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A Comparative Study on the Thyroid Status of Normal Healthy Newborns and Sick Newborns Suffering From Neonatal Sepsis or Perinatal Asphyxia

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Abstract

Background: *Neonatal sepsis and perinatal asphyxia are still among the leading two causes of neonatal mortality in the developing countries like India. It has been shown in many previous studies that many newborn babies have significantly low thyroid status during sickness.*

Objectives: *1. To study Thyroid status of sick term newborns in relation with perinatal asphyxia & Neonatal sepsis. 2. To compare the thyroid status of sick newborns with normal term newborn babies. 3. To correlate immediate neonatal outcome in sick newborns in relation with altered thyroid status.*

Methods*: 50 babies wereselected from the NICU suffering either from neonatal sepsis or perinatal asphyxia (cases) and another 50 normal term neonates were randomly selected from the postnatal ward avoiding any selection bias (controls). Along with other relevant investigations, blood samples were tested twice for serum levels of TSH, FT3 and FT4 using standard ELISA kits, once on admission and then repeated before discharge. The thyroid status was compared between the two groups of cases and controls.*

Results: *Mean TSH level is significantly (P= 0.04) higher in sick newborns (5.4±7.6μIU/ml) comparative to healthy (3.35±2.51μIU/ml) newborns. Mean FT4 level is lower in sick newborns (1.17±0.53ng/dl) comparative to healthy (1.29±0.28ng/dl) newborns but not statistically significant (P=0.22). Mean FT3 level is lower in sick newborns (219.68±12.94pg/dl) comparative to healthy newborns (223.3±17.78pg/dl) but not statistically significant (P=0.24). MeanTSH-1 is significantly (P=0.005) higher in bad outcome babies (7.26±8.95μIU/ml) than good (2.17±2.12μIU/ml) one. Mean FT3-1 is significantly (P=0.005) higher in good outcome babies (228.38±18.02pg/dl) than bad one (214.78±4.21pg/dl). Mean TSH is significantly (P=0.04) lower at the time of discharge (1.39±0.55μIU/ml) than admission (2.17±2.12μIU/ml) of good outcome babies.*

Conclusion: *1.Sick newborns have significantly increased TSH levels compared to the healthy newborns, indicating a subclinical Hypothyroidism in the former groups. 2. The neonates had significantly lowered levels of TSH & increased levels of FT4, FT3 at the time of discharge in comparison to the levels at the time of admission respectively. 3. The newborns with raised TSH & reduced FT3 levels are associated with poor outcome.*

Keywords: *hypothyroxinemia, sick newborns*

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I. Introduction:

Considerable efforts are devoted worldwide to improve the neonatal health [1]. Advances in diagnostic techniques and therapeutic intervention are designed to enhance the overall outcome of the ever-increasing number of surviving premature and critically-ill infants. According to National Neonatal Perinatal Database (NNPD) 2000 neonatal sepsis is the most common cause of deaths in the country followed by prematurity & birth asphyxia[2]. In developed world the incidence for severe perinatal asphyxia (causing death or severe neurological impairment) is approx. 1/1000 live births, as opposed to 5-10/1000 live births in developing countries[3]. The role of thyroid hormones in neurologic development of newborn has been elucidated & absence of adequate hormones as occurs in congenital hypothyroidism result in adverse neuro-developmental outcome

[4,5]. Currently the neonatal screening for congenital hypothyroidism is performed in all developed countries as well as few developing countries.

In this study we surveyed the thyroid function tests of the normal and sick newborns at the neonatal unit & associated obstetrics unit of Nilratan Sircar Medical College & Hospital, Kolkata, West Bengal to determine the prevalence of hypothyroxinemia among sick newborns suffering from neonatal sepsis or perinatal asphyxia and also to investigate the relationship between thyroxin level and short-term clinical outcome of the sick neonates. Our study also attempted to initiate generating a database on the cut off value of TSH, FT3, FT4 as the reference range, as there is no reference range available at this age group for Indian babies.

II. Materials And Methods:

The present study was conducted in Neonatal intensive care unit (NICU), department of Paediatric Medicine, Nilratan Sircar Medical College and Hospital, Kolkata which is a referral Paediatric Teaching Institution under the West Bengal University of Health Sciences. The duration of the study was a one-year period from April 2012 to March 2013. During this period, a selected group of 100 newborns who had been diagnosed as either Case (newborns diagnosed as PA & NNS) or Controls (Healthy newborns) were subjected to different investigations of blood, including quantitative estimation of TSH, FT4 & FT3 level, sepsis screening tests and blood and/or CSF culture. The neonates have been categorized depending on relevant information& investigations.

Perinatal asphyxia was defined as babies having any one of:a) One minute Apgar score < 4, b) Neonatal neurologic manifestations suggestive of hypoxic-ischemic encephalopathy (HIE), c) Evidence of multisystem organ dysfunction (e.g., CVS, Renal, GI, Hematologic or Pulmonary) consistent with a diagnosis of HIE.

Neonatal sepsis was defined as babies showing positive sepsis screen or Blood culture or both in the background of clinical sepsis. We included 50 neonates aged between 4 to 28 days, gestation: ≥37weeksand birth Weight: ≥2Kg who presented with features of perinatal asphyxia orneonatal Sepsis, as described above.50 babies were randomly selected as controls from the post natal wards avoiding any selection bias. All neonates with congenital anomalies e.g.; lobar Agenesis, TEF, TGA, Complex heart disease, Hydrocephalus were excluded from the study. Also the babies having features of overt congenital hypothyroidism and babies born to mothers having history of thyroid related dysfunction were excluded from the study.

After stabilizing the babies detailed anthropometric measurements were taken and New Ballard scoring system was used to determine the approximate gestational age of the baby. The following tests were done on most of the babies-

1. Routine blood examination: Hb%. TLC, DLC, band cells, Micro-ESR,ANC
2. Acute phase reactant: C-reactive protein.
3. Blood culture.
4. Urea, Creatinine, LFT.
5. USG of Brain
6. CT scan of Brain (if required)
7. Echocardiography (if required)
8. Thyroid status: TSH, freeT4, freeT3

Serum TSH, FT4, FT3 were checked twice after 72 hours of life; one on admission and the other before discharge from neonatal unit.Serum TSH, Free T4 and Free T3 were assayed by ELISA methods using standard ELISA Kits at the central laboratory of NRS Medical College & Hospital, Kolkata.

Statistical analysis has been done by requisite statistical methods using Microsoft windows, Excel 2003 and SPSS 10 statistical software.The results have been considered significant when the 'p' value is less than 0.05 with 95% confidence limit.

Ethical clearance was duly taken from institutional ethics committee and progress of study was duly intimated to the ethics committee time to time.

III. Results And Analysis:

Table. 1: Comparison between Sick & Healthy Newborns (n=100)

Parameters	Sick Newborns (n=50) (Mean±SD)	Healthy Newborns (n=50) (Mean±SD)	P-value
Age in days	6.56±2.1	6.36±1.95	0.59
Weight in Kg	2.64±0.41	2.87±0.52	0.08
AS(1)	2.48±1.56	5.08±0.98	0.00
AS(5)	4.2±2.4	7.08±1.1	0.00
TSH (mU/L)	5.4±7.6	3.35±2.51	0.04
FT4 (ng/dl)	1.17±0.53	1.29±0.28	0.22

FT3 (pg/dl)	219.68±12.94	223.3±17.78	0.24

AS (1) = Apgar score at 1 minute of birth
AS (5) = Apgar score at 5 minutes of birth

Table.2: Comparison between Good & Bad outcomes of Sick Newborns

Parameters	Bad Outcome (n=12) (Mean±SD)	Good outcome (n=38) (Mean±SD)	P-value
Age in days	6.62±2.05	6.44±2.22	0.72
Weight in Kg	2.68±0.46	2.56±0.27	0.28
AS(1)	2.56±1.56	2.33±1.6	0.50
AS(5)	4.43±2.58	3.77±2.15	0.26
TSH-1(mU/L)	7.26±8.95	2.17±2.12	0.005
FT4-1(ng/dl)	1.09±0.55	1.32±0.47	0.17
FT3-1(pg/dl)	214.78±4.21	228.38±18.02	0.005

**TSH, FT4 and FT3 samples taken during illness

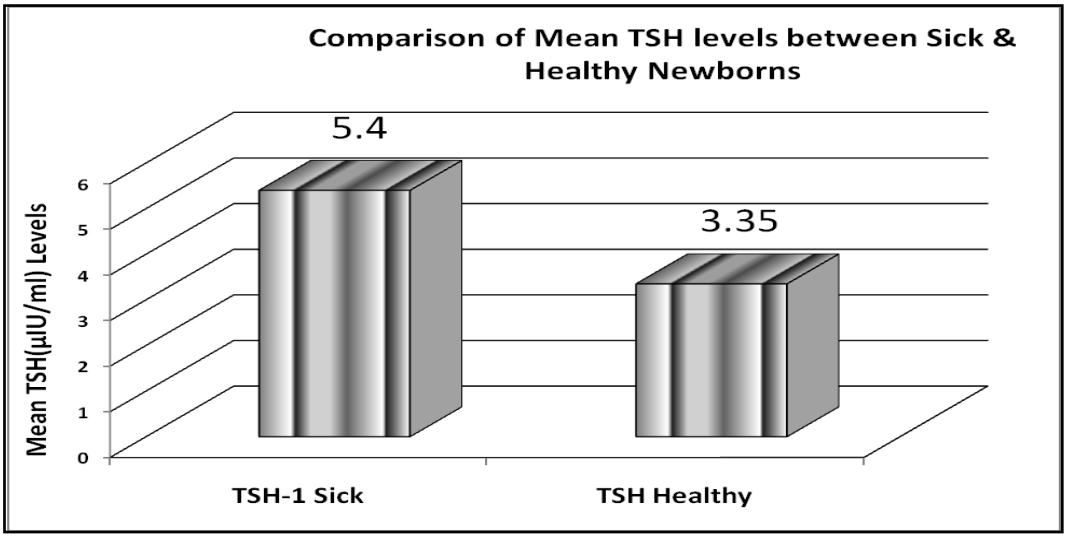

Fig:1. Comparison of Mean TSH levels between Sick & Healthy Newborns Above figure shows mean TSH level is significantly higher in sick newborns comparative to healthy newborns (P= 0.04).

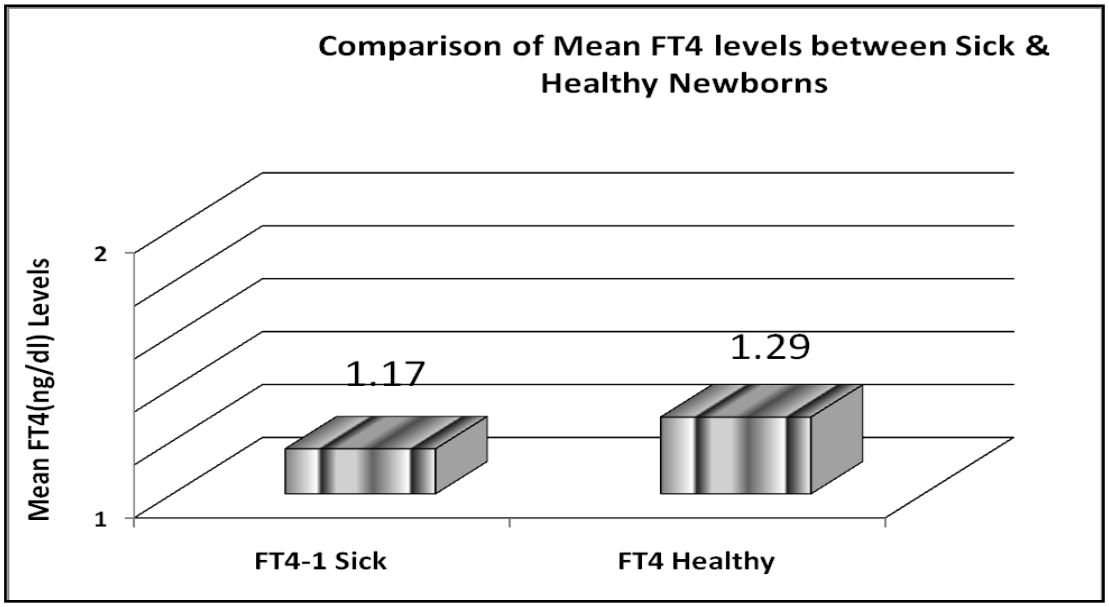

Fig:2 Comparison of Mean FT4 levels between Sick & Healthy Newborns Above figure shows mean FT4 level is lower in sick newborns comparative to healthy newborns but not statistically significant (P=0.22)

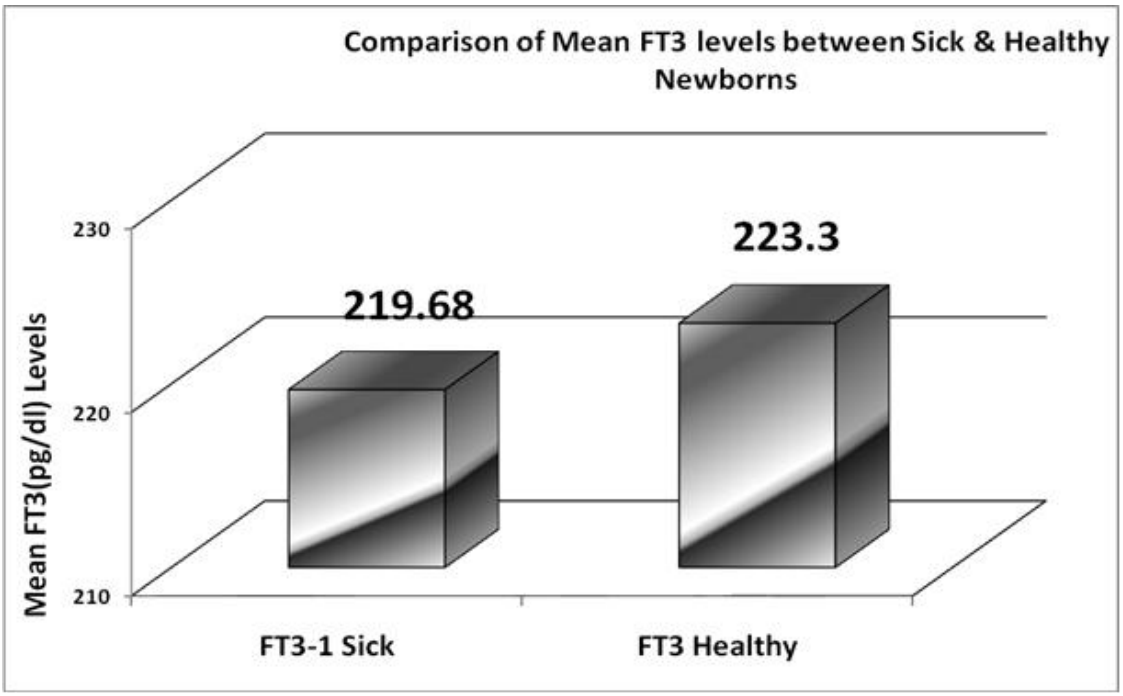

Fig:3 Comparison of Mean FT3 levels between Sick & Healthy Newborns Above figure shows mean FT3 level is higher in sick newborns comparative to healthy newborns but not statistically significant (P=0.24)

IV. Discussion:

After birth, the term baby experiences a surge of TSH as a physiological response to cold environment. The TSH concentration rises to 60-80 mU/L within 30 to 60 minutes after delivery and falls quickly in the first 24 hours to about 20 mU/L, followed by a slower decrease to below 10mU/L after the first postnatal week. The rise in TSH initiates increase of T4 and free T4 to peak levels of 17µg/dl and 3.5 ng/dL, respectively at 24 to 36 hours after birth with a slow decline to adult values over 4-5 weeks. Preterm infants demonstrate a similar but blunted response due to HPT axis immaturity[7].

Hemmati F, Pishva N in their study shows TSH levels (screening test) were about 40-fold higher in critically-ill neonates compared with healthy neonates, while more than four-fifths of them were detected normal in the second sampling done after recovery. The mean FT3 was significantly ($p < 0.001$) lower during the critical illness and it increased after recovery (2.537 and 3.232 pg/ml, respectively). Mean FT4 and mean TSH during the illness and after recovery did not have any significant difference [8].

B.K. Das, Pooja Agarwal, J.K. Agarwal and O.P. Mishra in their study shows the neonates with sepsis had significantly higher mean serum cortisol and lower mean serum total T4 at admission as compared to healthy neonates. The mean serum total T3 level was also lower, but the difference was not statistically significant. The mean serum TSH levels were comparable in both groups. The levels normalised following recovery. Sixteen neonates succumbed to the disease process. The non-survivors had significantly lower mean total T3 and total T4 levels as compared to the survivors. The endocrinal abnormalities are of transient nature as a response to sepsis. Low total T3 and total T4 are the predictors of adverse outcome in neonates with sepsis [9].

Maliheh Kadivar, Reza Parsaei and Arya Setoudeh stated in their study that hypothyroxinemia has considerable prevalence in neonatal intensive care setting and is related with lower birth weight and gestational age. The neonates with either sepsis or asphyxia had lower thyroxin levels compared to others. Whether thyroxin levels are a marker or mediator of short term clinical outcome remains to be determined by further studies [10].

Goldsmit GS, Valdes M, Herzovich V, Rodriguez S, Chaler E, Golombek SG, Iorcansky SSick newborns showed significantly lower T3 and T4 levels compared with healthy infants [T3: -0.97 µg/dL (95% CI -0.89, -1.13) and T4: -4.37 µg/dL (95% CI -2.95, -5.78)]. Only 29 out of 94 (31%) infants presented a normal profile; 37 (39%) infants showed isolated low T3 levels, 20 (21%) infants had low T3 and T4 levels and eight (9%) infants had low TSH, T3, and T4. Of this latter group, five of eight (62%) children died suggesting a significantly higher risk of death for patients with low T3 associated with low T4 and TSH [Risk ratio (RR) 10.75 95% CI 3.93, 29].[11]

Doyle J. Lim, Michelle Kantor Herring; Kathleen H. Leef, Jane Getchell, Louis E. Bartoshesky, and David A. Paul in their prospective study, showed that infants in the sick group had lower T4 on the fifth day of life as compared to infants in the well group and 34% of infants in the sick group had a T4 <10th percentile

compared to 6% of infants in the well group. T4 on day of life 5 was inversely correlated with Score for Neonatal Acute Physiology. However, whether T4 levels are a marker or a mediator of clinical outcome remains to be determined.

Pereira DN, Procianoy RS Shows in their study serum concentrations of TSH, T4, T3 and FT4 are lower in asphyxiated newborns than in normal newborns between 18 and 24 h of life; this suggests central hypothyroidism secondary to asphyxia. Asphyxiated newborns with moderate/severe hypoxic-ischemic encephalopathy present a greater involvement of the thyroid function and consequently a greater risk of death [12].

Kurt A, Aygun AD, Sengul I, Sen Y, Citak Kurt AN, Ustundag B in their study showed decreasedthyroid function at baseline might be associated with a worse outcome of patients with sepsis or septic shock. Although these findings are not consistent, the role of thyroid function in affecting or merely predicting the outcome of sepsis or septic shock merits further investigations[13].

In our study, 100 newborns who had been diagnosed as either Case (newborns diagnosed as PA & NS) or Controls (Healthy newborns) were subjected to different investigations of blood as already mentioned, including quantitative estimation of TSH, FT4 & FT3 level. Out of this 100 newborns 50 were cases (PA & NS) & 50 controls (Healthy). Of these 50 cases 12 expired & 38 survived.

Following are the distributions of outcome bad (NS-56.3%, PA-43.7%) & outcome good (NS-44.4%, PA-55.6%). Outcome bad is slightly more common in male (56.3%) babies, whereas outcome good is slightly more in females (55.6%). Mean TSH level is significantly (P= 0.04) higher in sick newborns (5.4±7.6μIU/ml) comparative to healthy (3.35±2.51μIU/ml) newborns [Fig1]. Mean FT4 level is lower in sick newborns (1.17±0.53ng/dl) comparative to healthy (1.29±0.28ng/dl) newborns but not statistically significant (P=0.22) [Fig2]. Mean FT3 level is lower in sick newborns (219.68±12.94pg/dl) comparative to healthy newborns (223.3±17.78pg/dl) but not statistically significant (P=0.24) [Fig3].

MeanTSH-1 is significantly (P=0.005) higher in bad outcome babies (7.26±8.95μIU/ml) than good (2.17±2.12μIU/ml) one. Mean FT3-1 is significantly (P=0.005) higher in good outcome babies (228.38±18.02pg/dl) than bad one (214.78±4.21pg/dl). Mean FT3 is significantly (P=0.012) higher at the time of discharge (226.72±18.25pg/dl) than admission (214.88±4.40pg/dl) of good outcome babies. Mean FT4 is significantly (P=0.00) higher at the time of discharge (2.53±0.97ng/dl) than admission (1.32±0.47ng/dl) of good outcome babies. Mean TSH is significantly (P=0.04) lower at the time of discharge (1.39±0.55μIU/ml) than admission (2.17±2.12μIU/ml) of good outcome babies.

V. Conclusion

Although our study has a very small sample size, the results are consistent with other trials depicting hypothyroxinemia in sick newborns. We can draw the following inferences from the above study-

1. Sick newborns have significantly increased TSH levels compared to the healthy newborns, indicating a subclinical Hypothyroidism in the former groups.
2. The neonates had significantly lowered levels of TSH & increased levels of FT4, FT3 at the time of discharge in comparison to the levels at the time of admission respectively.
3. The newborns with raised TSH & reduced FT3 levels are associated with poor outcome.

Whether preventive supplementation with thyroid hormones can improve the outcome of this group of patients is still uncertain and further studies with larger sample sizes are required to establish such a therapeutic possibility. Also the generation of a reference range of FT3, FT4 and TSH values in this age group needs large sample cohorts[14].

Limitations of the study: Single centre study with small sample size

Funding: None

Conflicts of interest: None declared

Ethical approval: Approved by the Institutional Ethics Committee and Institutional Scientific Committee

Bibliography:

[1]. Vidyasagar D. A global view of advancing neonatal health and survival. J Perinatol 2002; 22:513-5.
[2]. National Neonatology Forum. Report of National Neonatal Perinatal Database 2000 New Delhi.
[3]. McGuire W 2006 Perinatal asphyxia. Clin Evid511-519
[4]. Fisher DA. Disorders of thyroid in the newborn and infant. In: Sperling MA, editor. Pediatric Endocrinology. 2nd ed. Philadelphia, PA: WB Saunders; 2002. p. 161-86.
[5]. Hadeed AJ, Asay LD, Klein AH, Fisher DA. Significance of transient postnatal hypothyroxinemia in premature infants with and without respiratory distress syndrome. Pediatrics 1981;68(4):494-8.
[6]. Saex-Llorens X, McCracken GH. Sepsis syndrome and septic shock in pediatrics: current concepts of terminology, pathophysiology and management. J Pediatrics 1993; 123:497-508.
[7]. Vannucci SJ, Hagberg H 2004 Hypoxia-ischemia in the immature brain. J Exp Biol 207:3149-3154
[8]. Evaluation of thyroid status of infants in the intensive care setting Hemmati F, PishvaN; Singapore Med J 2009; 50(9): 875
[9]. Serum Cortisol and Thyroid Hormone Levels in Neonates with Sepsis ,B.K. Das, Pooja Agarwal, J.K. garwal and O.P. Mishra, **[**Indian J Pediatr 2002; 69 (8) : 663-665

[10]. The Relationship between Thyroxine Level and Short Term Clinical Outcome among Sick Newborn Infants MalihehKadivar, Reza Parsaei, and Arya Setoudeh;ActaMedicaIranica 2011; 49(2): 93-97.
[11]. Evaluation and clinical application of changes in thyroid hormone and TSH levels in critically ill full-term newborns.Goldsmit GS[1], Valdes M, Herzovich V, Rodriguez S, Chaler E, Golombek SG, Iorcansky SJ Perinat Med. 2011 Jan;39(1):59-64. doi: 10.1515/JPM.2010.120. Epub 2010 Oct 27
[12]. Effect of perinatal asphyxia on thyroid-stimulating hormone and thyroid hormone levels. Pereira DN, Procianoy RS. Pubmed, Acta Paediatr. 2003; 92(3):339-45**.**
[13]. Serum thyroid hormones levels are significantly decreased in septic neonates with poor outcome. Kurt A, Aygun AD, Sengul I, Sen Y, Citak Kurt AN, Ustundag B. J Endocrinol Invest. 2011 Apr; 34(4):e92-6. doi: 10.3275/7261. Epub 2010 Sep 9.
[14]. Mouzinho A, Rosenfeld CR, Sanchez PJ, Risser R. Revised reference ranges for circulating neutrophils in very-low-birth-weight neonates. Pediatrics 1994; 94: 76-82

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