

Incidence of congenital hypothyroidism by gestational age: a retrospective observational study

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Background: Congenital hypothyroidism (CH) is the leading cause of preventable physical and intellectual disabilities. This study aimed to assess the incidence and clinical characteristics of CH in newborns.

Methods: We retrospectively reviewed the medical records of all newborns delivered at the Pusan National University Hospital between January 2011 and March 2021. The incidence of CH was compared according to gestational age, birth weight, and small for gestational age (SGA). The patients aged ≥ 3 years who could not maintain normal thyroid function and required levothyroxine treatment were diagnosed with permanent CH. Logistic regression analysis was performed to compare CH risks.

Results: Of 3,722 newborns, 40 were diagnosed with CH (1.07%). Gestational age and birth weight were significantly associated with CH incidence. The odds ratios (ORs) of CH in infants delivered at 32–37, 28–31, and < 28 weeks were 2.568 (95% confidence interval [CI], 1.141–5.778), 5.917 (95% CI, 2.264–15.464), and 7.441 (95% CI, 2.617–21.159) times higher, respectively, than those delivered at term. The ORs of CH in infants weighing 1,500–2,499 g, 1,000–1,499 g, and $< 1,000$ g were 4.664 (95% CI, 1.928–11.279), 11.076 (95% CI, 4.089–29.999), and 12.544 (95% CI, 4.350–36.176) times greater, respectively, than those in infants weighing $\geq 2,500$ g. The OR of CH was 6.795 (95% CI, 3.553–13.692) times greater in SGA than in non-SGA infants.

Conclusion: The CH incidence in South Korea has increased significantly compared with that in the past. Gestational age, birth weight, and SGA were significantly associated with CH incidence.

Keywords: Congenital hypothyroidism; Gestational age; Incidence; Premature infant; Retrospective studies; Small for gestational age infant

Introduction

Congenital hypothyroidism (CH) is the leading cause of preventable physical and intellectual disabilities and is a common endocrine disease in pediatric patients [1,2]. Generally, patients with CH show no symptoms at birth; however, owing to the critical period of thyroid hormone-sensitive neurocognitive development during the first 3 years after birth, rapid diagnosis and treatment

are required [3-6]. Newborn screening for CH, first introduced in 1972 in Quebec (Canada) and Pittsburg (United States), has become a routine practice worldwide [7,8]. The global incidence of CH is one in 3,000 to 4,000 newborns and has increased to one in 1,600 to 2,600 newborns in certain regions, such as Quebec and Massachusetts (United States) [1,9-11].

In South Korea, approximately 3,707,773 newborns underwent screening between 1991 and 2005 through the Maternal and

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Child Health Project implemented by the government. Of these, 718 newborns were diagnosed with CH, with an incidence of one in 5,164 [12]. Since 2004, the Korean government has extended the project's scope to include all newborns. However, to date, no study has reported the incidence of CH in South Korea. Thus, this study aimed to retrospectively analyze the incidence and clinical features of CH in newborns in a South Korean hospital.

Methods

Ethical statements: The Institutional Review Board (IRB) of Pusan National University Hospital (PNUH) approved this study (IRB No: 2106-020-104) and waived the requirement for informed consent as this study analyzed anonymized patient data.

1. Participants

This retrospective study included 3,722 newborns delivered at PNUH between January 2011 and March 2021.

2. Methods

Data on gestational age, birth weight, sex, age, neonatal intensive care unit (NICU) hospitalization, morbidity, and maternal history were collected from the medical records of each patient. According to gestational age, patients were categorized into term (≥ 37 weeks), moderate-to-late preterm (32–37 weeks), very preterm (28–31 weeks), and extremely preterm (< 28 weeks) infants. Patients were also classified by birth weight as follows: normal-birth weight infants ($\geq 2,500$ g), low birth weight infants (LBWIs; 1,500–2,499 g), very low birth weight infants (VLBWIs; 1,000–1,499 g), and extremely low birth weight infants (ELBWIs; $< 1,000$ g). An infant with a birth weight less than the third percentile of the corresponding gestational age based on Korean references for birth weight by gestational age and sex was considered small for gestational age (SGA) [13].

As part of the newborn screening, levels of thyroid-stimulating hormone (TSH) and tetraiodothyronine (T₄), as well as serum TSH and free thyroxine (FT₄), were measured. CH was defined as TSH of ≥ 20 μ IU/mL or T₄ of < 11.0 μ g/dL on newborn screening, or TSH of ≥ 10 μ IU/mL or FT₄ of < 0.8 ng/dL in a serum thyroid function test (TFT) analyzed by radioimmunoassay (Shinjin Medic Inc., Goyang, Korea). Newborn screening results at this hospital could only be obtained after 2 weeks; thus, serum TFT was additionally performed for preterm infants and newborns in the NICU 7 days after delivery. A serum TFT was performed prior to treatment for all infants diagnosed with CH via

newborn screening.

Imaging included neck ultrasonography and thyroid scans with technetium-99m pertechnetate. The patients with ≥ 3 years of age who were prescribed levothyroxine were diagnosed with permanent CH and those who showed spontaneous recovery were diagnosed with transient hypothyroidism. Among the patients diagnosed with transient hypothyroidism, those who did not require levothyroxine treatment but had TSH levels of 5 to 10 μ IU/mL and normal FT₄ concentrations were diagnosed with subclinical hypothyroidism.

3. Statistical analysis

Categorical variables are presented as counts and percentages. The chi-square test was used to compare differences in the incidence of CH according to patient groups. Multiple logistic regression analysis was performed to compare the risk of CH according to participant characteristics. Statistical analyses were performed using the IBM SPSS ver. 23 for Windows (IBM Corp., Armonk, NY, USA), and statistical significance was set at $p < 0.05$.

Results

A total of 3,722 newborns were delivered at PNUH during the study period. Of these, 95 (2.55%) had either an abnormal newborn screening or abnormal serum TFT results; therefore, they underwent an additional serum TFT. Finally, 40 of 3,722 patients (1.07%) diagnosed with CH were included in this study, with an incidence of one in 93 newborns (Fig. 1).

Of the 40 patients with CH, 24 were female (60.0%). There were 31 (77.5%) preterm infants, with predominance of moderate-to-late preterm infants ($n = 17$, 42.5%). Among the 40 patients, most were LBWIs ($n = 17$, 42.5%). Fourteen SGA infants (35.0%) and 34 NICU infants (85.0%) were admitted due to premature birth or disease. Regarding comorbidities, bronchopulmonary dysplasia was the most common ($n = 8$, 20.0%), followed by intraventricular hemorrhage ($n = 4$, 10.0%) and sepsis ($n = 2$, 5.0%). Pre-eclampsia was the most common maternal history ($n = 10$, 25.0%), followed by diabetes mellitus ($n = 7$, 17.5%) and thyroid disease ($n = 3$, 7.5%). Of the mothers with thyroid disease, two had hypothyroidism and one had hyperthyroidism (Table 1).

Logistic regression analysis was performed to identify factors related to the incidence of CH. Compared with that in term infants, the risk of CH was 2.568, 5.917, and 7.441 times higher in moderate-to-late preterm (32–37 weeks), very preterm (28–31 weeks), and extremely preterm (< 28 weeks) infants, respectively (95% confidence interval [CI], 1.141–5.778, $p = 0.023$; 95% CI, 2.264–15.464, $p < 0.001$; 95% CI, 2.617–21.159, $p < 0.001$, respectively).

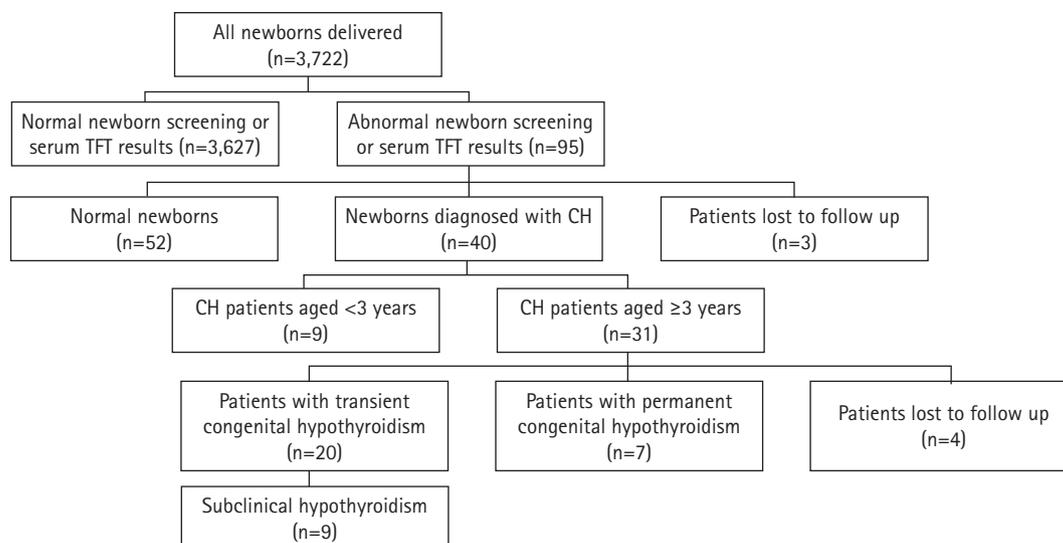


Fig. 1. Flowchart of patient inclusion and exclusion. Newborns with congenital hypothyroidism (CH) delivered at Pusan National University Hospital between January 2011 and March 2021 are included in this study. TFT, thyroid function test.

Table 1. Characteristics of CH patients

Characteristic	Data
No. of patients	40
Sex	
Male	16 (40.0)
Female	24 (60.0)
Gestational age (wk)	
Term, ≥ 37	9 (22.5)
Preterm	
Moderate-to-late preterm, 32–37	17 (42.5)
Very preterm, 28–31	8 (20.0)
Extremely preterm, < 28	6 (15.0)
Birth weight (g)	
Normal, $\geq 2,500$	7 (17.5)
LBWIs, 1,500–2,499	17 (42.5)
VLBWIs, 1,000–1,499	9 (22.5)
ELBWIs, $< 1,000$	7 (17.5)
SGA	14 (35.0)
NICU hospitalization	34 (85.0)
Morbidity	
None	25 (62.5)
Intraventricular hemorrhage	4 (10.0)
Bronchopulmonary dysplasia	8 (20.0)
Sepsis	2 (5.0)
Others ^{a)}	3 (7.5)
Maternal history	
None	20 (50.0)
Thyroid disease	3 (7.5)
Preeclampsia	10 (25.0)
Diabetes mellitus	7 (17.5)
Hypertension	1 (2.5)

Values are presented as number only or number (%).

CH, congenital hypothyroidism; LBWIs, low birth weight infants; VLBWIs, very low birth weight infants; ELBWIs, extremely low birth weight infants; SGA, small for gestational age; NICU, neonatal intensive care unit.

^{a)}Includes persistent pulmonary hypertension of the newborn, hypoxic brain damage, and omphalitis.

The incidence of CH was 0.48% ($n = 9$, one in 208) in term infants and 1.68% ($n = 31$, one in 60) in preterm infants ($p < 0.001$) (Table 2).

The risk of CH was significantly higher in LBWIs than in those weighing $\geq 2,500$ g. In particular, LBWIs (1,500–2,499 g), VLBWIs (1,000–1,499 g), and ELBWIs ($< 1,000$ g) were at 4.664, 11.076, and 12.544 times higher risk of developing CH, respectively (95% CI, 1.928–11.279, $p = 0.001$; 95% CI, 4.089–29.999, $p < 0.001$; 95% CI, 4.350–36.176, $p < 0.001$, respectively). Moreover, the risk of CH was 6.975 times higher in SGA infants than in non-SGA infants (95% CI, 3.553–13.692, $p < 0.001$) (Table 2).

During the follow-up period for infants with ≥ 3 years of age, 27 of the 31 patients diagnosed with CH were reexamined, and thyroid ultrasonography and thyroid scans were performed in 22 of the 27 patients. Based on the ultrasonography results, thyroid hypoplasia was detected in three of the 22 patients. Decreased uptake was observed in three of the 21 patients who underwent thyroid scans; the thyroid scan result of one patient was excluded because it was performed on day 19 of levothyroxine administration. Of the three patients with decreased uptake, one had normal thyroid ultrasonography findings, and thyroid hypoplasia was confirmed in the other two patients. Normal thyroid hormone levels after levothyroxine discontinuation were maintained in 20 patients, nine of whom were diagnosed with subclinical hypothyroidism. Seven patients had permanent CH (Table 3).

Thus, among the 2,658 children who were delivered at PNUH during the study period and were ≥ 3 years old, the incidence of transient CH was one in 215 term infants (six of 1,291, 0.46%) and one in 98 preterm infants (14 of 1,367, 1.02%), whereas the inci-

Table 2. Results of logistic regression analysis of the effects of participant characteristics on CH incidence

Characteristic	CH, n (%)	Non-CH, n	OR (95% CI)	p-value
Sex				
Male	16 (40.0)	1,933	1 (Reference)	
Female	24 (60.0)	1,749	1.675 (0.877–3.199)	0.118
Gestational age (wk)				
Term, ≥ 37	9 (22.5)	1,864	1 (Reference)	
Preterm				
Moderate-to-late preterm, 32–37	17 (42.5)	1,371	2.568 (1.141–5.778)	0.023*
Very preterm, 28–31	8 (20.0)	280	5.917 (2.264–15.464)	<0.001*
Extremely preterm, < 28	6 (15.0)	167	7.441 (2.617–21.159)	<0.001*
Birth weight (g)				
Normal, ≥ 2,500	7 (17.5)	2,145	1 (Reference)	
LBWIs, 1,500–2,499	17 (42.5)	1,117	4.664 (1.928–11.279)	0.001*
VLBWIs, 1,000–1,499	9 (22.5)	249	11.076 (4.089–29.999)	<0.001*
ELBWIs, < 1,000	7 (17.5)	171	12.544 (4.350–36.176)	<0.001*
Birth weight according to gestational age				
Non-SGA	26 (65.0)	3,404	1 (Reference)	
SGA	14 (35.0)	278	6.975 (3.553–13.692)	<0.001*

CH, congenital hypothyroidism; OR, odds ratio; CI, confidence interval; LBWIs, low birth weight infants; VLBWIs, very low birth weight infants; ELBWIs, extremely low birth weight infants; SGA, small for gestational age.

* $p < 0.05$, statistically significant difference.

Table 3. Imaging tests results and final diagnosis (n=31)^{a)}

Variable	Data
Imaging	
Ultrasonography	22
Normal	19 (86.4)
Ectopic	0 (0)
Hypoplasia	3 (13.6)
Aplasia	0 (0)
Thyroid scan	21
Normal	18 (85.7)
Ectopic	0 (0)
Increased uptake	0 (0)
Decreased uptake	3 (14.3)
Final diagnosis	27
Transient CH	20 (74.1)
Subclinical hypothyroidism	9 (45.0)
Permanent CH	7 (25.9)

Values are presented as number only or number (%).

CH, congenital hypothyroidism.

^{a)}Four patients (12.9%) were lost to follow up.

dence of permanent CH was one in 1,291 term infants (one of 1,291, 0.08%) and one in 228 preterm infants (six of 1,367, 0.44%), with a significantly higher incidence of CH in the preterm infants ($p = 0.014$).

Discussion

This study provides new information on the incidence of CH in Korea based on the latest data. We identified the following factors as being significantly correlated with the incidence of CH: low gestational age, low birth weight, and SGA. According to numerous studies, the high incidence of CH in preterm infants and low birth weight neonates can be attributed to developmental immaturity and various environmental factors [14,15]. Additionally, the increase in the incidence of premature births and survival of preterm infants due to improved healthcare access may contribute to this, despite the higher incidence of thyroid dysfunction in preterm infants and low birth weight neonates than in term infants [15,16]. In this study, the risk of CH was 1.675 times higher in female infants than in male infants, albeit not statistically significant. Nonetheless, the risk of CH significantly increases with decreasing gestational age and birth weight.

Waller et al. [17] conducted a cross-sectional study of 5,049,185 infants and reported 1,806 cases of CH. Female infants had a higher incidence of CH than did male infants at all birth weights. Furthermore, infants weighing < 2,000 g had a two-fold higher incidence of CH than those weighing 3,000 to 3,499 g. In a meta-analysis by Zhang and Li [18], low birth weight and preterm birth were identified as risk factors for CH in neonates (odds ratio [OR], 2.674; 95% CI, 1.895–3.772; OR, 2.567; 95% CI, 2.070–3.183, re-

spectively). In the present study, we found that the risk of CH was 6.975 times higher in SGA infants than in non-SGA infants. Numerous studies have recommended a second screening for CH in preterm and LBWIs, and our findings indicate that a second screening would also be beneficial for infants who are SGA [4, 15,19,20].

Preterm infants and low birth weight neonates have poorer adaptation to the environment and lower levels of thyrotropin-releasing hormone, thyroxine-binding globulin, T4, and triiodothyronine than healthy newborns, which is caused by the premature development of the hypothalamus-pituitary-thyroid axis. These infants are also prone to transient hypothyroidism caused by iodine overload due to the low level of iodine stored in the thyroid [21,22]. The 2020 to 2021 guidelines of the European Society for Paediatric Endocrinology recommend a second screening between postnatal days 10 and 14 for sick babies, including preterm infants and low birth weight neonates [23].

Ford et al. [24] reported that among 197 CH newborns delivered in Oregon between 2005 and 2011, 29 were diagnosed with CH based on a second screening. Among these patients, 24 were monitored for follow-up, and 17 were term infants. In our hospital, for term infants without any diseases, neither a second screening nor a serum TFT is performed if the newborn screening results are deemed normal. However, a term infant with a normal first screening result may have an abnormal second screening result. Therefore, a mandatory second screening test should be considered for preterm infants and neonates with low birth weights. In full-term infants, a second screening test is generally not necessary. Nevertheless, a second screening test is highly recommended for full-term infants with any disease.

Recent studies have reported an increased incidence of CH in newborns. For example, Mitchell et al. [10] investigated trends in CH incidence rates in Massachusetts. They found that from 2001 to 2004, there was an approximately two-fold increase in incidence (one in 1,660) compared with that from 1991 to 1994 (one in 3,010). They suggested that the increasing incidence of CH in Massachusetts reflected mild and delayed cases and that this increase was attributed to enhanced detection rather than an absolute increase in numbers. In South Korea, a CH incidence of 0.18% ($n = 2,133$, one in 533) was reported in a single-center study [25]. In contrast, the incidence of CH from 2011 to 2021 in this study was one in 93, a six-fold increase.

An increase in the incidence of transient CH with eutopic glands has been reported in various countries [26-28]. In a retrospective cohort study by Barry et al. [27], the percentages of patients with transient CH at the 3-, 5-, and 10-year follow-ups were 19.8%, 25.3%, and 36.7%, respectively. The authors suggested that prema-

ture birth was statistically related to transient CH. In addition, in a single-center study from 2003 to 2015 in South Korea, Park et al. [28] reported that 65% of patients had transient CH. In the present study, we also found a high proportion of patients (15 of 19, 78.9%) with transient CH and eutopic thyroid glands. These cases may be due to the difference in sample size; however, premature birth may also be a contributing factor.

CH can be classified as transient or permanent. Transient CH is a temporary deficiency of thyroid hormones with spontaneous recovery through normal thyroid hormone production. In contrast, permanent CH requires continuous treatment. The primary causes of permanent CH include abnormal thyroid differentiation, migration, and function [11,29]. Thyroid dysgenesis accounts for 80% to 85% of overt CH cases, whereas inborn errors in thyroid hormone synthesis (dyshormonogenesis) account for 10% to 15% of cases [29,30]. Permanent CH includes central hypothyroidism, which was not detected in any patient in our study. Meanwhile, seven of the 27 patients with CH were diagnosed with permanent CH. Of these seven patients, three had abnormal imaging results: one showed bilateral small-sized thyroid lobes on a thyroid ultrasonogram and decreased uptake on a thyroid scan, one had normal ultrasonography results and decreased uptake, and one had thyroid hypoplasia and no thyroid scan data. Notably, more than half of the patients with permanent CH (five of seven) had normal sonographic appearance of the thyroid gland. In addition, one patient with transient CH maintained a state of subclinical hypothyroidism without medication, despite thyroid hypoplasia and decreased uptake. These results indicate that, although imaging studies for CH could assist in identifying the causes of hypothyroidism, they cannot differentiate between transient and permanent CH. Therefore, clinicians should be aware of the various imaging techniques and their purposes, advantages, and limitations.

This study has some limitations. First, a large number of newborns delivered at PNUH, a tertiary medical institution, were preterm infants. Studies have indicated that the number of patients with transient hypothyroxinemia or transient CH is much higher in preterm infants than in term infants [22,23]. Similarly, we observed a two-fold higher frequency in preterm infants. Term infants born at tertiary medical institutions are likely to have maternal or perinatal problems. In this study, two term infants with CH (two of nine infants) had a mother diagnosed with disease; both mothers showed hypothyroidism, and one had hypertension as a comorbidity. Second, due to the retrospective study design, there were cases with missing perinatal data. Thus, to better examine the changes in CH incidence rates in South Korea, future prospective studies conducted at multiple centers with larger sample sizes are warranted.

In summary, our findings suggest that the incidence of CH in South Korea has increased significantly compared with that in the past. In addition, as gestational age, birth weight, and SGA were significantly associated with CH incidence, newborns with these conditions are recommended to undergo a second screening test.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: all authors; Data curation, Investigation: HYJ, MJK, EHY, HWY, SJP; Formal analysis: HYJ, MJK, EHY, YMK, SHC, KHP; Funding acquisition, Validation: MJK; Methodology: HYJ, MJK, SHC, KHP; Project administration: MJK, YMK; Visualization: HYJ, MJK, HWY, SJP; Resources, Software: HYJ, MJK; Supervision: MJK, YMK, SHC, KHP; Writing-original draft: HYJ, MJK, EHY, KHP, HWY, SJP; Writing-review & editing: HYJ, MJK, YMK, SHC.

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