REVIEW ARTICLE

Neonatal Thyroid-stimulating Hormone Test as Prevention of Congenital Hypoteroids in Newborn: Review

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ABSTRACT

Congenital hypothyroidism can cause lower intellectual abilities in children, which is caused by a lack of thyroid hormone while still in the womb. Data from medical records at the RSCM in Jakarta, Indonesia, and the RSHS in West Java, Indonesia, children's endocrine clinics in 2012-2013 shows that more than 70% of congenital hypothyroidism sufferers were detected after the age of 1 year, so that patients had experienced permanent lower intellectual abilities, so early detection of congenital hypothyroidism is very important. According to the 2014 Minister of Health Decree, the neonatal TSH examination is a sensitive examination for detecting primary congenital hypothyroidism using the Dissociation Enhanced Lanthanide Fluoro Immuno Assays (DELFIA) method at the age of the baby, 24 to 72 hours after birth.. The method used in writing this scientific article is article literature. This examination is very important to early detection of congenital hypothyroidism because the late diagnosis of congenital hypothyroidism can cause permanent intellectual instability in children with an average IQ value below 70. Neonatal TSH levels of less than 20 U/mL are normal, while Neonatal TSH levels of ≥ 20 U/mL show a high result and must be confirmed by T4 and FT4 examination. If the neonate's TSH level is high accompanied by an increase in T4 or low FT4 levels, then a diagnosis of primary congenital hypothyroidism can be made. Neonatal TSH examination for newborns is very important to prevent permanent lower intellectual abilities in children.
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INTRODUCTION

Congenital hypothyroidism (CH) is a disorder resulting from a low thyroid hormone in babies, which can be caused by anatomical abnormalities, such as abnormalities in the structure of the thyroid gland (dysplasia and hypoplasia), low thyroid hormone (atherosis), abnormalities in the thyroid gland (dysplasia and hypoplasia), location of the of the thyroid gland (ectopic gland), or the inability of the thyroid gland to produce thyroid thyroxine due to thyroid metabolism disorders (dysmorphogenesis). (1) (4) (5). Thyroid hormones are very important for neurological growth, especially at the age of 0–12 months (6). Thyroid hormones also function to regulate body metabolism and bone and nerve growth (2) (6). Infancy is an important period for brain growth; during this period, sufficient levels of thyroid hormone are needed (7) (11). If during this period thyroid hormone is deficient, it can cause mental retardation and growth failure (8) (9) (10). According to the Ministry of Health in 2015, the global CH incidence rate was 0.03% of live births. If this percentage ratio is adjusted, it is estimated that more than 1600 babies will suffer from hypothyroidism every year (12) (13). While in Asia Pacific countries the case of CH is in Singapore at 1:3500, Australia at 1:2125, China at 1:2468, New Zealand at 1:960, Thailand at 1:1809, Philippines at 1:2673, Malaysia at 1:3029. (IDA, 2017) (12). In Indonesia, from 11 provinces where screening was carried out from 2000 to 2013, 73 cases of congenital hypothyroidism were found in 199,708 babies (1: 2736). Based on this, thyroid hormone screening is very important to prevent congenital hypothyroidism (15). Neonate TSH is an examination that is currently recommended for screening neonate TSH. The purpose of this scientific literacy is to provide information regarding the importance of examining neonatal TSH in newborns as an effort to detect and prevent congenital hypothyroidism in children early (17).

The importance of neonatal TSH screening as a measure to detect congenital hypothyroidism cannot be overstated. Congenital hypothyroidism (CH) is a condition present at birth where the thyroid gland is either absent, underdeveloped, or malfunctioning, leading to insufficient production of thyroid hormones

(18). These hormones are crucial for normal growth and brain development, particularly in the early stages of life (17).

One of the most effective ways to screen for congenital hypothyroidism is through measuring thyroid-stimulating hormone (TSH) levels in newborns. TSH is a pituitary hormone that regulates thyroid hormone production. Elevated TSH levels in the blood may indicate an underactive thyroid gland, which is a characteristic feature of congenital hypothyroidism (18).

The primary reason for the significance of neonatal TSH screening is its role in mitigating the long-term effects of congenital hypothyroidism. Without early diagnosis and treatment, children with CH can experience irreversible damage to their cognitive and physical development. By identifying affected infants shortly after birth, healthcare providers can initiate treatment before the onset of symptoms, ensuring that these children can grow and develop normally. (17) (16)

Moreover, neonatal TSH screening has been shown to be cost-effective. The relatively low cost of the screening test is outweighed by the savings in healthcare costs associated with treating the complications of undiagnosed and untreated congenital hypothyroidism. Preventing the need for extensive medical care, special education, and other services for children with developmental delays and disabilities significantly reduces the financial burden on families and healthcare systems.

ETIOLOGY, CLINICAL SYMPTOMS, AND SCREENING TEST FOR CONGENITAL HYPOTHYROIDISM

Etiology of Congenital Hypothyroidism

Congenital hypothyroidism is a disorder in babies due to thyroid hormone deficiency that can be caused by anatomical abnormalities such as abnormalities in the thyroid structure (dysplasia and hypoplasia), lack of thyroid hormone formation (athiroisis), abnormalities in the location of the thyroid gland, or inability of the thyroid gland to produce thyroxine due to abnormality of the metabolism of the thyroid gland (dyshormogenesis) (18). Thyroid hormones are very important for neurological growth, especially in first-year life (19). Thyroid hormones too function to regulate the body's metabolism and bone and nerve growth (IDAI, 2017).
Congenital hypothermia is a cause of intellectual instability in children's; with an IQ score below 70, the child's IQ score will get lower as diagnosis and therapy are delayed (18) (19) (20). More than 95% of newborns with congenital hypothyroidism are asymptomatic at birth. A review of medical records at the pediatric endocrine clinic at Hasan Sadikin Hospital and Cipto Mangunkusumo Hospital in 2012-2013 shows that more than 70% of congenital hypothyroidism sufferers were diagnosed later in life. 1 year, so the child has experienced permanent mental retardation; only 2.3% can be recognized before the age of 3 months (12) (21). According to data from the Ministry of Health in 2015, there were 64 inpatients with neonatal jaundice at the Neonatal HCU at RSUP Dr. Moewardi Surakarta, and there were 5 subjects (7.8%) who were classified as having secondary hypothyroidism with TSH hormone levels that were more than normal (> 9 uIU/mL) and FT4 levels higher than normal values. Without early detection and therapy efforts, in the long term this situation will cause the quality of human resources in Indonesia to decline and will become a major public health problem in the future (20).

TSH (Thyroid Stimulating Hormone)

The thyroid is an endocrine gland. It is located at the front of the neck and consists of the right lobe and the left lobe (21). The two lobes are each 5 cm long and are fused in the midline like a butterfly (22). Thyroid disease is an abnormal condition resulting from disturbances in the thyroid gland in the form of changes in form or function (excessive, hypo, or normal) (21). The hormones produced by the thyroid gland are T3 (triiodothyronine) and T4 (thyroxine) (21). The active form of the T3 hormone is not only produced in the thyroid gland, but also in other body tissues by converting T4 to T3 (23). In the anterior pituitary gland, the hormone TRH (thyrotropin-releasing hormone) regulates the production of thyroid hormone in the hypothalamus and TSH (thyroid stimulating hormone) (23). The production of T3 and T4 hormones is influenced by a feedback mechanism involving the TSH hormone (24). When the body is deficient in T3 and T4, there is feedback from the pituitary gland to release more TSH (24). When there is too much T3 and T4 in the body, this process works in reverse (24). The pituitary gland provides feedback that it releases small amounts of TSH. This system only works if everything functions well.

Congenital hypothyroidism can be temporary or permanent. The severity of congenital hypothyroidism seen from serum TSH values > 100 µU/L is considered severe, as is the age of onset of hypothyroidism (severe intrauterine) (26). The most common form is permanent or primary congenital hypothyroidism due to thyroid dysgenesis with high serum TSH levels (25). Permanent congenital hypothyroidism requires lifelong treatment, while temporary congenital hypothyroidism does not need to (27). Screening for congenital hypothyroidism in newborn babies is one of the efforts to get a better generation, because screening for congenital hypothyroidism is very important. Hypothyroid screening should not only be carried out on newborns but also needs to be carried out on babies over six months because the clinical manifestations in hypothyroid babies will become more obvious as they get older (22).

Clinical Symptoms of Congenital Hypothyroidism

The clinical symptoms of congenital hypothyroidism in

children are delayed motoric development, constipation, decreased activity, macroglossia, paleness, distinctive face, difficulty eating, hypotonia, and umbilical hernia, while the typical symptoms are a swollen face (myxedema), pseudotelorism, skin mottling (Cutis marmorata), widened fontanel, large belly, large tongue, and widened fontanel (23).

The symptoms of congenital hypothyroidism at the beginning of a baby's life are very vague and atypical, while delays in treatment for congenital hypothyroidism will result in impaired physical growth and permanent mental retardation. Therefore, prevention and early treatment with thyroid hormones can prevent physical and mental morbidity, and monitoring is needed to produce optimal treatment results and child growth and development (24).

Pathophysiology of Congenital Hypothyroidism

Based on Figure 1 The hormones thyroxine (T4) and triiodothyronine (T3) are produced by the thyroid gland; the formation process is influenced by a feedback mechanism involving thyroid-stimulating hormone (TSH). When thyroid hormone production increases, TSH production decreases, and conversely, when thyroid hormone production is insufficient, TSH production increases (24). Thyroid hormone plays a very important role in various metabolic processes of proteins, carbohydrates, and fats and has a physiological influence on all organ systems of the human body. Deficiency or excess of thyroid hormone disrupts various physiological processes and functions and affects growth and development in various tissues, including the nervous system (25)

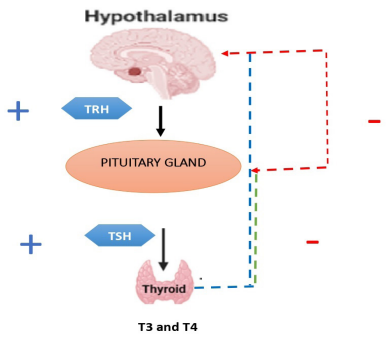

Figure 1: Mechanism of action of the TSH hormone

Prevention of congenital hypothyroidism

Neonatal thyroid stimulating hormone test in newborns Screening for congenital hypothyroidism is a test carried out on babies who are a few days old to select babies who suffer from congenital hypothyroidism from healthy babies. Newborn screening can detect congenital disorders as early as possible, so that if they are discovered immediately, intervention and treatment can be carried out as quickly as possible by Permenkes No. 78 of 2014, namely that every newborn aged 48–72 hours is screened for neonates, at least congenital hypothyroidism screening, and IDAI recommendations (No. 09/REK/PP/IDAI/07/2014, namely to carry out congenital hypothyroidism screening on all newborns (26)

One of the most effective screening examinations for congenital hypothyroidism is the Neonatal Thyroid Stimulating Hormone (TSH) test (22). According to the Indonesian Pediatrician Association (IDAI) in 2017, screening using the neonatal TSH test is the most sensitive examination to find primary congenital hypothyroidism. Primary CH screening is effective when the baby is more than 24 hours old, and the best screening peak is 48 hours to 72 hours after birth. (27).

Based on Figure 2, The method used for testing Neonatal Thyroid Stimulating Hormone is Dissociaton Enhanced Lanthanide Fluoro Immuno Assays (DELFIA). This method uses a two-site fluoroimmunometric assay based on the Direct Sandwich technique against two monoclonal antibodies that attach directly to two antigen determinant sites on the hTSH molecule.

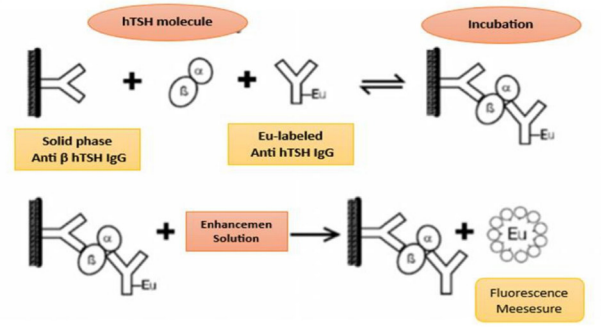

Figure 2: Principles of examining neonate TSH hormones using the DELFIA method

According to the 2014 Minister of Health Regulation on Congenital Hypothyroid Screening, TSH examination of neonates can be carried out using the Dissociation Enhanced Lanthanide Fluoro Immuno Assays (DELFIA) method. This method uses two fluoroimmunometric analysis points based on the direct sandwich antibody technique, which attaches directly to the two antigen-determining sites of the hTSH molecule. What is used is whole blood, which is taken through the baby's heel (heel prick), and then the capillary blood sample is dropped onto special paper that has been marked with the patient's identity until the paper circle is completely filled and then dried (28).

The most ideal time for blood specimen collection is when the baby is 48 to 72 days old. It is best not to take samples from babies aged 24 hours because at that time the neonate's TSH level is still high and will give a falsely high value (28). The specimen used for neonatal TSH examination is dried blood spot (DBS). If the results of the neonatal TSH examination are <20 µU/mL, then

the results are considered normal.

Based on Table I, TSH Level < 10 µU/mL result interpretation is normal; action required is No further testing is needed. Patients with TSH levels in this range are considered to have normal thyroid function and should follow routine follow-up schedules as advised by their healthcare provider. TSH Level 10–20 µU/mL result interpretation is borderline/indeterminate; a repeat dry blood spot (DBS) test should be conducted within 1-2 weeks. This interval allows for monitoring any potential changes in TSH levels that may indicate emerging thyroid issues. If TSH level > 20 µU/mL result interpretation is elevated/possible hypothyroidism, action required is immediate confirmatory testing with serum TSH and free T4 levels. Elevated TSH levels in this range strongly suggest hypothyroidism, and prompt confirmatory testing ensures accurate diagnosis and timely initiation of appropriate treatment. These guidelines ensure effective monitoring and management of thyroid function, helping to identify and address potential thyroid disorders promptly (IDAI, 2017). Based on Figure 3, if the neonate's serum TSH level is high, accompanied by low T4 or FT4 levels, a diagnosis of primary congenital hypothyroidism can be made, and thyroxine medication must be given immediately (26). The administration of thyroxine must be consulted with an endocrinologist or pediatrician (30). The results of the confirmation examination are communicated to the family, the doctor in charge of the health worker, or the midwife. Explanations are given by experienced officers (31).

Table I: Sample Examination Results and Confirmation Tests

TSH Level (µU/mL)	Result Interpretation	Action Required
< 10	Normal	No further testing needed. Routine follow-up.
10 - 20	Borderline/Indeterminate	Repeat DBS test within 1-2 weeks.
> 20	Elevated/Possible Hypothyroidism	Immediate confirmatory serum TSH and Free T4.

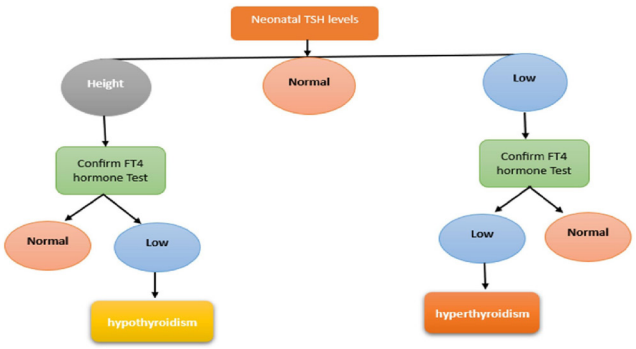

Figure 3: Algorithm for neonatal TSH examination results

CONCLUSION

Neonatal TSH screening is a vital public health measure that ensures the early detection and treatment of congenital hypothyroidism. By preventing the severe and often irreversible consequences of untreated CH, this screening test plays a crucial role in safeguarding the health and developmental potential of newborns. Ensuring that all infants undergo TSH screening shortly after birth is essential for promoting optimal health outcomes and enhancing the quality of life for affected children. Based on the results of the discussion above, it can be concluded that neonatal TSH examination is very important for newborns up to 72 hours of birth as an effort to early detect the presence of congenital hypothyroidism. Neonate TSH levels of less than 20 µU/mL are the norm, and neonatal TSH levels ≥ 20 µU/mL indicate high results. If the neonate's serum TSH levels are high, accompanied by low T4 or FT4 levels, then a diagnosis of primary (congenital) hypothyroidism can be made, so it must be immediately given the drug thyroxine.

REFERENCES

1. Trumpff C, Vandevijvere S, Moreno-Reyes R, Vanderpas J, Tafforeau J, Van Oyen H, et al. Neonatal thyroid-stimulating hormone level is influenced by neonatal, maternal, and pregnancy factors. Nutr Res [Internet]. 2015;35(11):975–81 .doi :org/10.1016/j.nutres.2015.09.002
2. Vandevijvere S, Coucke W, Vanderpas J, Trumpff C, Fauvart M, Meulemans A, et al. Neonatal Thyroid-Stimulating Hormone Concentrations in Belgium: A Useful Indicator for Detecting Mild Iodine Deficiency? PLoS One. 2012;7(10):3–8. doi: 10.1371/journal.pone.0047770
3. Lee SY. Perinatal factors associated with neonatal thyroid-stimulating hormone in normal newborns. Ann Pediatr Endocrinol Metab. 2016;21(4):206–11. doi: 10.6065/apem.2016.21.4.206
4. Vandevijvere S, Moreno-Reyes R, Vanderpas J, Tafforeau J, Van Oyen H, et al. Neonatal thyroid-stimulating hormone level is influenced by neonatal, maternal, and pregnancy factors. Nutr Res. 2015;35(11):975–81. doi :10.1016/j.nutres.2015.09.00
5. Ryckman KK, Spracklen CN, Dagle JM, Murray JC. Maternal factors and complications of preterm birth associated with neonatal thyroid stimulating hormone. J Pediatr Endocrinol Metab. 2014;27(9–10):929–38. doi :10.1515/jpem-2013-0366
6. Çaylan N, Tezel B, Özbaş S, Şahin N, Aydın Ş, Acıcan D, et al. Neonatal thyroid-stimulating hormone screening as a monitoring tool for iodine

deficiency in Turkey. JCRPE J Clin Res Pediatr Endocrinol. 2016;8(2):187–91. doi: 10.4274/jcrpe.2526
7. Lakshminarayana S, Sadanandan N, Mehaboob A, Gopaliah L. Effect of maternal and neonatal factors on cord blood thyroid stimulating hormone. Indian J Endocrinol Metab. 2016;20(3):317–23. doi: 10.4103/2230-8210.179998
8. Zhang Y, Du C, Wang W, Chen W, Shao P, Wang C, et al. Effect of maternal and neonatal factors on neonatal thyroid stimulating hormone: Results from a population-based prospective cohort study in China. J Trace Elem Med Biol . 2018;49(May):151–6. doi : 10.1016/j.jtemb.2018.05.008
9. Saleh DS, Lawrence S, Geraghty MT, Gallego PH, McAssey K, Wherrett DK, et al. Prediction of congenital hypothyroidism based on initial screening thyroid-stimulating-hormone. BMC Pediatr. 2016;16(1):1–5. doi: 10.1186/s12887-016-0559-0
10. Ames JL, Windham GC, Lyall K, Pearl M, Kharrazi M, Yoshida CK, et al. Neonatal Thyroid Stimulating Hormone and Subsequent Diagnosis of Autism Spectrum Disorders and Intellectual Disability. Autism Res. 2020;13(3):444–55. doi : 10.1002/aur.2247
11. Raza A, Barkat A, Fatima S, Farooqui FF, Chaudhri N, Haider S. Diagnostic evaluation of heel prick newborn screening of thyroid stimulating hormone on dissociation-enhanced lanthanide fluorescence immunoassay with the establishment of reference value in Pakistani neonates. J Pak Med Assoc. 2021;71(1B):191–4. doi: doi.org/10.47391/JPMA.561.
12. Tao Y, Hu L, Liu L, Yu M, Li Y, Li X, et al. Prenatal exposure to organophosphate esters and neonatal thyroid-stimulating hormone levels: A birth cohort study in Wuhan, China. Environ Int. 2021;156:106640. doi: 10.1016/j.envint.2021.106640
13. Kemenkes. 2014. Pedoman. Skrining Hipoteroid Kongenital SHK edisi revisi. Jakarta. Kemenkes RI : 2- 20. available from : https://gizikia.kemkes.go.id/assets/file/pedoman/PMK%20No.%2078%20ttg%20Skrinning%20Hipotiroid%20Kongenital.pdf
14. Lain SJ, Bentley JP, Wiley V, Roberts CL, Jack M, Wilcken B, et al. Association between borderline neonatal thyroid-stimulating hormone concentrations and educational and developmental outcomes: a population-based record-linkage study. Lancet Diabetes Endocrinol. 2016;4(9):756–65. doi: 10.1016/S2213-8587(16)30122-X
15. Anastasovska V, Kocova M. Newborn Screening for Thyroid-stimulating Hormone as an Indicator for Assessment of Iodine Status in the Republic of Macedonia. J Med Biochem. 2016;35(4):385–9. doi: 10.1515/jomb-2016-0023
16. Pokrovska T, Jones J, Guftar Shaikh M, Smith S, Donaldson MDC. How well does the capillary thyroid-stimulating hormone test for newborn thyroid screening predict the venous free thyroxine level? Arch Dis Child. 2016;101(6):539–45. doi: 10.1136/archdischild-2015-309529
17. Zhou Y, Xia X, Xu Y, Ke W, Yang W, Li Q. Application of europium(III) chelates-bonded silica nanoparticle in time-resolved immunofluorometric detection assay for human thyroid stimulating hormone. Anal Chim Acta. 2012;722:95–9. doi : 10.1016/j.aca.2012.01.065
18. Grob F, Gutiérrez M, Leguizamón L, Fabres J. Hyperthyrotropinemia is common in preterm infants who are born small for gestational age. J Pediatr Endocrinol Metab. 2020;33(3):375–82. doi: 10.1515/jpem-2019-0461
19. Silvestrin SM, Leone C, Leone CR. Detecção de hipotireoidismo congкnito pela triagem neonatal: a relevância dos valores de corte de hormônio estimulante da tireoide. J Pediatr (Rio J) [Internet]. 2017;93(3):274–80.doi: 10.1016/j.jped.2016.07.006
20. Zhang Y, Du C, Wang W, Chen W, Shao P, Wang C, et al. Effect of maternal and neonatal factors on neonatal thyroid stimulating hormone: Results from a population-based prospective cohort study in China. J Trace Elem Med Biol. 2018;49(May):151–6. doi: 10.1016/j.jtemb.2018.05.008
21. Saraswati, Dian, et al. Food Intake, Dietary Quality and Nutritional Status of Female Adolescent in Tasikmalaya, West Java, Indonesia. *Malaysian Journal of Medicine & Health Sciences*, 2023, 19.6. doi: 10.47836/mjmhs.19.6.13
22. Baridkazemi S, Bahrami H, Gol ER, Farkhani E.M & Hoseini SJ, 2018, Investigation of the Risk Factors for Congenital Hypothyroidism in Iran: A Population Based Case Control Study. International Journal of Pediatrics, doi: 10.22038/ijp.2018.32945.2909
23. Christine E. Cherella and Ari J. Wassner. 2017. Congenital hypothyroidism: insights into pathogenesis and treatment. International Journal of Pediatric Endocrinology. 10.1186/s13633-017-0051-0 : 2-8
24. Diaz A, Diaz EGL. Hypothyroidism. Pediatrics in Review. 2014; 35: 336-49
25. Elvira Dwijayanti et al. 2020. The Thyroid Stimulating Hormone and Free Thyroxine Levels in Correlation with Serum Bilirubin in Neonatal Jaundice. Indonesian Journal of Clinical Pathology and Medical Laboratory. , 27 (1) : 83 – 89. doi.: 10.24293/ijcpml.v27i1.1607
26. Fl6via C, Christensen-Adad et al. 2017. Neonatal screening: 9% of children with filter paper thyroid-stimulating hormone levels between 5 and 10 IU/mL have congenital hypothyroidism. Journal pediatrict 93 (6). doi: 10.1016/j.jped.2017.05.003 : 659-654
27. DELFIA® Neonatal hTSH kit. Perkin-Elmer USA
28. Pusat data dan informasi kementerian Kesehatan

RI. 2015. available from : https://scholar .google. com/ scholar? hl= en& as_sdt=0%2C5&q=Pusat\ t+data+dan+informasi+ kementerian+ Kesehatan+ RI.+ 2015 &bt nG=

29. Ikatan Dokter Anak Indonesia. 2017.Diagnosis dan tatalaksana hipoteroid kongenital. Jakarta. Badan Penerbit Ikatan Dokter Anak Indonesia : 12-18
30. Choo JE, Thambiah SC, Samsudin IN. Prolonged Neonatal Jaundice with Deranged Thyroid Function Test. Malaysian Journal of Medicine and Health Sciences. 2020 Nov 2;16(109).available from : https:// scholar. google. com/ scholar? hl=en &as_ sdt= 0%2C5 &q =Choo +JE% 2C+ Thambiah+ Jaundice+ with+ SC% 2C+ Samsudin+ IN.+ Prolonged+ Neonatal+ Deranged+ Thyroid+ Function+ Test.+ Malaysian+ Journal+ of+ Medicine+ and+ Health+ Sciences. +2020+ Nov+ 2%3 B16 %28 109 %29. &bt nG=
31. Cherella CE, Wassner AJ. Congenital hypothyroidism: insights into pathogenesis and treatment. International journal of pediatric endocrinology. 2017 Oct 2;2017(1):11. doi: 10.1186/s13633-017-0051-0
32. Olivieri A, Corbetta C, Weber G, Vigone MC, Fazzini C, Medda E, Italian Study Group for Congenital Hypothyroidism. Congenital hypothyroidism due to defects of thyroid development and mild increase of TSH at screening: data from the Italian National Registry of infants with congenital hypothyroidism. The Journal of Clinical Endocrinology & Metabolism. 2013 Apr 1;98(4):1403-8. doi: 10.1210/jc.2012-3273