

## Letter to the Editor

### Some Concerns About Newborn Screening for Congenital Hypothyroidism in China

Dear Editor,

About three decades passed since the first newborn screening program has been introduced into China. But still many concerns on newborn screening exist in this country with a high annual birth rate. Focusing on screening for congenital hypothyroidism, there is no unified guidelines on screening are recommended by the government and screening guidelines are variable in different regions. For example, cut-off value for congenital hypothyroidism is not unified in different screening centres though with the same screening protocol. Before 1998, laboratories of various screening centres in China employed RIA, which later was replaced by TRFIA. Only a few laboratories still use ELISA and EFIA currently. Most laboratories use 9 mU/L and some use 10 mU/L, 15 mU/L even 20 mU/L as cut-off value. Due to the variation in the socio-economical status and medical resources distribution through the whole country, the screening coverage rate varies in different regions. In some regions with high economical level, such as in Shanghai city and Zhejiang Province, the screening coverage reaches 95% or higher. But the screening coverage throughout the country is still very low of about 40%. The data in 2007 revealed that 28 provinces (not including Taiwan, Hong Kong and Macao) now perform the newborn screening program involving 143 newborn screening centre. Some provinces may have several newborn screening centre but with a very low screening capacity for each centre.<sup>1</sup> Though with several newborn screening centres in one province, the screening coverage may still be very low in some regions.

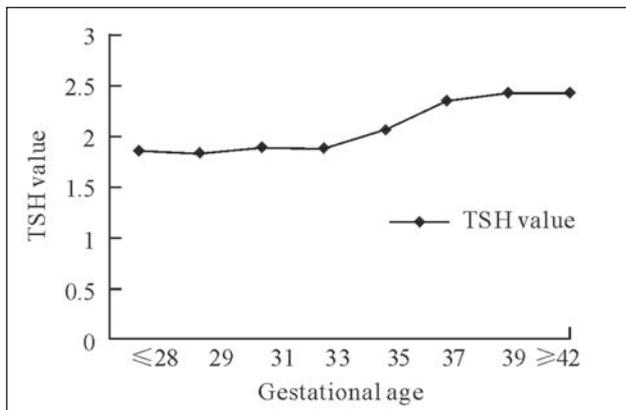
As one of the largest newborn screening centres in China, our screening centre provides newborn screening services for infants born in Zhejiang province including 10 cities, with an annual birth cohort of approximately 500,000. According to the current screening program for congenital hypothyroidism (CH) in China, we used a primary blood spot thyroid stimulating hormone (TSH) measurement, with a screening threshold of 9 mU/L for all infants. With this screening strategy, delayed TSH elevation in infants with

thyroid-binding globulin (TBG) deficiency, central hypothyroidism, and hypothyroxinemia will be missed.<sup>2</sup> Delayed TSH elevation is particularly common in infants with low birth weight (LBW, Birth weight: 1500-2499 g) and very low birth weight (VLBW, Birth weight <1500 g).<sup>3</sup> Even in the absence of technical and human errors, 5 to 10% of LBW and VLBW newborn infants with CH may have normal screening hormone concentrations.<sup>3</sup> Preterm infants may also have "inappropriately" low TSH concentrations due to an immature hypothalamo-pituitary-thyroid axis. However, no screening centre has given extra considerations to this subpopulation (premature infants and LBW infants) up to now.

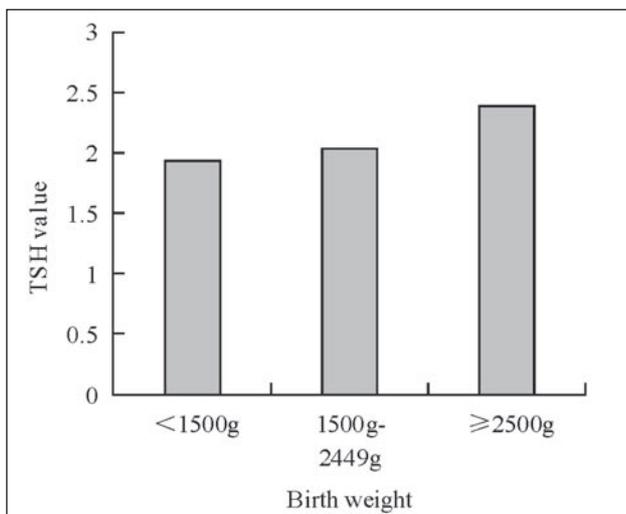
We retrospectively reviewed screening data through 1st January 2008 to 31st December 2008 in our centre. A total of 499,624 newborns were screened for congenital hypothyroidism (CH) in Zhejiang Province in the year of 2008. Among them, 22,028 (4.7%) were premature infants (less than 37 weeks of gestational age), 15,800 (3.2%) were LBW infants and 562 were VLBW infants. Totally 238 infants were diagnosed as having CH with an incidence of 1/2099; Seventeen were premature infants with an incidence of 1/1300, 16 were LBW infants with an incidence of 1/990, and 2 were VLBW premature infants with an incidence of 1/280.

We did not obtain sequential specimens or use a lower screening threshold for this subpopulation due to such a large screening population. Our screening data revealed a remarkable TSH rising at born in infants with gestational age of 33-36 weeks ( $P < 0.05$ , compared with those less than 32 weeks) (Figure 1). It indicates that delayed TSH levels rise may occur in some premature infants. Korada et al<sup>4</sup> showed that if a cut-off of 10 mU/L was selected, one infant out of the 2238 premature infants will be "missed" on the first screening that are subsequently found to have profound thyroid dysfunction and requires thyroxine replacement therapy; Korada et al<sup>4</sup> then suggested a second TSH screening in preterm infants may be unnecessary if a lower TSH threshold of 6 mU/L is adopted. Among the premature

infants in our screening data, 456 infants had a TSH value between 6.0 and 9.0 mU/L (in the upper half of the normal limits). According to their recommendation, all these infants should be recalled for repeat analysis at a corrected gestational age of 36 weeks, otherwise a significant number of hypothyroid cases may be "missed". Such "missing" may also more commonly occur in the LBW and VLBW infants. Our screening data showed that the LBW and VLBW infants had significantly lower TSH value at birth when compared to the NBW infants ( $1.95 \pm 1.42$  vs.  $2.4 \pm 1.59$ ,  $2.06 \pm 1.37$  vs.  $2.4 \pm 1.59$ , both  $P < 0.05$ ) (Figure 2). As reported, there is a high incidence of delayed TSH increase in VLBW infants and LBW infants. Therefore, some screening programs routinely screen again at 2 weeks and 6 weeks of age for all VLBW and all LBW infants in the neonatal intensive care unit. Incidence of hypothyroidism with delayed TSH



**Figure 1** Thyroid stimulating hormone (TSH) value in infants with different gestational age.



**Figure 2** Thyroid stimulating hormone (TSH) value in infants in different birth weight groups.

elevation in VLBW infants was reported to be 1:400.<sup>5</sup> Thus, a large number of LBW and VLBW hypothyroid infants in our cohort may have been missed. However, if the TSH threshold of 6 mU/L for premature babies is adopted, the recall rate will be extremely high and false-positive screening results may have an inadvertent effect on parental stress (both emotional and financial stress), family relationships, and perceptions of a child's health. So it is a paradox and is not advisable to be applied in mainland China now with such a large population base.

In order to avoid missing CH in the premature sick infants and low birth weight infants, we now retest all the sick newborns in the NICU at our hospital. It is far not enough, because they only account for a very small number in the whole province. But when the analysis is repeated, it means more financial burden for the parents since there is still a large portion of the children with no medical insurance. It also poses a big challenge for the newborn screening centre. Like other concerns aforementioned, repeating analysis or not for a particular population is still controversial in some regions with better economical status in China. The optional testing strategy which is appropriate for various parts of China should be further explored.

**References**

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