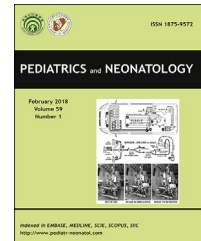




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Review Article

# Screening of congenital hypothyroidism in preterm, low birth weight and very low birth weight neonates: A systematic review



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## Key Words

congenital  
hypothyroidism;  
preterm;  
low birth weight;  
very low birth weight;  
thyroxine;  
thyroid stimulating  
hormone

Evidence from different screening programs indicated that the rate of congenital hypothyroidism (CH) was higher in pre-term and low-birth-weight (LBW) newborns than normal ones. Incomplete development of hypothalamic–pituitary axis in this group of neonates results in the delayed rise of TSH and missing cases with CH. Hence, there is a great need for a practicable systematic screening method for proper diagnosis of CH in this group of neonates. In this review, we systematically reviewed papers with the following key words ([Congenital Hypothyroidism AND Screening AND Thyroxine AND Thyroid Stimulating Hormone AND Low Birth Weight AND Premature]) in international electronic databases including PubMed, Scopus, and Google Scholar. After quality assessment of selected documents, data of finally included papers were extracted. In this review, 1452 papers (PubMed: 617; Scopus: 714; Google scholar: 121) were identified through electronic database search. One hundred and ninety four articles were assessed for eligibility, from which 36 qualified articles were selected for final

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evaluation. From the reviewed articles, 38.9%, 11.11% and 8.3% recommended rescreeing in this group of neonates, lowering the screening cutoff of TSH and using cutoffs according to the gestational age, respectively. Some of them (13.9%) recommended using both TSH and T4 for screening of preterm infants. After reviewing available data, we recommend repeating the screening test in pre-term, LBW and very-low- birth-weight (VLBW) infants at age of two, six and ten weeks by measuring TSH and FT4 levels simultaneously and considering TSH = 10 mU/L as the cutoff level for positive and suspicious cases.

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## 1. Introduction

Congenital hypothyroidism (CH) is the most common cause of preventable mental retardation in children. Thus screening programs of CH have been established for better management of the disorder and preventing its related neurodevelopmental consequences.<sup>1</sup>

The reported incidence rate of CH has significantly risen during past two decades. Suggested factors related to this high rate of CH occurrence are increased prevalence of CH and high rate of preterm infant births.<sup>2,3</sup>

Evidence from different screening programs indicated that the rate of CH was higher in pre-term and low-birth-weight (LBW) newborns than normal ones due to insufficient development of hypothalamic–pituitary axis.<sup>4</sup> Prevalence of this condition in very-low-birth-weight (VLBW) infants with birth weight of less than 1500 g has been approximately measured as 1 in 400 cases, which is significantly higher than its prevalence in full-term infants (1 in 4000 cases); however, only one-third of these infants can be diagnosed using the screening program.<sup>5,6</sup> Therefore, it is critical to screen CH in preterm infant, to prevent and minimize neurodevelopmental impairment. Some studies suggest that screening in VLBW newborns should be repeated, whereas others recommended other strategies, including lowering screening TSH cutoff and etc.<sup>5,7–9</sup>

Findings of different studies in this field are controversial.<sup>10–12</sup> It is difficult to interpret screening results of pre-term and extremely-low-birth-weight (ELBW) infants, and considering dissimilar findings of different studies. It was not possible to come to a general agreement on how to perform and repeat screening tests. In recent years, the survival rate of VLBW and ELBW infants has increased due to the improved neonatal care, which consequently results in higher incidence of CH. Therefore, there is need of a systematic highly sensitive screening program for early diagnosis of this condition in all infants at any gestational age.<sup>12</sup>

Hence, considering the high prevalence of CH especially in pre-term and VLBW infants and its severe but preventable consequences, we aimed to try to come to a general conclusion on screening in pre-term infants using a systematic review of some related studies. We tried to come to an approach for screening and early diagnosis of CH especially in pre-term infants, in order to decrease the rate of false negative cases.

## 2. Materials and methods

In this study, we systematically reviewed papers related to screening of CH in preterm and LBW neonates up to December 2015.

The protocol of this review was approved by pediatrics review board and regional ethics committee of Isfahan University of Medical Sciences (research project number 393247).

In this review all studies reporting the protocol of their CH screening program's protocols and published in English without any time limitation until December 2015 were included. Studies which reported as conference abstracts or letters and those without a full text were excluded.

### 2.1. Search strategy, study selection and quality evaluation

In electronic search, key words including ([Congenital Hypothyroidism AND Screening AND Thyroxin AND Thyroid Stimulating Hormone AND Low Birth Weight AND Premature]) in international electronic databases including PubMed, Scopus, and Google Scholar were used.

### 2.2. Study selection and quality evaluation

All selected papers were reviewed and duplicate results were omitted. Two researchers reviewed all titles and abstracts individually and extracted related results. If the two researchers could not come to an agreement, a third researcher, a pediatric endocrinologist expert in the field of CH screening made the decision. Full texts of the articles were obtained and reviewed. Quality of the documents regarding the protocol of the screening, sampling method and size and laboratory methods and variables evaluation process was evaluated by two experts in the field of CH screening. Related articles were selected and data such as names of authors, location and year of study, size of samples, purpose, measured variables and findings were extracted. Considering the results and findings of different studies regarding screening of CH in preterm neonates, a final decision was prepared for screening of this group of neonates.

## 3. Results

In this review, 1452 papers (PubMed: 617; Scopus: 714; Google scholar: 121) were identified through electronic

database search. One hundred and ninety four articles were assessed for eligibility, from which 36 qualified articles were selected for final evaluation (Fig. 1).

Details of all selected studies are presented in Table 1. According to the reports, normal TSH in three to six days after birth did not always imply normal function of the thyroid gland. TSH level of greater than 10 mU/L in the 2nd week of birth was diagnostically meaningful and TSH level of 10 mU/L–15 mU/L suggested “hypothyroidism with delayed TSH rise”. FT4 and T4 levels became normal two to eight weeks after birth.<sup>6,8–11,13–43</sup>

Regarding final recommendations for improving the screening of CH in prematurity, 38.9%, 11.11% and 8.3% recommended rescreening, lowering screening TSH cutoff and using cutoffs according to their gestational ages, respectively. Almost 14% of the studies recommended using both TSH and T4 measurements for this group of neonates. Two studies recommended delaying the screening program time in preterm infants. One did not confirm rescreening for CH screening in preterm infants. The reminders had no conclusive recommendations and only represented findings regarding the normalization time of TSH and T4 level or the rate of missing cases of CH in preterm infants.

## 4. Discussion

There is great need for a practicable systematic screening test with high sensitivity in order to reduce the missing cases of CH especially in preterm infants. Evidently preterm and LBW infants require special care and follow up.<sup>10,11</sup> In this review we tried to systematically review previous works in this field and provide a comprehensive protocol for screening of these high-risk neonates.

Up to this date, few approaches have been introduced in order to reach this goal. One is reducing the cutoff value in order to increase the sensitivity of the screening test and another is a repetition of the screening test in LBW and preterm infants in order not to miss the delayed rise of TSH. Moreover, some studies have suggested considering normal ranges of thyroid hormones’ levels based on gestational age, using both TSH and T4 measurement for CH screening or delaying the time of screening in preterm infants.<sup>6,8–11,13–43</sup>

The findings of this review indicated that many studies (40%) recommended retesting of TSH or T4 for proper diagnosis of CH in preterm infants.<sup>8,9,11,13,16,19,20,24–27,30–34,36,37,41,43</sup>

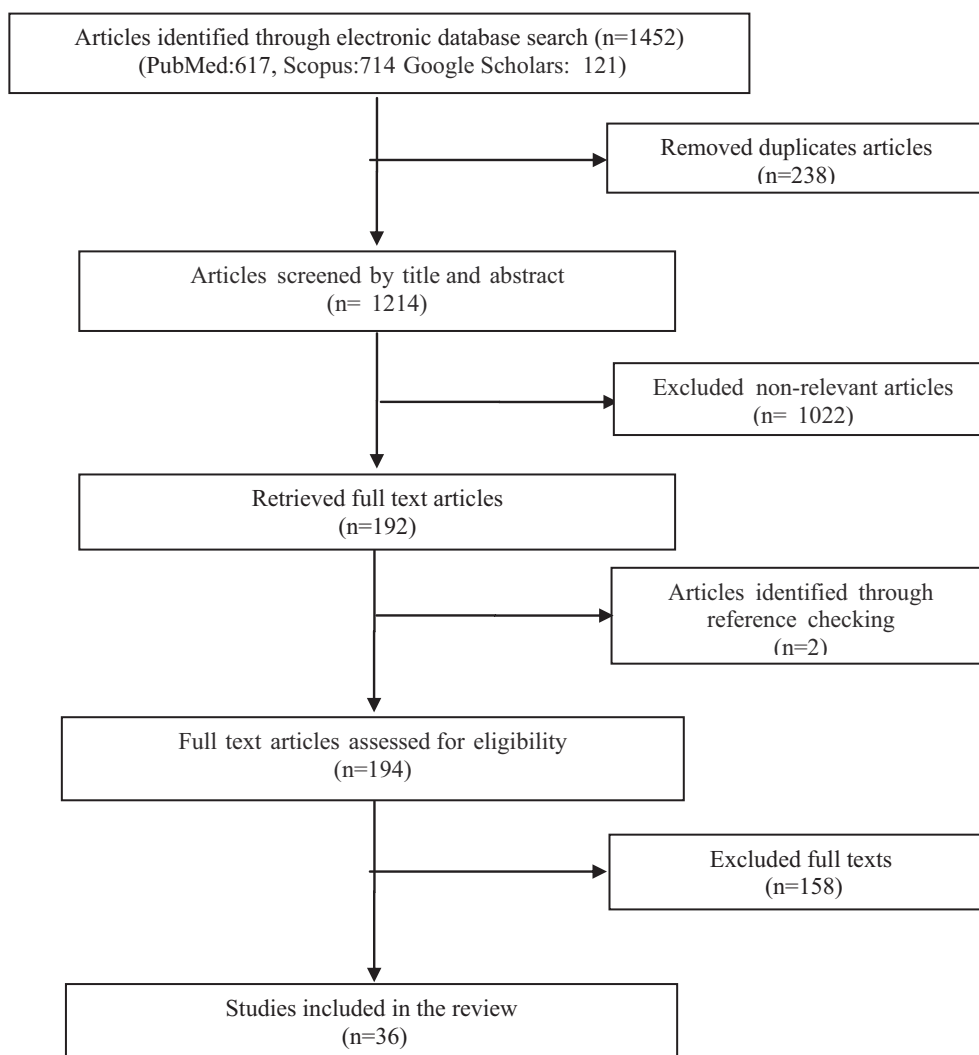


Figure 1 Flowchart of study selection.

**Table 1** Details of the studies.

	Name of first author, year	Title	Location	Population	Type of study	Finding (main result)
1	Jacobsen et al., 1977 <sup>13</sup>	Serum levels of thyrotropin, thyroxine and triiodothyronine in fullterm, small-for-gestational age and preterm newborn babies	Copenhagen, Denmark	93 fullterm and 37 small-for-gestational age (GA of 37–40 weeks) and 38 preterm (gestational age 27–36 weeks) neonates	Prospective cohort	<ul style="list-style-type: none"> <li>- At 5 days of age serum TSH level was normal in all groups of neonates and considering the level of T4 for screening may result in false positive diagnosis of CH.</li> <li>- For proper diagnosis of CH retesting of serum TSH from the 5th day of life will be favorable.</li> </ul>
2	Uhrmann et al., 1981 <sup>14</sup>	Frequency of transient hypothyroxinaemia in low birth weight infants, Potential pitfall for neonatal screening programs	Pennsylvania, USA	54 LBW infants during a 3-week period	A cross sectional study	<ul style="list-style-type: none"> <li>- In LBW infants with low T4 level, repeated measurement of both T4 and TSH is recommended for proper diagnosis of CH.</li> </ul>
3	Kok et al., 1983 <sup>15</sup>	Normal ranges of T4 screening values in low birth weight infants	Amsterdam, The Netherlands	115 LBW infants	A cross sectional study	<ul style="list-style-type: none"> <li>- Considering that the level of T4 is lower in LBW infants, so in screening program which used t4 for screening the level of T4 should be determined according to the birth weight and gestational age.</li> <li>- The appropriate time for T4 measurement in preterm infant is the 7th day of life.</li> </ul>
4	Delange et al., 1984 <sup>16</sup>	Increased risk of primary preterm infants hypothyroidism in preterm infants	Brussels, Belgium	103 newborn infants (42 full term and 61 preterm)	Longitudinal study	<ul style="list-style-type: none"> <li>- Preterm infants have higher basal TSH and TSH responses to TRH than full term. They also have lower T3 responses to TRH.</li> <li>- Thyroid function improves in preterm infants with increasing age after 4–6 weeks of age.</li> </ul>
5	Mercado et al., 1988 <sup>17</sup>	Thyroid function in very preterm infants	Melbourne, Australia	108 infants born (GA of 23–31 weeks)	A cross sectional study (June 1985–June 1986)	<ul style="list-style-type: none"> <li>- Preterm infants have significant delay in maturation of the hypothalamic-pituitary–thyroid axis. This group of infants had lower level of T4, TBG, FTI and T3.</li> </ul>
6	Adams et al., 1994 <sup>18</sup>	Reference ranges for newer thyroid function tests in premature infants	California, the USA	104 preterm infants with a GA of 25–36 weeks	A prospective study (March 1990–October 1993)	<p>Reference ranges for serum free T4 and TSH in preterm infants during the first week of life according to gestational ages;</p> <p>25–27 weeks;  FT4: 7.7–28.3 (0.6–2.2) (pmol/L [ng/dl])  TSH: 0.2–30.3 (mU/L)</p> <p>28–30 weeks;  FT4 7.7–43.8 (0.6–3.4) (pmol/L [ng/dl])  TSH: 0.2–20.6 (mU/L)</p> <p>31–33 weeks;</p>

						<p>FT4: 12.9–48.9 (1.0–3.8) (pmol/L [ng/dl])</p> <p>TSH: 0.7–27.9 (mU/L)</p> <p>34–36 weeks;</p> <p>FT4 15.4–56.6 (1.2–4.4) (pmol/L [ng/dl])</p> <p>TSH: 1.2–21.6 (mU/L)</p> <ul style="list-style-type: none"> <li>- Use both T4 and TSH measurement for CH screening is more favorable than TSH alone.</li> <li>- Measurement Ft4 level in all preterm neonates aged &lt;33 weeks during the 2nd week of life is recommended.</li> <li>- Retesting of both TSH and T4 at 2 and 4–6 weeks after birth in VLBW infants with normal TSH level during the first week of life is recommended.</li> <li>- By using this protocol most of the late-onset, transient hypothyroidism cases will be detected earlier.</li> </ul>
7	Rooman et al., 1996 <sup>19</sup>	Low thyroxinaemia occurs in the majority of very preterm newborns	Antwerp, Belgium	263 preterm neonates (GA of 26–41) admitted to NICU	A prospective study	
8	Frank et al., 1996 <sup>20</sup>	Thyroid function in very low infants: Effects on neonatal hypothyroidism screening birth weight	Massachusetts, USA	9324 term, 18,946 LBW, and 3450 VLBW infants for the retrospective phase and 48 VLBW infants at 2 weeks of age for the second prospective phase of the study	A combined retrospective and prospective study	<ul style="list-style-type: none"> <li>- For avoiding missing of atypical CH cases, serum T4 should be measured routinely in all LBW and VLBW infants, with a blood sampling.</li> <li>- The level of T4 was significantly lower in preterm infants than full terms.</li> <li>- Level of FT4 was normal in preterm infants</li> <li>- Use of FT4 measurements on filter paper spots in this group of infants is recommended.</li> </ul>
9	Mandel et al., 2000 <sup>8</sup>	Atypical hypothyroidism and the very low birth weight infant	Massachusetts, USA	311,282 infants participated in the CH screening program	A retrospective study (January 1993–December 1996)	<ul style="list-style-type: none"> <li>- FT4 concentrations were remarkably stable after the first week of life, despite wide variations in TSH concentrations</li> </ul>
10	Gruñeiro-Papendieck et al., 2000 <sup>21</sup>	Usefulness of thyroxin and free thyroxin filter paper measurements in neonatal screening for congenital hypothyroidism of preterm babies	Buenos Aires, Argentina	193 preterm neonates (GA of 26–37 weeks) and 153 full term neonates during their first week of life	A cross sectional study	<ul style="list-style-type: none"> <li>- Their findings did not support the contention of rescreening of VLBW infants for diagnosis of CH</li> </ul>
11	Clark et al., 2001 <sup>22</sup>	Reference ranges for thyroid function tests in premature infants beyond the first week of life	California, USA	120 healthy premature infants (GA of 25–36 weeks)	A cross sectional study	<ul style="list-style-type: none"> <li>- Monitoring of thyroid function test is necessary for preterm infants, but</li> </ul>
12	Vincent et al., 2002 <sup>10</sup>	Very low birth weight newborns do not need repeat screening for congenital hypothyroidism	Québec, Canada	465 VLBW infants referred for CH screening	Retrospective cohort (October 1993–October 1994)	
13	Rapaport et al., 2002 <sup>11</sup>	Thyroid function in the very low birth weight newborn: Rescreen or re-	New York, USA	–	Editorial	

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**Table 1** (continued)

Name of first author, year	Title	Location	Population	Type of study	Finding (main result)
	evaluate?				regarding rescreening of this group of infants more studies is needed.
14 Larson et al., 2003 <sup>9</sup>	Risk factors associated with delayed thyrotropin elevations in congenital hypothyroidism.	Massachusetts, USA	All neonates attended to the New England CH Screening program.	A Retrospective study (January 1989–June 2002)	- The average age at initial TSH elevation for patients with VLBW was 30 days and all of them should be re-evaluated regardless of their first thyroid screening results.
15 Carrascosa et al., 2004 <sup>23</sup>	Thyroid function in seventy-five healthy preterm infants thirty to thirty-five weeks of gestational age: a prospective and longitudinal study during the first year of life	Barcelona, Spain	75 healthy preterm infants (GA of 30–35 weeks)	A prospective and longitudinal study	- The level of TSH was lower in preterm than full-term infants in cord blood samples, at 1 h and at 24 h of life, but it was similar thereafter. - For T4 and T3, the value was not similar until the age of 2 months.
16 Tylek-Lemanska et al., 2005 <sup>24</sup>	Screening for congenital hypothyroidism: the value of retesting after four weeks in neonates with low and very low birth weight	Krakow, Poland	3854 neonates with body weight <2500 g	A cross sectional study (1999–2001)	- TSH retesting at 4th week of age will result in reducing false negative cases of CH and provide additional information for better treatment of CH. - Their used cutoff level for TSH in CH screening was 10 mU/L.
17 Korada et al., 2008 <sup>25</sup>	Repeat testing for congenital hypothyroidism in preterm infants is unnecessary with an appropriate thyroid stimulating hormone threshold	Newcastle Upon Tyne, UK	2238 preterm infants born over a 2-year period	A prospective study (April 2005–March 2007)	- By using a TSH screening cutoff of 10 mU/l, some cases of permanent CH will be missed. - TSH retesting in preterm infants is unnecessary if a lower TSH cutoff of 6 mU/l is used.
18 Chung et al., 2009 <sup>26</sup>	High incidence of thyroid dysfunction in preterm infants	Seoul, Korea	105 preterm infants who were born at <32 weeks of gestation	A Cross sectional study (July 2004–May 2006)	- Both excessive and insufficient iodine intake may be associated with CH in preterm infants. - Repeated thyroid function tests between 2nd and 4th week of age for all preterm infants including those with first normal thyroid function test is recommended.
19 Corbetta et al., 2009 <sup>27</sup>	A 7-year experience with low blood TSH cutoff levels for neonatal screening reveals an unsuspected frequency	Milan, Italy	629,042 newborns screened during CH screening program	Retrospective study (January 1999–December 2005)	- A second re-evaluation during the 3rd week of age for preterm neonates and start treatment at 4th week of age after confirming the diagnosis is recommended.

		of congenital hypothyroidism (CH)				<ul style="list-style-type: none"> <li>- By using low cutoff level for TSH(10 or 12 mU/l), we could diagnose more cases of CH</li> <li>- Using a TSH cutoff of 20 resulted in significant number of missed cases of CH and 40% of the missed cases were premature infants.</li> </ul>
20	Mengreli et al., 2010 <sup>28</sup>	Screening for congenital hypothyroidism: the significance of threshold limit in false negative results	Athens, Greece	311,390 neonates participated in CH screening program	A Prospective cohort study (January 2000 –December 2002)	
21	Korada et al., 2010 <sup>29</sup>	Difficulties in selecting an appropriate neonatal thyroid stimulating hormone (TSH) screening threshold	Newcastle upon Tyne, UK	65,446 infants screened for	A prospective study CH (April 2005–March 2007)	<ul style="list-style-type: none"> <li>- Using lower cutoff of TSH for screening would be more helpful for detecting cases of CH especially in preterm infants.</li> </ul>
22	Silva et al., 2010 <sup>30</sup>	Screening for congenital hypothyroidism in extreme premature and/or very low birth weight newborns: the importance of a specific protocol	Minas Gerais, Brazil	Preterm neonates with GA of <32 weeks and/or VLBW ones	A cross-sectional study (October 2004–September 2006)	<ul style="list-style-type: none"> <li>- For proper CH screening of VLBW neonates the protocol should be based on retesting method.</li> <li>- The first sample should be taken in the first week of life and the second one month after birth.</li> </ul>
23	Slaughter et al., 2010 <sup>31</sup>	The effects of gestational age and birth weight on false positive newborn-screening rates	Ohio, The USA	448,766 neonates participated in the Ohio State Newborn Screening Program	A retrospective cohort Study (2004 –2006)	<ul style="list-style-type: none"> <li>- False positive newborn-screening rates are significantly higher in VLBW infants and it would be reduced by delaying screening in preterm neonates until 24 –48 h.</li> <li>- High risk cutoff values for TSH (28–50 IU/ml) and T4 (8 µg/dL) was determined.</li> </ul>
24	Holzer de Moraes et al., 2011 <sup>32</sup>	Collection time of thyroid hormones and TSH in preterm newborns	Brazil	85 preterm newborns	Prospective study (June 2004 –December 2004)	<ul style="list-style-type: none"> <li>- CH in preterm neonates is characterized by low free T4 and normal TSH in the first 30 days of life.</li> <li>- The appropriate time for TSH and T4 collection was the 3rd and 7th day of life, respectively.</li> </ul>
25	Bijarnia et al., 2011 <sup>33</sup>	Newborn screening for congenital hypothyroidism in very-low-birth-weight babies: the need for a second test	New South Wales and the Australian Capital Territory, Australia	2313 newborns with a birth weight of ≤1500 g	A Prospective cohort (January 2006–December 2008)	<ul style="list-style-type: none"> <li>- Considering the delayed rise of TSH in preterm infants, a secondary screening at 1 month of age for diagnosis of CH is recommended</li> </ul>
26	Woo et al., 2011 <sup>6</sup>	Congenital hypothyroidism with a delayed thyroid-stimulating hormone elevation in very	Rhode Island, USA	814 infants weighed <1500 g, 885 had birth weights 1000–1499 g, and 929 had birth weights <1000 g	A retrospective analysis	<ul style="list-style-type: none"> <li>- VLBW and ELBW neonates have lower level of T4.</li> <li>- Delayed TSH elevation was seen during the first month of age.</li> </ul>

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Table 1 (continued)

Name of first author, year	Title	Location	Population	Type of study	Finding (main result)
27	Chee et al., 2011 <sup>34</sup> premature infants: incidence and growth and developmental outcomes Review of primary hypothyroidism in very low birth weight infants in a perinatal centre in Hong Kong	Hong Kong, China	20 VLBW infants with diagnosed primary CH during screening program using umbilical cord blood	Retrospective, descriptive review nested to a prospective VLBW cohort [January 2000–December 2008 (Vermont Oxford Database)]	<ul style="list-style-type: none"> <li>- Serum TSH and T4 was measured at 1st, 2nd and 4th weeks of age and then four weekly until they reached to the weight of 2 kg.</li> <li>- The peak of serum TSH was seen in between 2nd and 3rd weeks of age.</li> <li>- To capture TSH by screening tests within 8 weeks of life or using of unified cut-off of 12 mU/L for TSH is recommended.</li> </ul>
28	Srinivasan et al., 2012 <sup>35</sup> Permanent and transient congenital hypothyroidism in preterm infants	Newcastle Upon Tyne, UK	5518 preterm infants (GA < 35 weeks)	A prospective study (from April 2005 to March 2010)	<ul style="list-style-type: none"> <li>- Both transient and permanent CH cases will be appropriately diagnosed by a 'once-only' TSH screening strategy with a relatively low cut-off of 6 mU/L.</li> </ul>
29	Niwa et al., 2012 <sup>36</sup> Hyperthyrotropinemia at 2 weeks of age indicates thyroid dysfunction and predicts the occurrence of delayed elevation of thyrotropin in very low birth weight infants	Kyoto, Japan	47 VLBW infants with a GA of <30 weeks	A cross sectional study (January 2008–March 2011)	<ul style="list-style-type: none"> <li>- The hypothalamic–pituitary–thyroid axis could be established at 2 weeks of age even in VLBW infants.</li> <li>- Subclinical CH is diagnosed by increased level of TSH (&gt;10 mU/l) and a hyper-response to TSH releasing hormone stimulation tests.</li> <li>- In preterm infants, serum TSH level at about 2 weeks of age could be used for the evaluation of transient hypothyroxinemia and the prediction of delayed TSH elevation.</li> </ul>
30	Torkaman et al., 2012 <sup>37</sup> Thyroid function test in pre-term neonates during the first five weeks of life	Tehran, Iran	100 preterm neonates (GA < 35 weeks)	A concurrent cohort study	<ul style="list-style-type: none"> <li>- Level of thyroid hormones reached to the normal range after 3 or 6 weeks of life.</li> <li>- The level of TSH level is not affected by gestational age and standard level of TSH could be used for preterm infants also.</li> <li>- Re-evaluation of neonates with abnormal thyroid tests for concise diagnosis of CH is recommended.</li> </ul>
31	Langham et al., 2013 <sup>38</sup> Screening for congenital hypothyroidism: comparison of borderline screening cut-off points	London, UK	223,658 newborn infants screened for CH (January 2006–December 2007)	A retrospective study	<ul style="list-style-type: none"> <li>- By using a TSH cutoff point of &gt;10 mU/l for CH screening, a significant number of transient and permanent CH cases will be missed.</li> </ul>



		and the effect on the number of children treated with levothyroxine				- A lower cutoff point of 6 mU/l for TSH is recommended.
32	Muhammad et al., 2013 <sup>39</sup>	Comparison of serum TSH and T4 levels in preterm and term neonates for screening of congenital hypothyroidism	Peshawar, Pakistan	101 neonates aged 3–7 days, both preterm (n = 2) and full term (n = 49)	A cross-sectional study	- The prevalence of transient hypothyroxinemia without hyperthyrotropinemia is relatively higher among preterm infants. - Combined TSH and T4 measurement is the most appropriate strategy for CH screening.
33	Zhu et al., 2013 <sup>40</sup>	Reference intervals for serum thyroid hormones in preterm hospitalized infants	Beijing, China	247 hospitalized preterm infants aged 28–36 weeks of gestation	A cross sectional study	Reference intervals for FT3, FT4, T3, T4, and TSH according to the gestational ages; 28–30 weeks; FT3 (pmol/L) 1.61–5.51 FT4 (pmol/L) 8.44–25.58 TSH (μIU/mL) 0.68–12.53 31–33 weeks; FT3 (pmol/L) 1.84–4.97 FT4 (pmol/L) 10.47–26.25 TSH (μIU/mL) 0.68–12.53 34–36 weeks; FT3 (pmol/L) 1.88–6.00 FT4 (pmol/L) 10.28–34.87 TSH (μIU/mL) 0.68–12.53
34	Sun et al., 2014 <sup>41</sup>	Free thyroxine and thyroid-stimulating hormone reference intervals in very low birth weight infants at 3–6 weeks of life with the Beckman Coulter Unicel Dxl 800	Ottawa, Canada	308 VLBW infants	A retrospective cohort (from September 2006 to December 2010)	- Reference intervals for TSH was 1.14–11.04 mU/L and for FT4 was (10.9–21.4 pmol/L). - Repeating thyroid function screening in this group of neonates at 1 month is recommended.
35	Lee et al., 2015 <sup>42</sup>	Thyroid dysfunction in very low birth weight preterm infants.	Busan, Korea	VLBW infants admitted to the neonatal intensive care unit (January 2010–December 2012)	A prospective study	- Re-evaluation of both TSH and T4 is necessary for these high risk preterm neonates during CH screening program.
36	Giraldo et al., 2015 <sup>43</sup>	Evaluation of TSH levels in the program of congenital hypothyroidism newborn screening in a pilot study of preterm newborns in Bogota', Colombia	Bogotá, Colombia	Preterm infants (<37 weeks of gestation)	An exploratory study	- The level of TSH is lower in preterm infants and should be re-evaluated after the first screening.

CH, congenital hypothyroidism; LBW, low birth weight; VLBW, very low birth weight; TSH, thyrotropin.

Lowering the screening cutoff of TSH and using cutoffs according to the gestational age was the recommendation of 11.11%<sup>32,33,38,40</sup> and 8.3%<sup>15,18,40</sup> of the reviewed studies, respectively. Some of the studies (13.9%) recommended using both TSH and T4 for screening of preterm infants<sup>14,19,20,39,42</sup> and some had no recommendation for CH screening and only reported their findings about the normalization time of TSH and T4 in this group of patients.

Currently, screening of CH is based on either evaluation of early TSH, evaluation of early T4 with a TSH follow-up, or evaluation of early TSH and early T4. As mentioned above, only one episode of evaluation of TSH levels may have the chance to miss delayed rise of TSH.

Recently Lee et al.,<sup>42</sup> Muhammad et al.<sup>39</sup> and also some earlier studies emphasized measuring of both TSH and T4 for CH screening especially in preterm neonates. Evidence indicated that the screening based on measuring only TSH levels, which was common in many countries, did not have the ability to diagnose transient hypothyroidism. Therefore, measuring both FT4 and TSH in primary screening tests and following tests in order to increase the sensitivity are advisable and as a result a delayed rise of TSH could not be missed.<sup>19,26,34,37,39,41</sup>

Some researches such as Zhu, Adams and Kok et al. recommended using normal range references of hormone levels based on gestational age.<sup>15,18,40</sup> This was not practicable, as findings of different studies had variable results and using these references and their interpretation seems difficult. In addition, it seems that for different population the cutoffs will be different and there could be no single CH screening protocol for all communities.

Lowering the level of screening TSH cutoff is another recommendation for improving the CH screening among preterm infants. Mengreli et al. studied 311,390 screened infants in Greece and suggested that TSH cutoff level of greater than 20 mU/L could lead to missing 40 percent of pre-term infants with CH.<sup>28</sup>

Results of some studies indicated that decreasing the TSH cutoff level to 10–12 mU/L reduces the rate of false negative cases and allows detection of an unsuspected number of neonates with CH.<sup>27</sup>

Sirinvasan et al. evaluated the results of United Kingdom infants' screening program for five years which decreased the filter TSH cutoff level to 6 mU/L and considered TSH levels of 6 mU/L–20 mU/L as suspicious. They suggested that decreasing the cutoff level made it possible to run the test in only one session, at birth, and to repeat the test in gestational age at 36 weeks in newborns with suspicious results.<sup>35</sup> Moreover, in two separate studies on 2238 and 65,446 infants in England, Korada et al. proposed that, with decreasing TSH cutoff level to 6 mU/L, no cases of CH will be missed; therefore, repetition of the test would not be necessary.<sup>25,29</sup>

However, Bijarnia et al. proposed that the higher probability of hypothyroidism with delayed TSH rise in pre-term newborns, the greater would be the chance of both permanent and transient states of hypothyroidism; but the only way for a definitive diagnosis in these patients would be repetition of the screening test.<sup>33</sup> Despite what Korada et al. believed, Bijarnia proposed that decreasing the TSH cutoff level to 6 mU/L increased false positives by 28-folds, while some cases were still missed.<sup>25,29,33</sup>

It seems that decreasing the TSH cutoff level to 6 mU/L drastically increases false positives, causing financial and psychological burden on the health system and infants' families; hence, choosing this threshold does not seem wise and affordable.

Although decreasing the TSH cutoff level to lower than 20 mU/L seems inevitable in order not to miss CH cases, considering a cutoff level of 6 mU/L does not seem to be wise, as it drastically increases false positives. Thus, a cutoff level of 10 mU/L can improve the screening test for congenital hypothyroidism, whether in full-term or pre-term infants.<sup>36</sup>

Another suggested approach is a repetition of the screening test in order to find cases with delayed TSH rise that were missed using the primary test. However, the most suitable time for the 2nd test is disputed.

Chung et al., believed repetition of the test in pre-term newborns to be necessary, since infants could have a normal thyroid profile in the first days of their life. They recommended 2nd to 4th weeks of life as the most suitable time for the 2nd test.<sup>26</sup> In 2010 Chee et al. measured FT4 and TSH levels in low birth weight infants aged one-two and four weeks, and they proposed that TSH reached its maximum level on average at age of 2.4 weeks.<sup>34</sup>

In 2012, Niwa's team studied on 47 VLBW infants in Kyoto Hospital, Japan, and they proposed that measuring TSH level at the age of two weeks could be helpful in evaluating transient hypothyroxinemia of prematurity and in prediction of the occurrence of delayed rise in TSH.<sup>36</sup>

In Delange's study on 103 newborns, it was proposed that thyroid functional capacity of pre-term infants reached the same level as full-term newborns at the age of 4–6 weeks.<sup>16</sup>

Tylek-Lemanska's study on 3854 LBW infants in Poland had the same finding.<sup>24</sup>

Endocrinologists and pediatricians recommend diagnosing CH as soon as possible, and when the diagnosis of CH is definitive, they recommend starting the treatment as soon as possible, not later than age of four weeks. Therefore, it seems unwise to postpone the 2nd screening test to later than the 4th week, considering possible irreparable mental disorders.

Rooman et al. studied 263 infants with gestational age of 26–41 weeks and suggested that the best time for re-measuring FT4 and TSH levels was 2 weeks after birth.<sup>19</sup> Niwa also adds that the hypothalamic–pituitary axis in LBW infants, develops at the age of about 2 weeks, therefore, this age is recommended to be the most suitable time for repetition of the screening test.<sup>36</sup>

Considering the studies mentioned above and this systematic review of previous studies, two weeks seems to be the best age to perform the screening test, as the hypothalamic–pituitary axis development is initiated at this age and the remaining maternal T4 disappears. It is recommended that the treatment start as soon as the diagnosis of CH is confirmed.

## 5. Conclusions and implications

Screening in the first days of life seems to be the most important step in the approach to CH and replacement of

related deficient hormones, thus preventing consequences that cannot be remedied. Hence, optimizing the sensitivity of the screening test has great importance especially for this high risk group of neonates. Reviewing of present studies indicated that it was more favorable to retest premature infants for proper screening of CH, but considering the findings of all studies, we recommend the following:

1. Normal TSH during the first days of life in preterm infants could not rule out presence of CH.
2. We suggest repeating the screening of pre-term, LBW and VLBW infants at the age of two weeks, by measuring TSH and FT4 levels simultaneously and consider TSH = 10 mU/L as the cutoff level for positive and suspicious cases.
3. T4 and FT4 should return to normal levels after 2–8 weeks and 4–12 weeks in LBW infants and ELBW infants, respectively.
4. Free T4 concentrations were remarkably stable after the first week of life despite wide variations in TSH concentrations (0.8–2.6 ng/dL).
5. A TSH level of 10–15 mU/L after an episode of normal TSH level could be indicative of delayed TSH rise which consequently increases the possibility of permanent or transient CH diagnosis.
6. A normal level of TSH in 3rd to 6th day of life does not always imply normal thyroid function.
7. TSH level decreases in 5th to 14th weeks of life.
8. It is recommended that the screening test be repeated in 2nd, 6th and 10th weeks of life.
9. Infants with gestational age of less than 28 weeks should be treated for 6 weeks despite their normal TSH level.<sup>26</sup>
10. TSH level  $\geq 20$  mU/L in conjunction with any level of free T4 needs treatment.
11. Free T4 level  $< 0.7$  ng/dL during 3rd to 6th week of life in conjunction with a TSH level  $\geq 10$  mU/L needs treatment.
12. TSH 10–20 mU/L with normal FT4 for two times needs treatment.<sup>26,36,40,42,44,45</sup>

## Conflict of interest

The authors have no conflict of interest.

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