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Reference Interval of Reticulocyte Hemoglobin Equivalent In Healthy-Term Babies Seven Days After Birth

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ABSTRACT

Globally, the prevalence of anemia was highest among children under five years, at 39.7%. The main factor is iron deficiency (ID). However, the particular iron status parameter for early detection of ID in babies has yet to be determined. To establish reference intervals for reticulocyte hemoglobin equivalent (Ret-He) in healthy term babies seven days after birth. A cross-sectional study of Ret-He in healthy-term babies seven days after delivery was conducted from April to December 2018 at Idaman Banjarbaru Hospital. Two hundred seventy-seven healthy-term babies met the inclusion criteria. There were 145 (52.35%) male babies and 132 (47.65%) female babies. The reference interval for Ret-He at P2.5-P97.5, P3-P97, and mean ±2SD was 29.06 to 40.11pg, 29.24 to 39.97 pg, 29,46 to 38.01 pg, respectively. In addition, the reference interval for male babies Ret-He at P2.5-P97.5, P3-P97, and mean ±2SD was 28.17 to 41.44 pg, 28.54 to 41.25 pg, and 29.28 to 41.24 pg, respectively. The reference interval for female babies Ret-He at P2.5-P97.5, P3-P97, and mean ±2SD was 29.73 to 39.80, 30.00 to 39.60, 29.71 to 0.43 pg, respectively. Conclusion: The reference interval for Ret-He in healthy-term babies one week after birth can be used as a benchmark.

1. Introduction

Globally in 2019, anemia was 22.8%, with the highest prevalence in children under five years, 39.7%; and the leading cause was a nutritional iron deficiency [1]. Prevalence of anemia in most of Africa, Latin America, and Southeast Asia ranges from 28 to 65 percent in children [2], [3]. One study reported iron deficiency anemia (IDA) in 32% of 100 infants aged 9-11 months [4]. Another study stated that iron deficiency (ID) and IDA incidence in infants 1–4 months was 10.9% and 58.6% [5]. Low iron stores at birth, iatrogenic iron loss, and high growth velocity after birth make iron deficiency in term babies [6- 8]. Iron is vital in the maturation of the central nervous system and is crucial to neural myelination and neurotransmitter function [9], [10]. Early enteral iron supplementation should be given as soon as possible after birth to prevent ID [11], [12]. Neurological disorders will manifest in the long term if oral iron supplementation is delayed [13]. Although ID can be amended by iron supplementation, the cognitive and behavioral deterioration detected in children with ID may not be completely corrigible [14], [15]. Some term babies still develop ID even has been given iron supplementation; therefore, early ID detection should be ideal. Reticulocyte hemoglobin equivalent (Ret-He), generally formed during reticulocyte count by mostly hematological analyzers without an additional blood sample, seems promising. Reticulocyte hemoglobin equivalent indicates the sufficiency of iron in the bone marrow considering this test measures Hb in reticulocytes or iron input in red blood cells during erythropoiesis [16], [17]. Unlike erythrocytes, reticulocytes have a shorter lifespan, and thus their hemoglobin content better reflects current iron availability for hematopoiesis [18], [19]. The reference interval of reticulocyte parameters for babies under six months old is minimal. In one study, [20] report the reference range of reticulocyte parameters in healthy babies aged 1–4 months. Therefore, the study aims to establish reference ranges for reticulocyte hemoglobin content (Ret-He) in healthy-term babies seven days after birth.

2. Materials and Methods

2.1 Study Population

A cross-sectional study of Ret-He in healthy-term babies seven days after birth was conducted from April to December 2018 at Idaman Banjarbaru Hospital. Inclusion criteria are healthy-term babies (gestational age 37-42 weeks) with good tone, breathing or crying immediately, no resuscitation and a birth weight≥2500 g [21]. Exclusion criteria were hematological diseases, congenital anomalies, or a complete blood count (CBC) inadequacy within seven days after birth. Furthermore, from the history and physical examination of the babies conducted by the doctor-in-charge, all babies were declared clinically healthy, and the in-charge doctor excluded hematologic disease. The Apgar score for each baby is 8-10 in the 1st minute and 8-10 in the 5th minute. In addition, gestational age, birth weight, length, head, and chest circumference were obtained from the babies' medical records. A parent of each baby signed the informed consent. This study obtained ethical clearance from the Research Ethics Commission of the Medical Faculty of the University of Lambung Mangkurat.

2.2 Blood sampling

Every baby who meets the inclusion and exclusion criteria will be taken a blood sample of 1 ml from the median cubital vein. First, the blood sample was put in a tube with EDTA anticoagulant, homogenized by turning it over and stored in a storage box. Then, a complete blood count and Ret-He examinations were performed by putting a sample of the baby's blood into the Sysmex XN-450 Hematology Analyzer.

2.3 Statistical Analysis

Stipulation of the lower limit of P2.5, P3, or mean-2SD on examining specific parameters is generally used statistically. The WHO and CDC growth charts set the lower limit of Weight-for-age, Length/height-for-age, Head circumference-for-age, and Arm circumference-for-age at P3 [22]. [20] applied the lower limit of Hb at P3 and P5 to assert whether someone is anemic or not. Certainly, establishing the lower limit of Hb with P2.5, or P5, by considering race, ethnicity, age, gender, and altitude above sea level [23]. Another study used the lower limit of the parameter Mean±2SD, with the lower limit being <-2SD. One study declared that undernutrition and poor malnutrition were categorized into undernutrition status with a z-score <-2 SD [24]. The selection of the reference limits previously depends on the need. No consensus/data states that a specific parameter reference interval must have a peculiar reference limit. This study's results comply with all reference interval limits to be used flexibly. SPSS ver25 analyzes all infant anthropometry

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assessments and laboratory results of Ret-He for P2.5, P3, P97, P97.5, mean and standard deviation (SD). All data are presented in the narrative and table. Reference interval P2.5-P97.5 means that 95% of the average individuals have normal laboratory results, while the other 5% may not be sick outside the normal limits, in the same way for P3-P97, and mean±2SD.

3. Findings And Discussion

Two hundred seventy-seven babies met the inclusion and exclusion criteria, containing 145 (52.35%) male babies and 132 (47.65%) female babies. Healthy-term babies' characteristics can be seen in Table 1. Furthermore, the reference interval of Ret-He in healthy-term babies seven days after birth is shown in Table-2.

Table 1 Characteristics of healthy-term babies seven days after birth

Delivery / Labor	
Spontaneous Delivery	152 babies
Caesarean Section	125 babies
Gender	
Male	145
Female	132
Birth Weight	2,500 - 4,450 g
Birth Length	44.0 - 55.0 cm
Head circumference	27.0 - 37.5 cm
Chest circumference	26.0 - 37.5 cm

Table 2 displays the Ret-He values from the 2.5th to 97.5th percentiles, 3rd to 97th percentiles, and mean ±2SD for all babies, male and female babies. In addition, Table 2 presents the lower limit of Ret-He, which can be used to decide whether an infant has iron deficiency (ID) or iron deficiency anemia (IDA). Table 2 also shows that the lower limit of P2.5, P3, and mean ±2SD of Ret-He values for male babies is lower than for female babies.

Ferritin, soluble transferrin receptor (sTfR), and transferrin saturation are preeminent parameters to value a person's iron status, including babies. One study, applying indicators of CBC, ferritin, sTfR, and transferrin

Table 2 Reference interval of Ret-He in healthy-term babies seven days after birth

Ret-He (pg)	N	$P_{2.5} - P_{97.5}$	$P_3 - P_{97}$	Mean (SD)	Mean ± 2SD
All babies	277	29.06 - 40.11	29.24 – 39.97	35.17 (2,84)	29,46 – 38.01

Male babies	145	28.17 – 41.44	28.54 – 41.25	35.26 (2.99)	29.28 – 41.24
Female babies	132	29.73 – 39.80	30.00 – 39.60	35.07 (2.68)	29.71 – 40.43

saturation, got that the incidence of iron depletion, ID, and IDA was highest in babies aged 0 months, 9.5%, 14.2%, and 11.8%, respectively [11]. The obstacle is that the test needs a large amount of blood, is affected by the daily phase, inflammation, and infection, is costly and is qualified for specific health facilities. This study is proposed to achieve alternative tests that can establish the iron status of babies seven days after birth to assess the degree of iron deficiency, which can overcome iron deficiency earlier. The Ret-He test can be run in conjunction with the CBC examination. The amount of blood drawn is small in quantity, easy to do, low-cost, unaffected by inflammatory or infectious factors, and widely available in health facilities.

Reference interval data or normal range Ret-He for healthy-term babies do not yet exist in Indonesia. Assuming that a baby born at term with good tone, breathing, or crying immediately, does not have resuscitation weighing >2500 g, is a healthy baby. Table 1 displays that the lower limits of body length and head circumference of all babies in this study were above the WHO growth curve's 3rd percentile (P3); this affirms that all babies in this study were healthy and physically normal in size [25]. This study signifies that the lower limit Ret-He for healthy-term babies can be taken at P2.5, P3, or mean-2SD, i.e., 29.06 pg, 29.24 pg, or 29.46 pg. This study moreover presented that for male babies, the P2.5, P3, and mean-2SD values of Ret-He were 28.17 pg, 28.54 pg, 29.28 pg. For female babies, the P2.5, P3, and mean-2SD values of Ret-He were 29.73 pg, 30.00 pg, and 29.71 pg, respectively. Therefore, the lower limit value of Ret-He above is practically the same as the lower limit value of Ret-He for babies aged six months – 2 years, namely: 29 pg [26]. By knowing the lower limit of the reference range of Ret-He, we can determine ID and IDA with a combination of Hb values. A baby is said to be ID if his Hb is normal and his Ret-He value is below the lower limit of Ret-He. A baby is said to be IDA if the Hb is below normal and the Ret-He value is below the lower limit of Ret-He.

Until now, no definite cut-off value of Ret-He has been reported for detecting iron deficiency and IDA in babies, especially those under six months. Ret-He Cut-off values vary [27- 29]. The Ret-He cut-off value for iron deficiency in babies regardless of gestational age was 25 pg [30]. Ret-He cut-off values for term babies aged two days, four months, and 12 months were 31.6 pg, 29.2 pg, and 29.0 pg, respectively [28]. Löfving's study showed that the cut-off value of Ret-He was significantly lower in babies aged four months, namely 25.6 pg compared to 27.4 pg at birth and 28.1 pg at 28-72 hours [31]. [5] report that Ret-He cut-off values for IDA at 1, 2, 3, and 4 months were 22.25 pg, 20.3 pg, 19.05 pg, and 17.55 pg. The difference in the cut-off value (lower limit of P2.5, P3, P.5, Mean-2SD) of Ret-He in this study compared to the studies mentioned above may be due to variations in the characteristics of the study subjects and risk factors that increase the prevalence of iron deficiency.

4. Conclusion

The reference range of Ret-He in healthy-term babies within seven days after birth can be set to P2.5-P97.5, P3-P97, and mean ±2SD was 29.06 to 40.11 pg, 29.24 to 39.97 pg, 29,46 to 38.01 pg, respectively. In addition, the reference interval for male babies Ret-He at P2.5-P97.5, P3-P97, and mean ±2SD were 28.17 to 41.44 pg, 28.54 to 41.25 pg, and 29.28 to 41.24 pg, respectively. The reference interval for female babies Ret-He for Ret-He at P2.5-P97.5, P3-P97, and mean ±2SD was 29.73 to 39.80 pg, 30.00 to 39.60 pg, 29.71 to 0.43 pg, respectively. Therefore, the reference interval of Ret-He for healthy-term babies seven days after birth can be used as a benchmark in Indonesia. In the future, this study's results can be developed

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by examining ferritin, transferrin saturation, and C-reactive protein so that the reference interval of Ret-He can be more reliable.

Ethical Clearance:
This study attained ethical clearance from the Research Ethics Commission of the Medical Faculty of the University of Lambung Mangkurat.

Informed Consent Statement:
Informed consent was gained from all subjects committed to the study.

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