(i) Original article

(ii) The risk factors of infant anemia in perinatal period

(iii) Risk factors of infant anemia

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Abstract

Background

Infants are at particular risk of iron-deficiency anemia. We investigated the changes in the blood count of mother and infant as well as the relationship between them and the relationship between an infant's nutrition method and infant anemia.

Methods

This retrospective cohort study included healthy neonates born between August 2011 and July 2014 in St. Luke's International Hospital, Tokyo, Japan. Data from blood samples of mothers obtained during late pregnancy and those of infants obtained at birth and at the age of 3, 6, and 9 months were analyzed. Using multivariate logistic regression, we investigated nutrition methods, maternal anemia, and other clinical relevant parameters that were potential risk factors for infant anemia.

Results

In total, data for 3472 infants and their mothers were analyzed. Nutrition method was the most significant risk factor for infant anemia, with risk of future anemia decreasing in the following order: exclusively breastfeeding, partially breastfeeding, and formula feeding. Furthermore, low umbilical

cord blood hemoglobin lead to a tendency for the child to suffer from anemia

Conclusion

The method of infant nutrition was the most significant factor related to anemia in late infancy. "Late clamping" of the umbilical cord is a potentially effective way to prevent infant anemia with the risk tending to decrease because of the high level of umbilical cord blood hemoglobin

Key words

anemia, breastfeeding, hematopoiesis, resuscitation, and umbilical cord

Background

Iron deficiency remains common, and infants are at particular risk.(1) In neonates, hematopoiesis uses iron received through the placenta during the fetal period before neonates begin a secondary process of producing blood components with their own bone marrow using the iron they ingest.(2) Because of the rapid physical growth after birth, hematopoiesis is often insufficient to keep up with requirements. A limited iron supply *in utero* and during the initial years of life is associated with long-term cognitive, motor, and behavioral impairments in the later years of life despite iron supplementation.(3) (4)Infant anemia is usually diagnosed during periodic health check-up at a clinic at late infancy, and the infants sometimes require additional oral iron supplementation. Untreated iron deficiency during infancy and childhood may lead to neurodevelopmental impairments that cannot be corrected later by iron supplementation.(5) Iron accretion in the fetus predominantly occurs during the third trimester of pregnancy. In healthy, normal newborn infants, iron reserves at birth are sufficient to cover the iron demands for growth during the first 4–6 months of life. In conditions such as pregnancy-induced diabetes and placental insufficiency, iron transfer is limited, resulting in a higher risk of compromised iron stores in infants of up to 1 year of age.(6)

One prophylactic technique for infant anemia is “late clamping” by medical staff, which involves intentionally delayed clamping of the baby’s umbilical cord at the time of delivery.(7) This maneuver was recommended for neonates in the latest edition of International Liaison Committee on Resuscitation-Consensus on Science with Treatment Recommendations (ILCOR-CoSTR) 2015 guidelines. Some groups have suggested that milking an umbilical cord is a safe procedure that reduces the need for red blood cell transfusions and circulatory and respiratory support in preterm infants. However, another group has speculated that the need for phototherapy increases with delayed cord clamping because the newborn's hemoglobin is increased by this procedure. For this reason, the latest version of Japanese guidelines for neonatal cardiopulmonary resuscitation does not recommend "late clamping."

A diagnosis of anemia in pregnant mothers and infants is usually based on a serum hemoglobin level below 10–11 g/dl and iron supplementation is then provided in the hospital.(8) (9) However, the validity of the diagnosis of anemia based on this standard has yet to be verified, and the influence of anemia on the fetus and its relationship with infant anemia still demands clarification. There is an opinion that the diagnosis of infant anemia should be based on erythrocyte indices such as mean corpuscular volume (MCV).

In this study, we investigated changes in the blood count in late pregnancy, in the umbilical cord blood just after birth, and in infancy, examining the relationship between the blood counts of mother and infant as well as the relationship between infant nutrition methods and anemia.

Methods

This retrospective analysis included healthy newborns (delivered from more than 37 to under 42 gestational weeks) born at St Luke’s International Hospital, Tokyo, Japan, between August, 2011 and July, 2014, excluding babies with hematological diseases, such as leukemia, severe neonatal asphyxia, and chromosomal anomaly . Ethical approval was obtained from the Clinical Human Research Ethics Committee of St Luke’s International University.

The study evaluated blood data gathered as part of the routine clinical follow-up examination for mothers and their babies. We used the mother’s blood data to check as a prenatal follow up from late pregnancy, evaluated from the specimen collected at 36 weeks of pregnancy or within the time window near and before delivery. Specimens of umbilical cord blood from just after birth were collected by medical staff (obstetrician or midwife) assisting in the delivery room for transvaginal delivery or the operation theatre for caesarean section using standard blood sampling tool . The umbilical cord was usually clamped immediately after delivery, within 15 seconds of birth; delayed clamping was not performed. Infant blood data used results for blood samples were collected for clinical reasons during the 30 days before or after the infant reaching the age of 3, 6, and 9 months old. The reason behind checking the blood sample was to rule out differential diagnosis of various clinical symptoms (respiratory, circulatory, anemia, etc.), and also as a pre-operation check (inguinal hernia, imperfectly descended testis etc.) and routine check to follow-up for neonatal events.

The complete blood count and anemic parameters of mothers and babies were measured with the ADVIA 120 blood analyzer (Siemens, Eschborn, Germany) at a central laboratory in St Luke's International Hospital, Tokyo, Japan. Cord blood hemoglobin was measured with the i-STAT system (Abbott Point of Care, Princeton, New Jersey, USA) or Radiometer Blood Gas Analyzer (Radiometer, Copenhagen, Denmark). There was no significant difference between the hemoglobin measurements obtained with these measuring instruments.

Data obtained from medical records in the hospital chart systems included whether phototherapy for jaundice or iron supplementation had been administered, the sex of the infant, gestational age, birthweight, and the baby's nutrition methods. The nutrition methods were classified in three groups—breastfeeding, partially breastfeeding, and formula feeding. They were decided by medical records at the time of the blood check for infants. Partially breastfeeding implied that the baby was fed either breast or formula milk. Infant and maternal anemia during pregnancy were defined by iron status being below the reference levels of MCV <75 fl and <85 fl, respectively.(10)(11)

Statistical analysis

Statistical analyses were carried out using SPSS 22.0 (IBM Corp., Armonk, NY, USA). Multivariate logistic regression was used to calculate the adjusted odds ratio for each risk parameter. Statistical significance was considered to be $P < 0.05$.

Results

The study population is shown in Figure 1. Between August 2011 and July 2014, 3480 infants were delivered who fulfilled our study criteria. We excluded 8 newborns whose umbilical cord blood hemoglobin or their mother's hematologic data in late pregnancy had not been measured. Ultimately, we investigated 3472 infants and their mothers. The baseline characteristics of all babies are shown in Table 1. The mean gestational age at delivery was 39 weeks, and the mean birth weight was 3053.0 g. The mean maternal age at delivery was 34.8 years. Phototherapy for neonatal jaundice was administered to 6.0%of all infants (207/3472); among these, 6.7% of infants (13/193) had blood data analyzed when they were 6 and 9 months old.

Hematologic characteristics are shown in Table 2. The serum hemoglobin in the late pregnancy for mother and the umbilical cord blood hemoglobin at birth showed a normal distribution, and their mean values were 11.2 g/dl and 16.0 g/dl, respectively. We defined 6- and 9-month-old babies as late infancy. The baseline characteristics of late infancy are shown in Table 3. The hemoglobin and MCV of infants at 6 and 9 months old were also distributed normally (Figure 2). Both maternal and infant hemoglobin showed normal distribution although there was no significant association between them.

A multivariate regression analysis of possible factors related to anemia at 6 and 9 months old showed different nutrition methods were associated with infant anemia to differing degrees (Table 4). The risk of future anemia decreased in the following order exclusively: breastfeeding, partially breastfeeding, and formula feeding. Low umbilical cord blood hemoglobin may leads to anemia in the child; however, this was not correlated with phototherapy for jaundice. Umbilical cord blood hemoglobin level was significantly associated infant anemia (odds ratio 0.73, 95% confidence interval 0.60–0.89). The incidence of infant anemia increased with lower levels of umbilical cord blood hemoglobin. We also found that exclusively breastfeeding resulted in the greatest risk for infant anemia at age 6–9 months. Formula feeding brought the least risk for infant anemia. Detailed results, including adjusted odds ratios, are presented in Table 1. Mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) are generally used to diagnose various hematologic disorders; however, there were no significant differences between them and infant anemia.

Discussion

It is well established that iron-deficiency anemia in pregnancy treated with iron supplementation is a possible cause of infant anemia.(12) Maternal iron-deficiency anemia during pregnancy is a risk factor for retinopathy in prematurity,(13) and infant anemia is one cause of the development of neurological retardation.(14)

In Japan, the treatment of anemia during pregnancy is based on reference serum hemoglobin levels in accordance with the clinical guideline from the Japan Society of Obstetrics and Gynecology.(15) The guideline recommends that the starting points for iron therapy are hemoglobin levels less than 10.5 g/dl at 13 weeks gestation, 10 g/dl at 30 weeks, and 9.5 g/dl at 37 weeks. The World Health Organization's recommendation is that the diagnostic cut-off for anemia is set at a serum hemoglobin level of less than 11.0 g/dl and hematocrit less than 33%. Other indices of anemia such as MCV, MCH, and MCHC are not generally used.(16) However, we decided to use MCV as index of anemia because it provides a better reflection of the state of anemia, as was supported by the results of this study.

The study showed an association between anemia in late infancy and nutrition method, suggesting that infants who are breastfed are more likely to present with iron-deficiency anemia in the late infancy period than those who were partially breastfed or who received formula feeding. As there was no association between infant anemia and the mother receiving iron supplemental therapy for maternal anemia, it is likely in a developed country that the anemia of late infancy was mainly because of reduced iron storage in the baby following a long duration of breast feeding that included low levels of iron than a result of insufficient iron transfer through the placenta in pregnancy.(17)

The ILCOR-CoSTR 2015 guidelines recommend a delay in clamping the umbilical cord of at least 1 min for newborns who do not require resuscitation. This delay improves iron status through early infancy. The mechanism is explained with the effect to happen by blood transfusion from umbilical cord to neonate. However, it is expected to increase the risk of jaundice that requires phototherapy. The Japan Resuscitation Council (JRC) guideline 2015 does not recommend delaying umbilical cord clamping by at least 1 min because Asian babies are, for reasons of race, more likely to develop jaundice requiring phototherapy.(18)

It is unknown whether the blood volume and quantity of iron in the umbilical cord of an average newborn baby transferred by late cord clamping is sufficient to prevent the development of infant anemia. The blood volume transfused by milking 30 cm of umbilical cord in an extremely low birth weight infant is 18 ml/kg.(19) This is equivalent to 13 ml/kg when converted into a red blood cell suspension, from the standard hematocrit level of umbilical cord blood. For example, for a healthy newborn baby with a body weight of 3 kg at term, the volume of umbilical cord blood would be 54 ml, and the cord's blood iron content would be estimated to be approximately 150 μg/dl. As of yet, no report has provided strong evidence about the serum iron content for neonates, but it has been shown that the iron level suddenly decreases after birth and remains at a low value in the neonatal period. It is still unknown whether transfusing the iron included in the cord blood during the neonatal period can prevent later iron-deficiency anemia. However, according to our analysis, there was little anemia of the late infancy so that the umbilical cord blood hemoglobin was high. Therefore, the further increase of the hemoglobin value at birth may prevent the anemia. Hence the results of the present study suggest that the technique of late clamping and milking of the umbilical cord could prevent the development of anemia in late infancy in Japan, just as in other countries. Our multivariate regression analysis showed no association between phototherapy for neonatal jaundice and anemia in late infancy. Thus, the potential need for phototherapy should not be a reason to deny late clamping.

This study had a number of limitations. The data may not reflect blood counts of healthy infants because the blood samples were collected when the blood needed to be checked for clinical reasons. Aging may have influenced the result because the maternal age at delivery in our hospital is older than the average for Japan. Finally, this study did not examine whether the iron content in breast milk may be affected by a state of maternal anemia during the lactation period.

Conclusion

We investigated maternal blood count during late pregnancy by assessing blood count in the umbilical cord blood just after birth, blood count during infancy, and the relationship between these and infant anemia. Nutrition method was the factor most strongly related to anemia in late infancy, with the risk of anemia decreasing in the following order: exclusively breastfeeding, partially breastfeeding, and formula feeding. In addition, it was suggested that “late clamping” of the umbilical cord may be effective in Japan, as it is in other countries, because this tended to reduce the risk of anemia due to the umbilical cord’s high blood hemoglobin level.

Acknowledgments

None

Disclosure Statement

The authors have no conflicts of interest to disclose.

Author Contributions

MH conceived the study. MH, IK and HY designed the study. MH, IK and MY did the data collection and processing. SO did the statistical analysis. MH wrote the report, which was revised and approved by all authors. MH, IK and HY take overall responsibility for the integrity of the study.

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Table 1 Baseline characteristics

Cases	n =	3472
Sex	**Female**	**1695 (49%)**
	Male	**1777 (51%)**
Gestational age at birth	**37 weeks~**	**361 (10%)**
	38 weeks~	**754 (22%)**
	39 weeks~	**946 (27%)**
	40 weeks~	**942 (27%)**
	41 weeks~	**469 (14%)**
Birth weight (g)	**3053.0**	**(±367.7)**
Mother's age at birth (years)	**34.8**	**(±4.4)**
Iron supplementation to mother	**Yes**	**930 (27%)**
	No	**2542 (73%)**
Phototherapy to infant for jaundice	**Yes**	**207 (6%)**
	No	**3265 (94%)**

Data are means ± SDs, unless otherwise specified.

Table 2 Hematologic characteristics

Mothers in pregnancy	**Hemoglobin(g/dl)**	**11.2**	**±1.11**
	MCV	**87.4**	**±5.47**
Umbilical cord blood	**Hemoglobin(g/dl)**	**16.0**	**±1.78**
Infants at 3 months	**Hemoglobin(g/dl)**	**10.9**	**±1.20**
	MCV	**82.3**	**±4.87**
Infants at 6 months	**Hemoglobin(g/dl)**	**11.7**	**±1.01**
	MCV	**75.1**	**±4.92**
Infants at 9 months	**Hemoglobin(g/dl)**	**11.5**	**±1.41**
	MCV	**73.6**	**±6.17**

Data are means ± SDs

Table 3 Baseline characteristics in late infancy

Cases	**n=**	**193**
Age of blood checking (months)	**6**	**83**
	9	**110**
Sex	**Female**	**70 (37%)**
	Male	**123 (63%)**
Infants hemoglobin(g/dl)	**11.57**	**(±1.25)**
Infants MCV	**74.3**	**(±5.67)**
Breast feeding	**100**	**(52%)**
Partial breast feeding	**60**	**(31%)**
Formula feeding	**33**	**(17%)**
Phototherapy to infant for jaundice	**Yes**	**13 (7%)**
	No	**180(93%)**

Data are means ± SDs, unless otherwise specified.

Table 4 Multivariate regression analysis of infant anemia.
Infant anemia was diagnosed by MCV <75.

	OR	95%		CI	*P*-value
Breast feeding	1.0(Ref.)				.007*
Partially breast feeding	.459	.229	～	.986	.028*
Formula feeding	.281	.115	～	.687	.005*
Mother's MCV 85>	1.205	.609	～	2.383	.593
Cord blood hemoglobin	.842	.727	～	.976	.023*
Iron therapy for mother	1.134	.535	～	2.403	.743
Phototherapy for jaundice	.571	.132	～	2.473	.454

*P<0.05

Figure 1 Study population

Figure 2 MCV in late infancy

Figure 1 Study population.

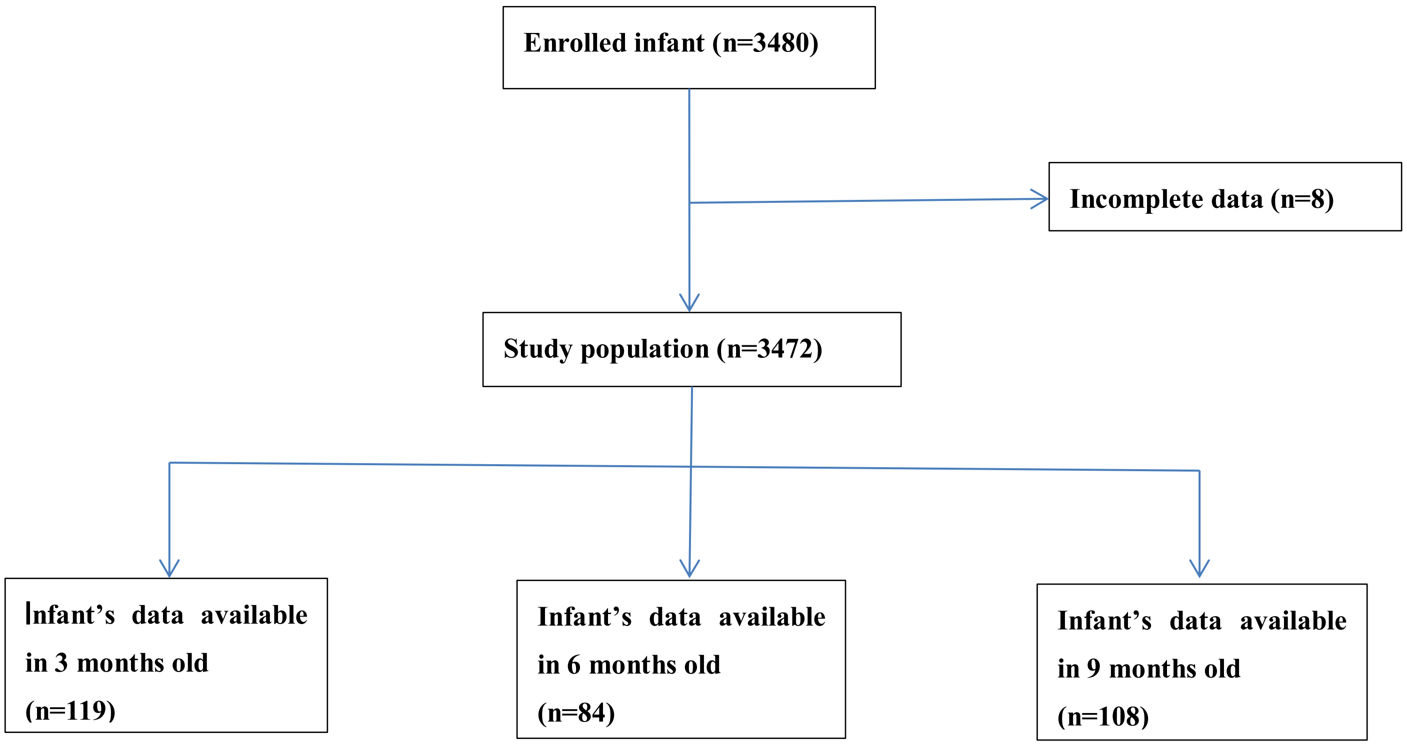

Figure 2 MCV in late infancy.