled for all the neonates.

Results: Of 3600 neonates screened, 126 were presented with had TSH above 5 mIU/l, of which 7 had high TSH and low T4 and were diagnosed with transient hypothyroidism (5.3%). The mean weight of the neonates with hypothyroidism of significantly lower, $p = 0.001$. However, the type of delivery was not associated with the prevalence of hypothyroidism, $p = 0.999$. The relationship between maternal hypothyroidism, preterm birth and intake of antithyroid drugs and transient hypothyroidism was statistically significant, $p < 0.001$, respectively.

Conclusions: The incidence of congenital hypothyroidism was 1 in 514 births and was significantly associated with preterm birth, mean weight, maternal hypothyroidism and intake of antithyroid drugs. Routine screening in high prevalence regions are therefore importance, considering the associated factors.

1. Introduction

Congenital hypothyroidism can be transient or permanent where permanent hypothyroidism is characterized by lifetime deficiency of thyroid hormone, requiring lifelong supplementations. In the cases of transient hypothyroidism, the levels of thyroid hormones return back to normal within few months [1]. During the neonatal period, the reference range of thyroid stimulating hormone (TSH), T3 and T4 is different in that of adults. Thyroid hormones are likely to upsurge during first 24–36 h until 2–3 days of the birth [2]. Transient hypothyroidism is defined as deficiency of thyroid hormone along with weak or absent surge of TSH [3].

Screening of neonates and early detection of congenital hypothyroidism followed by appropriate management can prevent mental retardation in these children [4]. Persistence of hypothyroidism in confirmatory tests might call for the requirement of replacement therapy

[5]. Excessive intake of iodine by pregnant mother can suppress the production of thyroid hormone in fetus and the reduce levels of thyroid hormones and impair mental development in later life. Treatment of congenital hypothyroidism in 2–4 weeks of birth is associated with improved cognitive abilities [6]. Other risk factors that can contribute to transient hypothyroidism include low birth weight, premature birth, maternal intake of anti-thyroid agents and genetic variations [5].

The prevalence of hypothyroidism is reported with great variability due to geographical and ethnical variations, screening protocol of thyroid hormone and genetic diversity. Its prevalence in Iran is reported higher than other regions [7]. A cross-sectional study conducted in the central part of Iran on more than 400,000 neonates reported that the prevalence transient congenital hypothyroidism in this region is 1 in 294 live births [8]. Its prevalence in Mazandaran province (Northern Iran) is reported to be 1 in 491 live births [9].

The aim of this study is to evaluate the prevalence of transient

[☆] The study was approved by the Ethics Committee of Khorramabad University of Medical Sciences.

* Corresponding author. Lorestan University of Medical Sciences, Khorramabad, Iran.

E-mail address: se.rafieialavi@gmail.com (E.R. Alavi).

<https://doi.org/10.1016/j.amsu.2021.103083>

Received 27 October 2021; Received in revised form 14 November 2021; Accepted 16 November 2021

Available online 22 November 2021

2049-0801/© 2021 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

congenital hypothyroidism in (XXX) and associated factors.

2. Methods

This cross-sectional study was conducted in (XXX) on 3600 neonates who were screened for hypothyroidism within 3–5 days of their birth (by TSH measurement on a filter paper with blood spots), referred to our center for the diagnosis of hypothyroidism. The initial levels of TSH among these infants were evaluated and the initial levels were seen as TSH >5 mIU/L. Written consent was obtained from all the parents for the participation in the study. Neonates with congenital malformations, inadequate blood samples and those who did not consent to participate were excluded from the study.

In the initial stage, a sampling form was prepared for all the infants who were to be screened. Infants with TSH in bloodspot screening test >20mIU/L were suspected positive for hypothyroidism. The neonate's demographic characteristics, place of sampling, gender, need for re-sampling after the second week for TSH level, birth weight, type of hypothyroidism and preterm birth (less than 37 weeks of gestational age) was filled in the form. The TSH and T4 was measured using ELISA kit purchased from (XXX).

Blood sample for TSH measurement was obtained using capillary blood sampling with chemiluminescence immunoassay and if the serum TSH serum level was lower than 5mIU/L, an infant was considered healthy. If the TSH level was between 5 and 9.9 mIU/L and 10–19.9 mIU/L and more than 20 mIU/L, the result of the screening test was considered suspicious and further analysis of TSH and T4 test from venous blood for definitive diagnosis of neonatal hypothyroidism was performed. In infants with an increase in TSH levels and reduction in T4 transient hypothyroidism was diagnosed. Following two weeks of first measurement, TSH and T4 were measured again to confirm the diagnosis of CH where TSH >10mIU/L and T4 < 6.5 µg/dl cutoff was used, based on the previous studies [8].

The data was computerized and statistically analyzed using SPSS v22. Descriptive statistics were used to describe the data using mean and frequency. Chi-square test was used to analyze the data and p-value <0.05 was considered to be statistically significant.

Unique identifying number is: researchregistry7298.

This cross-sectional study has been reported in accordance with STROCSS 2021 guideline [10].

3. Results

Of 3600 neonates, 126 had TSH, of which 109 had TSH between 5 and 9.9, 16 had TSH between 10 and 19.9, and 1 had TSH above 20. Intravenous samples were taken and TSH and T4 levels were re-evaluated. Out of 126 patients, 7 had high TSH and low T4, in whom the diagnosis of transient hypothyroidism was made (Table 1).

Thus, the prevalence of non-transient hypothyroidism is 7 out of 3600 infants (0.002%), and the prevalence of transient hypothyroidism is 126 cases out of 3600 infants (3.5%) (Table 2).

In this study, the relationship between transient neonatal hypothyroidism and maternal history of hypothyroidism was investigated. Of the 3600 neonates studied, 69 had a history of maternal hypothyroidism and in 126 infants with transient hypothyroidism, there were 15 cases of

Table 1

Frequency distribution of 3-5-day old infants in the first six months of the year based on TSH level.

Number TSH level	Number	%
5>	3474	96.5
5<TSH<9.9 mIU/L	109	3.03
10<TSH<19.9 mIU/L	16	0.44
TSH>20 mIU/L	1	0.03
Total	3600	100

Table 2

Frequency distribution of infants with early TSH impaired based on TSH and retest measured after two weeks.

Type of hypothyroidism	TSH and T4 level	Number	%
Non-transient hypothyroidism	TSH>5 mIU/L, T4<66 µg/dL	7	5.6
Transient hypothyroidism	TSH<5 mIU/L, T4>66 µg/dL	119	94.4
Total		126	100

maternal hypothyroidism. The correlation between maternal hypothyroidism and transient hypothyroidism was statistically significant, $p < 0.001$ (Table 3).

It was found that out of 3600 neonates studied, 75 mothers were consuming antithyroid agents for the treatment of hyperthyroidism. Of these 75 cases, 60 had healthy infants and 15 infants had transient hypothyroidism. The relationship between transient hypothyroidism and maternal antithyroid agent consumption was statistically significant, $p < 0.001$ (Table 4).

In this study, the correlation of transient hypothyroidism and preterm birth was investigated, of which 132 out of 3600 neonates were premature infants. Out of 126 infants with transient hypothyroidism, 21 were premature infants. The prevalence of transient hypothyroidism in premature infant was significantly correlated $p < 0.001$ (Table 5).

In this study, the mean weight of healthy neonates was 3269 g and the mean weight of neonates with transient hyperthyroidism was 3050 g. The mean weight of the neonates with hypothyroidism of significantly lower, $p = 0.001$ (Table 6).

Of 126 infants with transient hypothyroidism, 60 infants were born with normal delivery and 66 infants were born by cesarean section. The type of delivery and hypothyroidism was not significantly correlated, $p = 0.999$ (Table 7).

4. Discussion

Hypothyroidism is one of the most common preventable causes of mental retardation. Immediately following the birth, it is usually asymptomatic and late diagnosis can delay the treatment, which can lead to mental retardation. Birth screening is performed in case of infection with timely initiation of mental retardation treatment. Congenital hypothyroidism may be monotonous or familial. In some cases, thyroid hormone deficiency is severe, and symptoms appear in the first week of life. In others, the deficiency is less severe, and the manifestations appear with a delay of several months.

Of the 3600 neonates screened in our study, 7 were diagnosed with transient hypothyroidism. The prevalence of transient hypothyroidism is 1 in 4000 cases, globally. However, its prevalence can vary geographically and with the intake of iodine.

In this study, 126 neonates out of 3600 neonates had 5mIU/L >TSH who were referred to our center and 7 of these were identified as transient hypothyroidism based on their TSH and T4 levels. As a result of the above study, hypothyroidism was greatly prevalent in our population.

In this study, 69 infants had a history of maternal hypothyroidism, of which 15 infants had transient hypothyroidism. The presence of TSH receptor blocking antibodies in mothers under antithyroid drug treatment can cause hypothyroidism in infants [11]. Salt, bread and other foods significantly reduce the prevalence of cretinism, but iodine deficiency is still the most common cause of preventable mental retardation in infants. Antithyroid drugs like propylthiouracil and methimazole can cross the placenta and cause thyroid disorders in neonates [12]. Among neonates presented with hypothyroidism, 1/6th was preterm birth. The thyroid gland develops in the third week of pregnancy from the floor of the throat and after the development from the embryonic period it is able to make thyroid hormone. The development of the thyroid gland is controlled by a set of transcription factors called TTF [13]. In some infants, due to mutations in this factor, thyroid dysgenesis or dysmorphogenesis may occur and its prevalence is higher in premature infants

Table 3

Frequency distribution and correlation of 3-5-day old infants in the first six months of the year based on hypothyroidism and family history.

Hypothyroidism History	Yes		No		Total		P-value
	Number	%	Number	%	Number	%	
Yes	15	11.9	54	1.6	69	1.9	<0.001 ^a
No	111	88.1	3420	98.4	3531	98.1	
Total	126	100	3474	100	3600	100	

^a Significant value.**Table 4**

Frequency distribution and correlation of 3-5-day old infants based on hypothyroidism and history of thyroid drug use by mother.

Hypothyroidism Taking drug	Yes		No		Total		P-value
	Number	%	Number	%	Number	%	
Yes	15	11.9	60	1.7	75	2.1	<0.001 ^a
No	111	88.1	3414	96.3	3525	97.9	
Total	126	100	3474	100	3600	100	

^a Significant value.**Table 5**

Frequency distribution and correlation of 3-5-day old infants based on hypothyroidism and preterm labor.

Hypothyroidism Premature	Yes		No		Total		P-value
	Number	%	Number	%	Number	%	
Yes	21	16.7	111	3.2	132	3.7	0.001*
No	105	88.3	3363	96.8	3468	96.3	
Total	126	100	3474	100	3600	100	

Table 6

Correlation of mean neonatal weight in people with hypothyroidism with healthy individuals.

neonatal weight	Number	Mean	Standard deviation	t	p-value
Health	3474	3269	476	3.48	<0.001 ^a
Hypothyroidism	126	3050	÷		

^a Significant difference.**Table 7**

Frequency distribution and correlation of 3-5-day old infants based on hypothyroidism and type of delivery.

Hypothyroidism Type of delivery	Yes		No		P-Value
	Number	%	Number	%	
Natural childbirth	60	47.6	1650	47.5	0.999
Cesarean	66	52.4	1821	52.5	
Total	126	100	3471	100	

which may be one of the reasons for the higher prevalence of hypothyroidism in preterm infants [14]. Srinivasan et al. [15] indicated that transient hypothyroidism might be common in preterm infants however, the risk development of congenital hypothyroidism might be same as term infants. Similarly, Mengreli, et al. [16] reported higher incidence of transient hyperthyroidism in preterm infants than term infants. A study by Medda et al. [17] also reported preterm birth as an independent risk factor of congenital hypothyroidism.

In a study conducted in Babol, Iran, by Haghshenas et al. [18] the incidence of transient hypothyroidism was reported as 5.7 per 10,000 births. In a study conducted in Kashan on 3005 infants, the prevalence of hypothyroidism was reported 1 in 303 live births [19]. In our study, the prevalence of hypothyroidism was approximately 1 in 514 live births. The incidence from a screening program conducted from 2006 to 2014 in Tehran, Iran was reported to be 2 in 1000 live birth [20]. In a study

conducted in Isfahan, the prevalence of hypothyroidism was 1 in 370 live births and a significant relationship between low birth weight and hypothyroidism was reported similar to our study [21].

In a study conducted at Shahid Beheshti University, the relationship between hypothyroidism and cesarean delivery was reported to be significant, which is contrary to our findings. A study in Greece conducted from 1995 to 2005, the prevalence of hypothyroidism was 1 in 1800 live births, which was estimated to be 1 in 3957 live births. Geographical variations and intake of iodine can be the reasons of these discrepancies. Neonatal hypothyroidism screening program has been implemented in Iran since 2006 that aims to provide early diagnosis of CH during 3rd and 5th day of the birth [22].

Some of the limitations of our study include the lack complete family history, genetics of the neonates and data regarding the treatment. Confounding variables like iodine deficiency and excessiveness, thyroperoxidase or thyrotropin receptor gene-sequence variations and thyroid imaging were not considered in this study.

5. Conclusion

The incidence of transient hypothyroidism in our study was 5.3% which was significantly correlated with the birth weight, maternal hypothyroidism, and intake of antithyroid drugs. Considering the risk factors and associated parameters, early screening in high prevalence areas is significant in the management of the disease and prevent development-related disorders.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Sources of funding

No funding was secured for this study.

Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent

Not applicable.

Author contribution

Dr. Ezatollah Rafiei Alavi: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Niloofar Rafiei: Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Dr. Romina Rafiei and Dr. Ermia Farokhi: Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Registration of research studies

Name of the registry: ResearchRegistry

Unique Identifying number or registration ID: 7298

Hyperlink to the registration (must be publicly accessible): <https://www.researchregistry.com/register-now#home/registrationdetails/617717a32efae8001e40c94c/>

Guarantor

Dr. Ezatollah Rafiei Alavi.

Human and animal rights

No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

Consent for publication

Informed consent was obtained from each participant.

Availability of data and materials

All relevant data and materials are provided with in manuscript.

Funding

None.

Declaration of competing interest

The authors deny any conflict of interest in any terms or by any means during the study. All the fees provided by research center fund and deployed accordingly.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2021.103083>.

References

- [1] S.R. Rose, R.S. Brown, AAO Pediatrics, A.T. Association, Update of newborn screening and therapy for congenital hypothyroidism, *Pediatrics* 117 (6) (2006) 2290–2303.
- [2] M. Mutlu, G. Karagüzel, Y. Aliyazicioğlu, İ. Eyüpoğlu, A. Ökten, Y. Aslan, Reference intervals for thyrotropin and thyroid hormones and ultrasonographic thyroid volume during the neonatal period, *J. Matern. Fetal Neonatal Med.* 25 (2) (2012) 120–124, <https://doi.org/10.3109/14767058.2011.561894> [published Online First: Epub Date].
- [3] N. Kanike, A. Davis, P.S. Shekhawat, Transient hypothyroidism in the newborn: to treat or not to treat, *Transl. Pediatr.* 6 (4) (2017) 349–358, <https://doi.org/10.21037/tp.2017.09.07> [published Online First: Epub Date].
- [4] N. Taei, M. Faraji Goodarzi, M. Safdari, A. Bajelan, A 10-year prevalence of congenital hypothyroidism in Khorramabad (Urban Western Iran), *Molecular genetics & genomic medicine* 7 (8) (2019) e817.
- [5] O.E.M. Bekhit, R.M. Yousef, Permanent and transient congenital hypothyroidism in fayoum, Egypt: a descriptive retrospective study, *PLoS One* 8 (6) (2013), e68048, <https://doi.org/10.1371/journal.pone.0068048> [published Online First: Epub Date].
- [6] A. Ahmet, M.L. Lawson, P. Babyn, A.C. Tricco, Hypothyroidism in neonates post-iodinated contrast media: a systematic review, *Acta Paediatr.* 98 (10) (2009) 1568–1574, <https://doi.org/10.1111/j.1651-2227.2009.01412.x> [published Online First: Epub Date].
- [7] N. Taei, M.F. Goodarzi, M. Safdari, A. Bajelan, Pentology of cantrell in full term neonate, *AJP reports* 9 (2) (2019) e144.
- [8] M. Ghasemi, M. Hashemipour, S. Hovsepian, et al., Prevalence of transient congenital hypothyroidism in central part of Iran, *J. Res. Med. Sci. : the official journal of Isfahan University of Medical Sciences* 18 (8) (2013) 699–703.
- [9] Z. Beheshti, R. Rezaei, A. Alipour, M. Kosarian, S. Saatsaz, A 7-year study on the prevalence of congenital hypothyroidism in northern Iran, *Electron. Physician* 10 (4) (2018) 6689–6696, <https://doi.org/10.19082/6689> [published Online First: Epub Date].
- [10] R. Agha, G. Mathew, J. Albrecht, et al., Stross 2021: strengthening the reporting of cohort, cross-sectional and case-control studies in surgery, 2021, 103026.
- [11] E. Medda, A. Olivieri, M.A. Stazi, et al., Risk factors for congenital hypothyroidism: results of a population case-control study (1997–2003) 153 (6) (2005) 765, <https://doi.org/10.1530/eje.1.02048> [published Online First: Epub Date].
- [12] O. Diav-Citrin, A. Ornoy, Teratogen update: antithyroid drugs—methimazole, carbimazole, and propylthiouracil, *Teratology* 65 (1) (2002) 38–44.
- [13] M. Castanet, S.-M. Park, A. Smith, et al., A novel loss-of-function mutation in TTF-2 is associated with congenital hypothyroidism, thyroid agenesis and cleft palate, *Hum. Mol. Genet.* 11 (17) (2002) 2051–2059.
- [14] M.C. Vigone, S. Caiulo, M. Di Frenna, et al., Evolution of thyroid function in preterm infants detected by screening for congenital hypothyroidism, *J. Pediatr.* 164 (6) (2014) 1296–1302, <https://doi.org/10.1016/j.jpeds.2013.12.048> [published Online First: Epub Date].
- [15] R. Srinivasan, S. Harigopal, S. Turner, T. Cheetham, Permanent and transient congenital hypothyroidism in preterm infants, *Acta Paediatr.* 101 (4) (2012) e179–e182, <https://doi.org/10.1111/j.1651-2227.2011.02536.x> [published Online First: Epub Date].
- [16] C. Mengreli, C. Kanaka-Gantenbein, P. Girginoudis, et al., Screening for congenital hypothyroidism: the significance of threshold limit in false-negative results, *J. Clin. Endocrinol. Metab.* 95 (9) (2010) 4283–4290, <https://doi.org/10.1210/jc.2010-0057> [published Online First: Epub Date].
- [17] E. Medda, A. Olivieri, M.A. Stazi, et al., Risk factors for congenital hypothyroidism: results of a population case-control study (1997–2003), *Eur. J. Endocrinol.* 153 (6) (2005) 765–773.
- [18] M. Haghshenas, Y.Z. Pasha, M. Ahmadpour-Kacho, S. Ghazanfari, Prevalence of permanent and transient congenital hypothyroidism in Babol City-Iran, *Med. Glas.* 9 (2) (2012) 341–344.
- [19] M.H.A. Taghavi, Z. Mosaiiebi, et al., Screening for congenital hypothyroidism in Kashan, Iran, *Journal of Mazandaran University of Medical Sciences* 15 (2005).
- [20] M. Taheri-Soodejani, H. Fallahzadeh, M.H. Lotfi, A. Dehghani, A. Ghaderi, Screening for congenital hypothyroidism in Shahr-e-Kord: prevalence and recall rate during 2006–2014, *Fez Journal of Kashan University of Medical Sciences* 20 (6) (2017) 574–580.
- [21] M. Hashemipour, M. Amini, R. Iranpour, et al., Prevalence of congenital hypothyroidism in Isfahan, Iran: results of a survey on 20,000 neonates, *Horm. Res.* 62 (2) (2004) 79–83, <https://doi.org/10.1159/000079392> [published Online First: Epub Date].
- [22] Y. Veisani, K. Sayehmiri, S. Rezaeian, A. Delpisheh, Congenital hypothyroidism screening program in Iran; a systematic review and metaanalysis, *Iran. J. Pediatr.* 24 (6) (2014) 665–672.