Original Article

Prevalence of neonatal anemia in well-appearing term neonates Running head: Prevalence of anemia in healthy term neonates

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Abstract

Background: Anemia in infancy is a global public health challenge. Low hemoglobin at birth is one of the significant risk factors to develop anemia in late infancy. However, prevalence of neonatal anemia remains unclear. Therefore, we conducted the study to assess the prevalence of neonatal anemia in well-appearing term infants.

Methods: This was a retrospective study conducted in a university hospital in Thailand. Well-appearing term infants born between March 2017 and June 2017 in the Thammasat University Hospital (TUH) were included. Exclusion criteria were severe congenital malformation, syndromes, admitted in NICU or death within 48 hours of life. Neonatal anemia was defined as venous hematocrit less than 45%. Data collection was obtained from medical records. Prevalence and causes of anemia were presented in percent; Fisher's-exact and Student's t-test were used to analyze risk factors of anemia.

Results: Data of 455 neonates were analyzed. Thirty-three neonates had anemia (7.3%). Most common identified causes of anemia were feto-maternal transfusion (11 neonates, 33.3%) and feto-placental transfusion (8 neonates, 24.2%). There were 10 neonates (30.3%) in whom causes of anemia can not be identified with our basic investigation.

Conclusion: In our small study, neonatal anemia was not uncommon. Feto-maternal and feto-placental transfusions were the two leading causes of neonatal anemia. Therefore, there must be awareness of this condition in healthy term neonates to prevent long-term effects.

Keywords: Neonatal anemia, term infants, feto-maternal transfusion, feto-placental transfusion

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Introduction

Anemia in infancy is a global public health challenge in the developing and developed countries. Anemia may be caused by nutritional deficiency, infection, hematological or hereditary diseases. Iron deficiency anemia is one of the major causes of anemia in infancy. It is correlated with higher child mortality and increased risk of cognitive and psychomotor developmental impairment.[1 - 4] The negative effects of iron deficiency on cognitive function may be irreversible, even with iron supplementation.[2] Normally, infant birth iron stores play a major role in protecting iron deficiency anemia during early infancy. However, in some situation such as low maternal iron status, impaired placental iron transport or blood loss during perinatal period e.g. feto-maternal and feto-placental transfusion may compromise infants' body iron stores. These infants were at risk of iron deficiency anemia especially during exclusive breast-feeding.[1]

Thus, neonatal anemia is a significant issue because without proper diagnosis and treatment, it can lead to anemia in early infancy. The etiology of neonatal anemia is multifactorial and involves three major causes consisting of blood loss, low red cell production and red cell destruction such as feto-maternal transfusion, placenta abnormalities, birth injuries, infections, marrow or systemic diseases.[5] Normally, infants should have physiologic anemia between 2 - 3 months of age. Consequently, infants with neonatal anemia might develop anemia with extraordinary speed and severity. Most neonates with anemia were asymptomatic and can only be detected by screening. This differs from neonates with severe anemia, who might develop restlessness, tachycardia and heart failure.

Most studies of neonatal anemia were focused primarily on preterm infants. The prevalence of neonatal anemia in well-appearing term infants has not been well studied. Therefore, our project was conducted to assess the prevalence and etiology of neonatal anemia in low-risk term infants.

Methods

This was a retrospective study conducted at Thammasat University Hospital (TUH) during March to June 2017. The inclusion criterion was well-appearing, full-term neonates born at TUH and exclusion criteria were: (i) genetic anomaly or severe congenital disabilities, (ii) admitted to the Neonatal Intensive Care Unit, or (iii) expired within 48 hours of life. The following data were collected from medical records consisting of maternal and neonatal demographic characteristics, weight of placenta, hematocrit taken within 48 hours after birth. For anemic neonates, further investigation included complete blood count, peripheral blood smear for red cell morphology, inclusion body, reticulocyte count, blood group, G6PD-enzyme activity, neonatal direct antiglobulin test, and maternal Kleihauer-Betke test and indirect antiglobulin test. During the study, we routinely did pre-discharge bilirubin and hematocrit screening at 48 hours after birth in all healthy term infants, and delayed umbilical cord clamping was not routinely done. Anemic infants were followed-up after discharge in the high risk clinic for at least 2 months.

In this study, anemia was defined as a hematocrit < 45% within 48 hours postpartum of a full-term neonate.[6] Feto-maternal transfusion was diagnosed if maternal Kleihauer-Betke test was positive.[7] A presumed feto-placental transfusion was assumed to have occurred if the placental weight > 25% of neonatal birth weight.[9, 10] ABO incompatibility was diagnosed in blood group A or B neonates who had blood group O mothers with one or more of the following: positive direct anti-globulin test in infants, positive indirect anti-globulin test in mothers, or peripheral blood smear compatible with ABO incompatibility such as microspherocytosis or polychromasia. Well-appearing neonates was defined as term neonate with no congenital malformation or syndromes, infants who did not require intensive care or infants who were died within 48 hours after birth.

Data from previous studies reported the prevalence of neonatal anemia were 0.5% - 25%.[7, 8] From our institutional previous data, we assumed the prevalence of neonatal anemia in our population was 2%. Based on our assumption with the level of significance of 0.05, power of 0.8, this resulted in 449 participants for the study.

This research was approved by the Institutional Review Board, Faculty of Medicine, Thammasat University.

Statistical analysis

We used descriptive statistics to analyze the prevalence and etiology of neonatal anemia. Analytical statistics were compared to determine factors with potential effects on the prevalence of anemia. The Student's t-test was used for continuous data, and the Fisher's exact test was used for categorical data. Statistical significance (P - value) was specified at < 0.05.

Results

Data of 455 mother-infant dyads were extracted from medical records, 33 of neonates (7.25%) were anemic. Baseline maternal and neonatal characteristics were listed in Tables 1 and 2. Mean maternal age at delivery was 29 ± 5.9 years old and gestational age at delivery was 38 ± 0.9 weeks. Mean birth weight was 3153 ± 404 g. No neonates required positive pressure ventilation during delivery. Basic investigations for neonatal anemia were done in 30 neonates, another 3 neonates weren't performed investigation and only 22 mothers had Kleihauer-Betke test results and 19 mothers had indirect anti-globulin tests, 14 infants of blood group O mothers whose IAT had not done, had no hemolytic blood picture. One mother of positive Kleihauer-Betke test had beta thalassemia trait.

Table 1 Maternal baseline characteristics.

Demographic Variables	Anemic Neonate N = 33 N (%) or mean ± SD	Normal Neonate N = 422 N (%) or mean ± SD	P - value
Ferrous supplement (N)	27 (81.8)	285 (67.5)	0.118
Cesarean delivery (N)	11 (33.3)	211 (50)	0.072
Maternal underlying conditions (N)			
- Gestational diabetes	3 (9.1)	34 (26.4)	0.743
- PIH	0	10 (7.8)	1.0
- Thalassemia	8 (24.2)	62 (14.7)	0.140
- Anemia	0	1 (0.8)	1.0
- SLE	0	1 (0.8)	1.0
Age (years)*	28.5 ± 6.05	29.3 ± 5.9	0.439
Gestational age (weeks)*	38.5 ± 0.91	38.3 ± 0.92	0.519
Hematocrit before delivery*	35.3 ± 2.87	35.7 ± 3.01	0.534
MCV at 1st ANC*	81 ± 9.27	82.2 ± 9.03	0.481
Blood Loss (mL)*			
-Normal labor	281.8 ± 259.4	222.2 ± 160.3	0.769
-Cesarean delivery	448.2 ± 203.3	399.8 ± 175.7	1.00
Placental weight (grams)*	732.2 ± 137.7	680.1 ± 156.7	0.064

*data were described in mean ± SD

Table 2 Neonatal baseline characteristics.

Demographic Variables	Anemic Neonate N = 33 N (%) or mean ± SD	Normal Neonate N = 422 N (%) or mean ± SD	P - value
Gender (N)			
- Male	19 (57.6)	201 (47.6)	0.284
Jaundice requiring treatment	5 (15.2)	47 (11.1)	0.395
Birth weight (grams)*	3248.9 ± 419	3145.70402.6	0.158
Length (cm)*	52 ± 2.17	51.3 ± 2.26	0.080
Median (min-max) Apgar score at 1 min	9 (6-9)	9 (2-9)	0.315
Median (min-max) Apgar score at 5 min	10 (10-10)	10 (8-10)	1.000

*data were described in mean+SD

The etiology of anemia in the 33 neonates is shown in Figure 1. There were 11 neonates who had feto-maternal transfusion (33.3%), 8 neonates (24.2%) who presumed to have feto-placental transfusion, 3 infants (9.1%) who were diagnosed with ABO incompatibility, 1 infant (3%) who had anemia from large cephalhematoma. There were 2 infants included in unidentified with hemolytic blood pictures (one was negative KB-test and another was maternal blood group B), but further investigation was not done. In our study, there were 10 infants without definite causes of anemia.

There were 17 and 9 patients seen at 4 and 8 weeks of age, respectively. There was 1 patient with ABO incompatibility requiring blood transfusion at 4 weeks of age due to moderate anemia (Hct 24%). Mean hematocrit at 4 and 8 weeks of age were 32 ± 5% and 31 ± 2.1%.

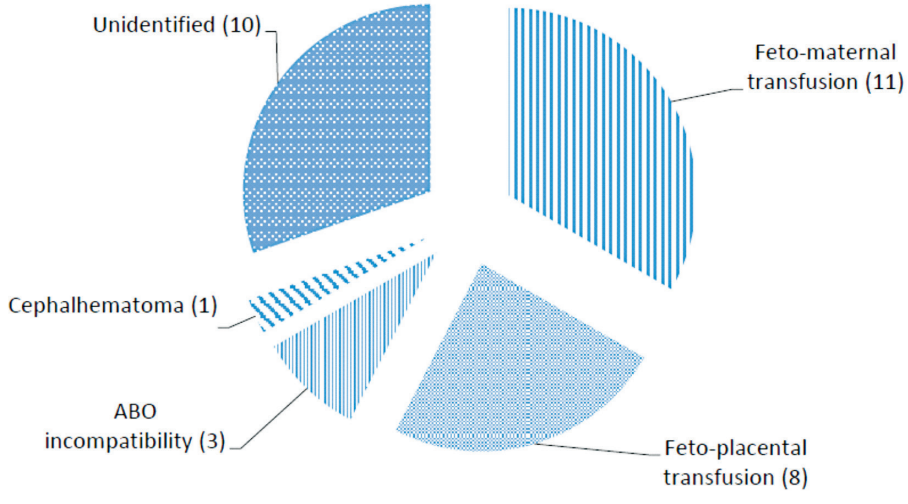

Figure 1 Etiology of anemia (N)

Discussion

The prevalence of neonatal anemia in our institution was just over 7% which is higher than the previous retrospective cohort study.[8] We were not be able to demonstrate any differences in baseline characteristics and effects of maternal diseases such as gestational diabetes (GDM) or pregnancy-induce-hypertension (PIH), which might affect iron transport in utero, between normal and anemic infants. In contrast, there was a report of the impact of cesarean sections on iron-related hematological indices in term neonates;[11] they found that neonates delivered by cesarean delivery had significantly lower levels of hematocrit.

The most common identified causes of anemia in our neonates was feto-maternal transfusion (33.3%); As 11 infants did not have maternal Kleihauer-Betke tests performed or collected blood after 48 hours which made false negative result, the proportion of neonates with feto-maternal transfusion might be underestimated. There has been a heightened awareness of feto-maternal transfusion with the increased use of the Kleihauer-Betke test. In the USA, a very large retrospective study found an overall rate of neonatal anemia of 0.46%, whilst the rate of feto-maternal transfusion detection increased 9 times after the physician educational intervention on fetomaternal hemorrhage.[8] Also, there were a possibility of false positive Kleihauer-Betke test in mothers because Thailand has high prevalence of hemoglobinopathies such as thalassemia[12] and it is not included in routine antenatal screening. The second leading cause was presumed feto-placental transfusion (24.2%) which has no definite diagnostic criteria. Based on studies conducted in Thailand, the median (10^{th}, 90^{th} percentiles) placental weight to birthweight ratio (PWR) was 16.7% (14.1%, 21.6%) at 37 weeks; 16.7% (14.1%, 20.2%) at 38 weeks; 16.5% (13.5%, 19.3%) at 39 weeks; and 16.1% (13.6%, 18.7%) at 40 weeks.[9] We assumed having PWR > 25% classified neonates with a possibility of feto-placental transfusion.

Hence, low umbilical cord blood hemoglobin was one of the most significant factors related to anemia in late infancy.[12] It is critical to pay more attention to diagnosis and long-term follow-up of neonatal anemia, to prevent long-term negative effects on cognitive and psychomotor development in children.

There were several limitations. First of all, the absolute number of anemic neonates was small; only 33 neonates had anemia, and this limited statistical power to identify risk factors of neonatal anemia. secondly being a retrospective study, we were reliant on the data in the medical records, which were not complete in some neonates. Finally, there were some neonates and mothers with incomplete investigation and some neonates who should have received further investigation in order to have definite diagnosis.

Our small study has highlighted a relatively high rate of neonatal anemia in otherwise healthy term neonates. Major causes of neonatal anemia were feto-maternal and feto-placental transfusion. Iron supplements should be considered in these infants in order to prevent irreversible long-term complications. Developing countries, such as Thailand need to place more emphasis on routine, inexpensive preventative care for early childhood conditions like anemia which have ramifications on the population quality.

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Declaration of interest: none

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บทคัดย่อ

ความชุกในการเกิดภาวะโลหิตจางของทารกเกิดครบกำหนดในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ

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ความเป็นมา: ภาวะซีดในเด็กเล็กถือเป็นปัญหาที่สำคัญและพบบ่อยทั่วโลก ภาวะเม็ดเลือดแดงต่ำในตอนแรกเกิดนั้นถือเป็นปัจจัยเสี่ยงที่สำคัญของการเกิดภาวะซีดในวัยเด็ก อย่างไรก็ตามในปัจจุบันข้อมูลเกี่ยวกับความชุกและปัจจัยเสี่ยงของภาวะซีดในทารกแรกเกิดนั้นยังไม่มีการศึกษาที่แพร่หลาย ดังนั้นผู้วิจัยจึงมีความสนใจที่จะศึกษาความชุกของภาวะซีดในทารกแรกเกิดครบกำหนดปรกติทั่วไป

วิธีการศึกษา: การศึกษานี้เป็นการศึกษาแบบเก็บข้อมูลย้อนหลังจากเวชระเบียนของทารกครบกำหนดที่เกิดในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติเป็นระยะเวลา 3 เดือน ทารกที่มีความผิดปรกติแต่กำเนิด (congenital malformation) ทารกที่มีลักษณะเข้ากับกลุ่มอาการต่างๆ และทารกที่เข้ารับการรักษาในหอผู้ป่วยทารกแรกเกิดวิกฤติหรือเสียชีวิตภายใน 48 ชั่วโมงจะถูกคัดออกจากการศึกษา ทารกที่มีความเข้มข้นของเลือดต่ำกว่า 45% จะได้รับการวินิจฉัยภาวะซีดและได้รับการตรวจทางห้องปฏิบัติการเพิ่มเติม ข้อมูลจะถูกนำเสนอในรูปร้อยละ ส่วนปัจจัยที่มีผลต่อภาวะซีดจะได้รับการวิเคราะห์โดยใช้ Fisher's-exact test และ Student's T-test

ผลการศึกษา: ทารกเข้าร่วมการศึกษาทั้งหมด 455 ราย ในจำนวนนี้มี 33 ราย (7.3%) ที่มีภาวะซีด สาเหตุของภาวะซีดที่พบบ่อยที่สุดคือ feto-maternal transfusion (11 ราย หรือ 33.3%) และ feto-placental transfusion (8 ราย หรือ 24.2%) ในจำนวนนี้มีทารก 10 ราย (30.3%) ที่ไม่ทราบสาเหตุของภาวะซีด

สรุปผลการศึกษา: ในการศึกษานี้พบว่าภาวะซีดในทารกแรกเกิดเป็นภาวะที่พบได้พอสมควร สาเหตุของภาวะซีดที่พบได้บ่อยที่สุดคือ feto-maternal transfusion และ feto-placental transfusion ดังนั้นแพทย์ผู้ดูแลทารกกลุ่มนี้ควรตระหนักถึงความสำคัญของภาวะนี้เพื่อให้การดูแลและป้องกันการซีดในวัยทารกต่อไป

คำสำคัญ: ภาวะซีดในทารกแรกเกิด, ทารกแรกเกิดครบกำหนด, สาเหตุของภาวะซีด