

Incidence and Risk Factors of Iron Deficiency Anemia in Term Infants

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Objective: To compare the incidence of iron deficiency anemia (IDA) between breast-fed (BF) and formula-fed (FF) infants and to identify the risk factors of IDA in these infants.

Design: Cohort study.

Material and Method: A study of 140 full-term infants (70 BF and 70 FF) was conducted at BMA Medical College and Vajira Hospital from February 2002 to November 2003. All infants were followed at the age of 1, 2, 4, 6, 9 and 12 months for growth and developmental assessment. Blood samples were analyzed for hemoglobin (Hb), hematocrit (Hct) and mean corpuscular volume (MCV) at 9-12 months; and infants with Hb < 11.0 g/dl were further investigated for the cause of anemia.

Results: The mean values of Hb, Hct, MCV and serum ferritin of BF infants were 10.8 g/dl, 32.8%, 70.9 fl and 16.7 ng/ml respectively, which were significantly lower than those of FF infants (11.4 g/dl, 35.1%, 73.3 fl, and 36.9 ng/ml, $p < 0.05$). Anemia was found in 27 BF infants (38.6%) compared with 10 FF infants (14.3%). The incidence of IDA in BF infants was significantly higher than FF infants (25.7% vs 2.9%, $p < 0.001$). Risk factors of IDA included low birth weight, breastfeeding and inadequate complementary food (adjusted RR (95% CI): 3.1(1.1-9.1), 6.3(1.5-25.0), 7.7(2.8-20.0), respectively).

Conclusion: IDA is more prevalent in BF than FF infants. Risk factors of IDA are low birth weight, breastfeeding and inadequate complementary food. Prevention of IDA in infants should be achieved through adequate iron-rich complementary food and screening for Hb or Hct at 9-12 months of age in high risk infants.

Keywords: Anemia, Breastfeeding, Formula feeding, Infant, Iron deficiency anemia

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Iron deficiency anemia (IDA) is the most common nutritional deficiency worldwide. Infants aged between 6 and 24 months, school-age children and pregnant women are the high risk groups of iron deficiency⁽¹⁾. The consequences of IDA in young children include abnormalities of immune function, increased risk of infection, poor growth and neuro-cognitive impairment⁽²⁻⁵⁾. Therefore, prevention and early treatment of IDA are essential.

The strategies for prevention of IDA in infants include exclusive breastfeeding for 4-6 months of age,

the use of iron-fortified formulas in infants who are not breast-fed, consumption of iron-rich complementary food after 6 months and screening for anemia in high risk infants⁽⁶⁾. Previous studies about iron status in infants showed that breast-fed (BF) infants had anemia and IDA more than formula-fed (FF) infants^(7,8). Because of numerous benefits of breast milk⁽⁹⁾, promotion of breastfeeding is the public health policy worldwide so awareness of IDA in BF infants should be of concern. The reports of the Third and Fourth National Nutrition Survey in Thailand showed that the prevalence of anemia among school-age children and pregnant women were decreasing^(10,11), but there were few studies on the prevalence of anemia and IDA in Thai infants⁽¹²⁾.

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In the present study, the authors prospectively followed the infants who were either BF or FF for 1 year with controlled for age of introduction of complementary food and socioeconomic status. The objectives of this study were (1) to compare the incidence of IDA between BF and FF infants and (2) to identify the risk factors of IDA in these infants.

Material and Method

This cohort study was conducted at a nutrition clinic and well baby clinic, BMA Medical College and Vajira Hospital from February 2002 to November 2003. This study protocol was approved by Ethical Committee of Bangkok Metropolitan Administration. The study subjects comprised 156 full term infants born at BMA Medical College and Vajira Hospital.

Inclusion criterias were:

1. Healthy infants born at 37-42 weeks of gestation.
2. Five-minute apgar score ≥ 7
3. Hematocrit at birth $> 45\%$
4. Maternal hematocrit at pregnancy $> 33\%$
5. Mothers planned to feed their infants either breast milk or iron-fortified formula for 1 year.
6. Parental informed consents

Exclusion criterias were:

1. Multiple pregnancies
2. Infants with congenital anomalies
3. Infants or mothers who had a chronic illness or needed some medications on a regular basis.

Of the 156 infants, 78 were BF and 78 were FF. Type of milk feeding was the mother's decision. The investigator discussed the detail of study protocol to the parents of all infants before obtaining the written informed consents. Instructions for infant feeding conformed to the recommendations provided by the Royal College of Pediatricians of Thailand and the Pediatric Society of Thailand⁽¹³⁾. Milk was the only food source during the first 4 months; BF infants were fed only breast milk or breast milk with infant formula less than 4 oz/day and FF infants were fed only infant formula or initially breast milk but weaned off breastfeeding before 2 months. Solid foods were introduced after 4 months of age. Adequate complementary food was defined as: (1) consumed a variety of food from various food groups (rice and grains, fruits, vegetables, milk, meats, egg and fat) and (2) had adequate amounts of nutrients and energy compared with Thai Recommended Dietary Allowances⁽¹⁴⁾.

All infants were followed at the age of 1, 2, 4, 6, 9 and 12 months for anthropometric measurement

and developmental assessment. At each visit, the parents were asked about type and amount of milk and complementary food used 24 hours recall and the infants were measured for body weight, length and head circumference by trained personnel according to standard procedures. Malnutrition was defined as a weight for age (W/A), length for age (L/A), or weight for height (W/H) $<$ mean - 2 standard deviation (SD) of the Thai references⁽¹⁵⁾.

At the age of 9-12 months, a 1 ml of venous blood was drawn from a peripheral vein for hemoglobin (Hb) concentration, hematocrit (Hct), and mean corpuscular volume (MCV). All infants were in good health without concurrent infection at the time of blood sampling. The infants who had Hb concentration < 11.0 g/dl were diagnosed as anemia⁽¹⁶⁾. All infants with anemia were invited back in 1-2 week(s) for a repeat blood sample for Hb concentration and serum ferritin. Infants with Hb < 11.0 g/dl and serum ferritin < 12 ng/ml were classified as IDA and treated with oral iron (ferrous sulfate) 3-6 mg/kg/day for 3 months⁽¹⁶⁾. Anemic infants with serum ferritin > 12 ng/ml and MCV < 70 fl were investigated for thalassemia by hemoglobin typing; and in suspected α thalassemia carrier, DNA analysis was performed. Hb, Hct and MCV were measured by the electrical impedance method in a Coulter Counter (Coulter STKS). Serum ferritin was measured by the electrochemiluminescence immunoassay method (Elecsys 1010, Roche).

Statistics

Statistical analyses were performed by Stata version 7.0. Categorical datas were expressed as per cent and comparison between the two groups by Chi-square test. Continuous datas were expressed as mean \pm SD and comparison between the two groups by student's t-test. The relative risk (RR) and 95% confidence interval (95%CI) were used to compare the incidence of anemia and IDA between BF and FF infants, and multiple logistic regression (poisson regression) was used to evaluate the factors associated with IDA. A p-value < 0.05 was considered statistically significant.

Results

Of the 156 infants, 16 were excluded before the end of the study (8 BF and 8 FF infants). The reasons for exclusion were stopped breast milk or fed with infant formula > 4 oz/day (5 BF), received solid foods before 4 months (2 BF, 5 FF), and moved to other provinces or were lost to follow up (1 BF, 3 FF). Table 1 shows baseline characteristics of 140 infants

who completed the study. Baseline characteristics of both groups of infants were similar except maternal occupation; BF mothers were housewives or worked at home more than FF mothers ($p < 0.001$).

Table 2 compares the hematologic data at 9-12 months of age of BF with FF infants. The mean values of Hb, Hct and MCV of BF infants were significantly lower than FF infants. Anemia was found in 37 infants (26.4%); 27 BF (38.6%) and 10 FF (14.3%). All anemic infants were measured for serum ferritin and found that the mean values of serum ferritin of BF infants were lower than FF infants (16.7 ± 15.8 and 36.9 ± 31.0 ng/ml respectively, $p 0.01$). IDA was found in 18 BF (25.7%) and 2 FF infants (2.9%). The incidence of anemia and IDA in BF infants were significantly higher than FF infants (RR (95% CI): 2.8(1.4-5.9) for anemia and 9.1(2.2-33.3) for IDA).

Of the 37 anemic infants, 20 (54.1%) were IDA, 12 (32.4%) were carrier state of thalassemia and hemoglobinopathies, and 5 (13.5%) were malnourished infants whose anemia was improved after appropriate nutrition management and multivitamin supplementation. All 20 infants with IDA were treated with oral iron (ferrous sulfate) 3-6 mg/kg/day for 3 months. Repeated blood sampling after 1 month of iron therapy found that all infants had increased Hb concentration and recovered completely after 3 months of treatment.

Table 3 shows that factors associated with IDA in infants included type of milk feeding, birth weight and complementary food. Breastfeeding, low birth weight and inadequate complementary food increased risk of IDA in infants. Multivariate analysis showed that these 3 factors remained statistically significant and inadequate complementary food was the most significant risk factor (Table 4).

Discussion

The present study demonstrated that anemia and IDA in infants were still prevalent and the incidence of anemia and IDA of BF infants were higher than FF infants. These findings were in agreement with previous studies^(7,8). Pizzaro et al⁽⁷⁾ reported that IDA was found in 14.7% of BF compared with 0.6% of FF infants, whereas Calvo et al⁽⁸⁾ reported the prevalence of anemia at 9 months of age in BF infants was 27.8% compared with 7.1% in FF infants and IDA was found in 27.8% of BF infants but none of FF infants. Studies of prevalence of anemia and IDA in Thai infants are limited. A study of iron status at 1 year of age in 72 Thai infants from rather high income families revealed the prevalence of anemia and IDA were 9.2%

Table 1. Characteristics of 140 studied infants

	Total n = 140	Breast-fed infants n = 70	Formula-fed infants n = 70	p
Maternal age, yr ⁺	26.8±6.2	27.0±6.3	26.5±6.1	0.68
Maternal education (%)				0.79
: primary school	57(40.7)	30 (42.9)	27 (38.6)	
: secondary school	74(52.9)	35 (50.0)	39 (55.7)	
: graduate	9(6.4)	5 (7.1)	4 (5.7)	
Maternal occupation (%)				<0.001*
: housewife or work at home	114(71.4)	67 (95.7)	47 (67.1)	
: work outside	26(18.6)	3 (4.3)	23 (32.9)	
Household income, baht/month (%)				0.73
: 5,000-10,000	88(62.9)	45 (64.3)	49 (70.0)	
: 10,001-20,000	52(37.1)	25 (35.7)	21 (30.0)	
Parity (%)				0.47
: primiparous	94(67.1)	45 (64.3)	43 (61.4)	
: multiparous	46(32.9)	25 (35.7)	27 (38.6)	
Infant sex (%)				1.00
: male	70(50.0)	35 (50.0)	35 (50.0)	
: female	70(50.0)	35 (50.0)	35 (50.0)	
Birth weight (%)				1.00
: > 2,500 g	132(94.3)	66 (94.3)	66 (94.3)	
: ≤ 2,500 g (low birth weight)	8(5.7)	4 (5.7)	4 (5.7)	
Gestational age, week ⁺	38.4±1.2	38.4±1.2	38.5±1.3	0.89
Birth weight, kg ⁺	3.0±0.4	3.0±0.4	2.9±0.4	0.77
Birth length, cm ⁺	48.9±3.0	48.9±2.6	48.9±3.4	1.00
Head circumference at birth, cm ⁺	32.9±1.8	32.9±1.6	32.9±2.0	0.91
Hematocrit at birth (%) ⁺	53.3±5.6	53.0±5.6	53.5±5.6	0.61

⁺ mean ± SD, * $p < 0.05$

Table 2. Hematologic data at 9-12 months of age

	Breast-fed infants n = 70	Formula-fed infants n = 70	p
Hemoglobin, g/dl ⁺	10.8±1.1 (8.3-12.4)	11.4±0.7 (9.0-12.6)	<0.001*
Hematocrit, % ⁺	32.8±3.3 (24.5-42.0)	35.1±2.4 (27.2-39.1)	<0.001*
MCV, fl ⁺	70.9±6.3 (47.2-83.2)	73.3±3.8 (62.2-81.4)	0.009*
No. of anemic infants, (%)	27 (38.6)	10 (14.3)	0.004*
No. of infants with IDA, (%)	18 (25.7)	2 (2.9)	<0.001*

⁺ mean ± SD (range), * $p < 0.05$

and 1.4%, respectively⁽¹²⁾. The incidence of anemia and IDA of infants in the present study were higher than the previous studies because this study included

Table 3. Univariate analysis of factors associated with iron deficiency anemia

	No. of infants	No. of infants with IDA (%)	Rate/100 person-year (95% CI)	Relative risk (95% CI)	p
Type of milk feeding					<0.001*
: infant formula	70	2 (2.9)	2.9 (0.7-11.4)	1	
: breast milk	70	18 (25.7)	26.5 (16.7-42.0)	9.1 (2.2-33.3)	
Sex of infant					0.39
: girl	70	8 (11.4)	11.7 (5.8-23.3)	1	
: boy	70	12 (17.1)	17.2 (9.8-30.3)	1.5 (0.6-3.6)	
Birth weight					0.003*
: > 2,500 g	132	16 (12.1)	12.2 (7.5-19.9)	1	
: ≤ 2,500 g (low birth weight)	8	4 (50.0)	56.0 (21.0-149.2)	4.6 (1.5-14.3)	
Complementary food					<0.001*
: adequate	108	5 (4.6)	4.6 (1.9-11.0)	1	
: inadequate	32	15 (46.9)	51.5 (31.1-85.4)	11.1 (4.0-33.3)	
Maternal education					0.65
: primary school	57	9 (15.8)	16.2 (8.5-31.2)	1	
: secondary school or higher	83	11 (13.3)	13.3 (7.4-24.0)	0.8 (0.3-2.0)	
Household income, baht/month					0.10
: ≤ 10,000	88	16 (18.2)	18.7 (11.5-30.5)	1	
: > 10,000	52	4 (7.7)	7.6 (2.9-20.2)	0.4 (0.14-1.22)	
Maternal occupation					0.32
: housewife or work at home	114	18 (15.8)	16.0 (10.1-25.4)	1	
: work outside	26	2 (7.7)	7.7 (1.9-31.0)	0.5 (0.1-2.1)	

* p < 0.05

Table 4. Multivariate analysis of factors associated with iron deficiency anemia (Poisson regression)

Variable	Crude relative risk (95% CI)	Adjusted relative risk [†] (95% CI)	p
Type of milk feeding			0.01*
: infant formula	1	1	
: breast milk	9.1 (2.2-33.3)	6.3 (1.5-25.0)	
Birth weight			0.04*
: > 2,500 g	1	1	
: ≤ 2,500 g (low birth weight)	4.6 (1.5-14.3)	3.1 (1.1-9.1)	
Complementary food			<0.001*
: adequate	1	1	
: inadequate	11.1 (4.0-33.3)	7.7 (2.8-20.0)	

[†] Adjusted for type of milk feeding, birth weight and complementary food, * p < 0.05

low birth weight infants and most infants had a relatively low socioeconomic status which were at high risk for IDA^(6,17,18).

The causes of anemia of infants in the present study were IDA (54.1%) and the carrier state of thalassemia and hemoglobinopathies (32.4%), which were different from a study of Chuansumrit et al⁽¹²⁾ that anemia was caused by carrier state of thalassemia more than IDA. These may have resulted from the relatively

low socioeconomic status of the studied infants increased risk of IDA, and in this study, DNA analysis was performed only in anemic infants with serum ferritin > 12 ng/ml so carrier state of thalassemia in non-anemic infants and carrier state that co-exist IDA were not included. The prevalence of the carrier state of thalassemia among a Thai population was high (30-40%); and iron deficiency co-existing with carrier state of thalassemia were common^(12,19). However, in a clinical setting where CBC is the only available test, the infants with microcytic anemia should have presumptive diagnosis as IDA and therapeutic diagnosis by elemental iron 3-6 mg/kg/day is recommended^(6,16). An increase in Hb concentration of ≥ 1 g/dl after 1 month of iron treatment confirm the diagnosis of IDA and continuation of iron therapy for 2-3 months is needed. If anemia does not respond after 1 month of iron treatment despite good compliance, the carrier state of thalassemia is suspected and further investigation by Hb typing and DNA analysis should be done^(12,19).

Despite numerous benefits of breast milk, BF infants had IDA more than FF infants. This may be explained by the low iron content in breast milk⁽²⁰⁾. Breast milk contains 0.3-0.5 mg/L of iron with 50% of iron absorption compared with 8-12 mg/L of iron content and 4-10% of absorption in iron-fortified formula^(20,21). Therefore, BF infants received iron from milk less than

FF infants; BF infants who had inadequate complementary food were at risk for IDA. The findings with the incidence of anemia and IDA in BF infants were high (38.6% and 25.7%); it was justified to screen for anemia at 9-12 months of age in BF infants. In contrast, FF infants had a 14.3% chance of anemia and 2.9% of IDA so it was less necessary to screen for anemia in FF infants. The risk factors of IDA in infants in the previous studies included maternal anemia^(22,23), low birth weight^(17,24), low socioeconomic status⁽¹⁷⁾, prolonged breastfeeding with inadequate iron-rich complementary food⁽¹²⁾, and early introduction of cow milk before 12 months of age^(18,24). Risk factors of IDA of infants in the present study (which was controlled for maternal anemia and age of introduction of complementary food) were breastfeeding, low birth weight and inadequate complementary food. However, breastfeeding was not a risk factor of IDA in some studies^(18,24). Recommendations to prevent and control iron deficiency in infants provided by Centers for Diseases Control and Prevention (CDC) were exclusive breastfeeding for 4-6 months of age, the use of iron-fortified formulas in infants who are not breast-fed, consumption of iron-rich complementary food after 6 months and screening for anemia in high risk infants including preterm and low birth weight infants, infants fed with cow milk or non-iron-fortified formula and BF infants who had inadequate iron from complementary food⁽⁶⁾. In Thailand, the Royal College of Pediatricians of Thailand and the Ministry of Public Health recommended that screening for anemia should be done in all infants at 6-12 months of age^(13,25). However, in clinical practice most pediatricians and general practitioners do not screen infants for anemia. Anemic children with Hb of 9-10 g/dl are usually asymptomatic and detection of pale conjunctiva is a late sign of iron deficiency anemia⁽¹⁶⁾. Determination of Hb or Hct by capillary blood is cheap and available in most clinical settings so every infant (especially infants with risk factors) should be screened for anemia by Hb or Hct at 9-12 months of age.

The importance of IDA in young children is of concern because of its association with adverse neurodevelopmental outcome^(4,5,26). Longitudinal studies indicated that children who were anemic in early childhood continued to have poor cognitive development and school achievement in later life^(26,27). The children who had IDA as infants had developmental scores less than non-anemic control children, suggesting that IDA at a critical period of brain growth and differentiation may produce irreversible abnormalities^(26,27). Because of long term consequences of

IDA, it should be prevented in every child. Recent double-blinded, randomized-controlled trials of iron supplementation in BF infants and preschool children demonstrated that the supplemented group had iron status and psychomotor development better than the placebo group^(28,29). However, a randomized controlled trial in Sweden and Honduras showed that iron supplementation of BF infants had no benefit or may be harmful in populations where IDA is uncommon and those with normal Hb⁽³⁰⁾. Further studies on risk and cost effectiveness of iron supplementation for prevention of IDA in infants are required before the policy of iron supplementation be established.

The limitation of this study was serum ferritin was measured only in anemic infants so the iron deficient, non-anemic infants who may benefit from iron supplementation can not be detected.

Conclusion

IDA is more prevalent in BF than FF infants. Risk factors of IDA in infants are low birth weight, breastfeeding and inadequate complementary food. The present study emphasized the importance of screening for anemia in infants by Hb or Hct at 9-12 months of age and introduction of iron-rich complementary food for early detection and prevention of IDA in infants.

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อุบัติการณ์และปัจจัยเสี่ยงของภาวะโลหิตจางจากการขาดธาตุเหล็กในทารกคลอดครบกำหนด

สุภาพรณ ตันตราชีวะธร, สิริณ โลหะเจริญทรัพย์

วัตถุประสงค์: เพื่อเปรียบเทียบอุบัติการณ์ของภาวะโลหิตจางจากการขาดธาตุเหล็กระหว่างทารกที่ได้รับนมแม่กับนมดัดแปลงสำหรับทารก และหาปัจจัยเสี่ยงของภาวะโลหิตจางจากการขาดธาตุเหล็กในทารก

รูปแบบการวิจัย: การศึกษาแบบ cohort

วิธีดำเนินการวิจัย: ศึกษาในทารกคลอดครบกำหนด 140 ราย (ทารกที่ได้รับนมแม่และนมดัดแปลงสำหรับทารกกลุ่มละ 70 ราย) ที่วิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาล ตั้งแต่เดือนกุมภาพันธ์ พ.ศ. 2545 ถึงเดือนพฤศจิกายน พ.ศ. 2546 ติดตามทารกที่อายุ 1, 2, 4, 6, 9 และ 12 เดือน เพื่อประเมินการเจริญเติบโตและพัฒนาการเมื่อทารกอายุ 9-12 เดือน ตรวจวัดระดับฮีโมโกลบิน ฮีมาโตคริต และขนาดของเม็ดเลือดแดง ทารกที่มีระดับฮีโมโกลบิน < 11.0 กรัม/ดล จะได้รับการตรวจค้นเพิ่มเติมเพื่อหาสาเหตุของภาวะโลหิตจาง

ผลการศึกษา: ค่าเฉลี่ยของฮีโมโกลบิน ฮีมาโตคริต ขนาดของเม็ดเลือดแดงและซีรั่มเฟอร์ริตินของทารกที่ได้รับนมแม่คือ 10.8 กรัม/ดล, 32.8%, 70.9 ฟล และ 16.7 นาโนกรัม/มล ตามลำดับ ซึ่งมีค่าต่ำกว่าทารกที่ได้รับนมดัดแปลงสำหรับทารกอย่างมีนัยสำคัญทางสถิติ (11.4 กรัม/ดล, 35.1%, 73.3 ฟล, และ 36.9 นาโนกรัม/มล, $p < 0.05$) พบภาวะโลหิตจางในทารกที่ได้รับนมแม่ 27 ราย (38.6%) และนมดัดแปลงสำหรับทารก 10 ราย (14.3%) อุบัติการณ์ของภาวะโลหิตจางจากการขาดธาตุเหล็กในทารกที่ได้รับนมแม่สูงกว่าทารกที่ได้รับนมดัดแปลงสำหรับทารกอย่างมีนัยสำคัญทางสถิติ (25.7% และ 2.9%, $p < 0.001$) ปัจจัยเสี่ยงของภาวะโลหิตจางจากการขาดธาตุเหล็ก ได้แก่ น้ำหนักตัวแรกเกิดน้อย ทารกที่ได้รับนมแม่ และการได้รับอาหารเสริมไม่เพียงพอ (adjusted RR (95% CI): 3.1(1.1-9.1), 6.3(1.5-25.0) และ 7.7(2.8-20.0) ตามลำดับ)

สรุป: ภาวะโลหิตจางจากการขาดธาตุเหล็ก พบในทารกที่ได้รับนมแม่มากกว่าทารกที่ได้รับนมดัดแปลงสำหรับทารก ปัจจัยเสี่ยงของภาวะโลหิตจางจากการขาดธาตุเหล็ก ได้แก่ น้ำหนักตัวแรกเกิดน้อย ทารกที่ได้รับนมแม่ และการได้รับอาหารเสริมไม่เพียงพอ เพื่อป้องกันภาวะโลหิตจางจากการขาดธาตุเหล็ก ทารกควรได้รับอาหารเสริมที่มีธาตุเหล็กเพียงพอ และตรวจระดับฮีโมโกลบินหรือฮีมาโตคริตที่อายุ 9-12 เดือนในทารกกลุ่มเสี่ยง