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A Retrospective Case-Control Study of the Determinants of Iron Deficiency Anemia in Infants in an Urban Community in Shanghai, China Between 2010–2015

Authors' Contribution:
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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Iron deficiency anemia (IDA) is a global public health problem. This study aimed to analyze the social determinants of IDA in infants living in Shanghai, China, between 2010–2015.

Material/Methods: Data were analyzed retrospectively from the Shanghai Children's Health Check Record system in the Tangqiao Community Health Service Center for infants aged <24 months between January 1, 2010, and December 31, 2015. A study group was identified with IDA, and an age-matched and gender-matched healthy control group was identified.

Results: The five-year prevalence rate of IDA was 11.49% (150/1305). Infants with IDA had significantly lower birth weights (3228.720±456.200 gm *vs.* 3376.870±393.719 gm; P<0.01), a higher percentage of premature births (10.67% *vs.* 1.33%; P<0.001), a longer exclusive breastfeeding period (10.63±4.844 months *vs.* 7.08±5.039 months; P<0.001), a higher rate of exclusive breastfeeding within four months after birth (P<0.001), a later start for complementary feeding (7.32±1.633 months *vs.* 6.93±1.794 months; P<0.05), and a higher rate of starting complementary feeding after 6 months of age (P<0.05). There were no significant differences between the two groups for maternal child-bearing age, mode of delivery, infant birth height, and birth rank.

Conclusions: The introduction of an iron-fortified formula for exclusively breastfed infants at 4 months of age, starting complementary feeding promptly before 6 months of age, and improving perinatal care for pregnant women to avoid premature birth and reduce low birth weight may be effective measures to prevent IDA.

MeSH Keywords: **Anemia, Iron-Deficiency • China • Infant Nutrition Disorders • Social Determinants of Health**

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Background

Worldwide, iron deficiency anemia (IDA) is a significant public health problem and causes greater harm to infants than children and adults [1]. In 2013, the Report on Nutrition Development of Chinese Children Aged 0 to 6 years stated that the overall prevalence rate of anemia in China among children under 5 years of age was 12.6% and that infants aged 6–24 months had the highest prevalence of anemia [1]. In 2015, a cross-sectional study of infants aged 6–36 months in Beijing, Shanghai, Nanjing, Shenzhen, and Chengdu showed that the prevalence of anemia in infants was17.2% [2]. One of the main objectives regarding children's health in the National Program of Action for Child Development in China, 2011–2020, is to reduce the prevalence of anemia to 12% or less in children less than 5 years of age [3].

Recent studies have shown that iron deficiency may harm children's growth and development, as well as motor skills and immune function [4–6]. Severe iron deficiency in infants may adversely affect their cognitive and learning abilities and behavioral development, which may not be reversed by treatment with iron supplements [7–9]. Therefore, reducing the determinants of IDA is important to prevent health impairment in infants, and priority should be given to reduce the prevalence rate of anemia among infants aged 6–24 months to reach the target of reducing the prevalence rate of anemia in infants less than one year of age. The community health center is the main site for the implementation of systematic childcare management, which means that it is important to investigate the determinants of IDA in infants and to explore community-based preventive measures.

The Tangqiao Community Health Service Center, is located in Pudong New Area, Shanghai, one of the most economically developed cities in China. Therefore, this study aimed to analyze the social determinants of IDA in infants living in Shanghai, China, between 2010–2015. This study was conducted to identify factors to support community-based primary and secondary public health intervention measures to reduce IDA in infants.

Material and Methods

Ethical approval

Data from this case-control study were analyzed retrospectively from the Shanghai Children's Health Check Record system in the Tangqiao Community Health Service Centre for infants aged <24 months between January 1, 2010, and December 31, 2015. A study group was identified with iron deficiency anemia (IDA), and an age-matched and gender-matched healthy control group was identified. This study was approved by the Ethics Committee of Zhongshan Hospital affiliated to Fudan University. Patient data were anonymized, and each participant was given a unique code during data analysis. The government-financed physical check-up was offered free of charge, and participation was voluntary. Information technology professionals from the district information center secured and exported the data used for analysis, as specified in the study design.

Data collection

The factors that were analyzed were basic demographic information, including family members and their education, parental occupation, and infant information including date of birth, birth weight, whether the birth was premature, and the infant's birth order. The records of the physical examinations for eight points in time were recorded at 1, 2, 4, 6, 9, 12, 18, and 24 months of age, including height, weight, head circumference, chest circumference, fontanel closure, dental growth, language and movement abilities, and other growth parameters. Data on feeding patterns and complementary feeding details were recorded. The results of laboratory tests were recorded, including routine blood testing of healthy infants at 6, 12, 18, and 24 months of age. Infants that were classified into high-risk or low weight categories received an additional routine blood examination at 4 months of age. For infants diagnosed with anemia, routine examinations were conducted every month until the hemoglobin levels were restored to within the normal range.

After the study design was approved, the anonymized data were exported from the Shanghai Children's Health Check Record database without any identifying details. All infants that were newly diagnosed with IDA whose ages ranged from 0–24 months between January 1, 2010, and December 31, 2015, were classified as the case group. The same number of healthy infants was selected as the control group of the same gender and age. The infants included three groups: <6 months old; 6–12 months old; and 12–24 months old. The following variables were obtained from the database: date of birth; birth weight; birth height; premature birth or not; firstborn or not; maternal age at delivery; mode of delivery; feeding pattern; exclusive breastfeeding; complementary feeding period; and a complete blood count (CBC) of the infants.

The diagnosis of IDA and response to iron therapy

The IDA diagnosis was made according to the recommendations of the Pediatrics Subbranch of the Chinese Medical Association [10]. The diagnostic criteria for infant IDA included a hemoglobin level <110 g/l, a mean corpuscular volume (MCV) <80 fl, a mean corpuscular volume (MCV) <27 pg, and a mean corpuscular hemoglobin concentration (MCHC) <310 g/l. The response to iron therapy was defined as an increase in

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hemoglobin to >20 g/l after undergoing iron therapy for four weeks. Infants with microcytic hypochromic anemia were identified as having IDA after reviewing the medical history and relevant laboratory results and excluding other types of anemia. The World Health Organisation (WHO) has recommended that the hemoglobin level is used as a screening indicator for IDA [10], and IDA may be clinically diagnosed if iron supplementation is effective.

Calculation of the study sample size

Based on the case-control study design, assuming that the percentage of children with anemia starting complementary feeding earlier than 6 months of age was 40% (p_1), while the percentage of children without anemia starting complementary feeding earlier than 6 months of age was 60% (p_2), the case-control ratio was 1: 1, and the statistical efficiency was 0.9, the required study sample size was estimated as:

$$n = [\frac{u_\alpha\sqrt{2\bar{p}(1-\bar{p})} + u_\beta\sqrt{p_1(1-p_1)+p_2(1-p_2)}}{p_1 - p_2}]^2 = 130$$

The number of cases in the study group was identified as 130 and the number of cases in the control group was also identified as 130. The total number of all infants with newly diagnosed IDA from the database between January 1, 2010 and December 31, 2015 was 150, which was identified as an adequate study sample size for statistical analysis.

Statistical analysis

Data were expressed as the mean, the frequency, and the percentage to describe the characteristics of the groups studied. A paired t-test and the chi-squared (χ^2) test were used to determine the differences in the continuous and categorical variables between the IDA and non-IDA groups, respectively. Multivariate logistic regression analysis was used to determine the factors associated with IDA. Statistical analysis was performed using SPSS version 19.0 software (IBM, Chicago, IL, USA). A P-value <0.05 was considered to be statistically significant.

Results

General information

There were 1,305 infants who received regular follow-up at the Child Care Clinic of Tangqiao Community Health Service Center between January 1, 2010, and December 31, 2015. There were 150 infants diagnosed with iron deficiency anemia (IDA) (82 male infants and 68 female infants). The overall five-year prevalence rate of IDA between 2010–2015 was 11.49% (12.75% for male infants and 10.27% for female infants). There was no significant difference in the prevalence of IDA between male and female infants (P>0.05) (Figure 1). When classified by the age at the time of diagnosis of IDA, 11 infants (7.33%) were <6 months old, 111 infants were 6–12 months old (74%), and 28 infants (18.67%) were 12–24 months old. The 6–12 month age group had the highest prevalence of IDA (P<0.01) (Figure 2).

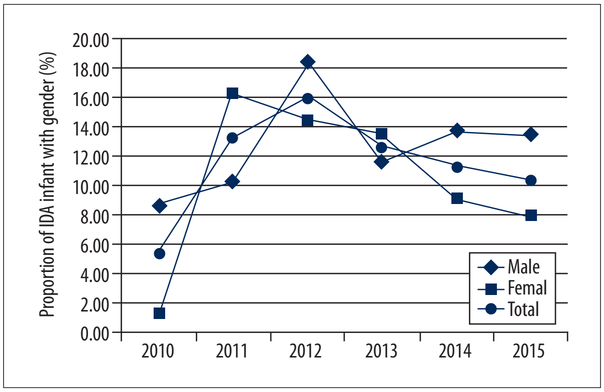

Figure 1. The prevalence of iron deficiency anemia (IDA) in male and female infants in an urban community in Shanghai, China between 2010–2015. The prevalence of IDA in male and female infants was not significantly different (P>0.05).

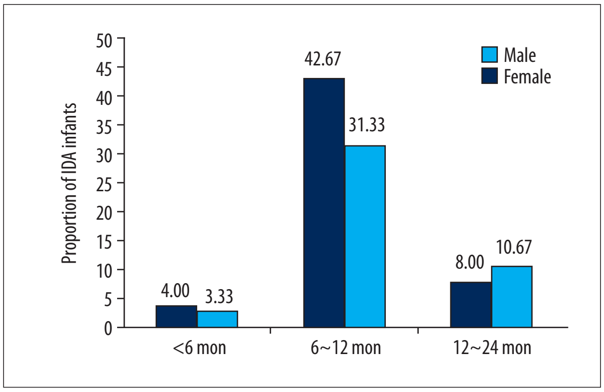

Figure 2. 0Distribution of the age at the time of diagnosis of iron deficiency anemia (IDA) in infants in an urban community in Shanghai, China between 2010–2015. Age at the time of diagnosis of IDA included 11 (7.33%) infants <6 months old, 111 (74%) infants between 6–12 months old, and 28 (18.67%) infants between 12–24 months old. The 6–12 month age group had the highest prevalence of IDA (P<0.01).

Social determinants of IDA

As shown in Table 1, the IDA group had a lower birth weight (3228.720±456.200 gm *vs.* 3376.870±393.719 gm; P<0.001), a longer exclusive breastfeeding period (10.63±4.844 months *vs.* 7.08±5.039 months; P<0.001) and a later start for complementary feeding (7.32±1.633 months *vs.* 6.93±1.794 months;

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Table 1. The clinical and demographic characteristics of the infants with iron deficiency anemia (IDA) and the matched control group in an urban community in Shanghai, China between 2010–2015.

Determinant	IDA group		Control group		P-value
Maternal age at delivery (years)	30.460±3.348		30.160±3.359		0.377
Birth weight (gm)	3228.720±456.200		3376.870±393.719		0.005
Birth height (cm)	49.519±3.1721		49.990±0.919		0.078
Duration of exclusive breastfeeding (months)	10.603±4.844		7.080±5.039		<0.001
Start of complementary feeding (months)	7.320±1.633		6.930±1.794		0.041
Maternal age at delivery (years)					
<30	58	(39.46)	65	(44.22)	0.435
≥30	89	(60.54)	82	(55.78)	
Mode of delivery					
Natural labor	66	(44.00)	63	(42.00)	0.824
Cesarean birth	84	(56.00)	87	(58.00)	
Premature birth					
Yes	16	(10.67)	2	(1.33)	<0.001
No	134	(89.33)	148	(98.67)	
First delivery					
Yes	119	(79.33)	129	(86.00)	0.174
No	31	(20.67)	21	(14.00)	
Mode of feeding within 4 months after birth					
Breastfeeding	127	(85.23)	80	(53.69)	<0.001
Mixed feeding	17	(11.41)	49	(32.89)	
Formula feeding	5	(3.36)	20	(13.42)	
Duration of exclusive breastfeeding (months)					
<4	8	(5.37)	40	(26.85)	<0.001
≥4	141	(94.63)	109	(73.15)	
Start of complementary feeding (months)					
≤6	74	(49.66)	93	(62.42)	0.027
>6	75	(50.34)	56	(37.58)	

$P<0.05$) when compared with the control group. There were no significant differences in maternal age at delivery and infant birth height between the two groups ($P>0.05$) (Table 1).

The percentage of premature births was significantly higher in the IDA group than in the control group (10.67% *vs.* 1.33%; $P<0.001$). Also, the prevalence of exclusive breastfeeding within four months after birth was significantly higher in the IDA group than in the control group ($P<0.001$). The percentage of infants who received exclusive breastfeeding for more than four months after birth was significantly higher in the IDA group than in the control group ($P<0.001$). Infants in the IDA group were more likely to receive complementary feeding after 6 months of age, which was significantly later than the control group ($P<0.05$). Differences in maternal age at delivery, mode of delivery, and whether the child was the first birth in the family were not significantly different between the IDA group and the control group ($P>0.05$) (Table 1). Factors associated with

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Table 2. Logistic regression analysis of the determinants of iron deficiency anemia (IDA) in infants in an urban community in Shanghai, China between 2010–2015.

	P-value	Odds ratio (OR)	95% confidence interval (CI)	
			Lower	Upper
Maternal age at delivery	0.286	0.941	0.842	1.052
First birth or not	0.395	0.683	0.284	1.642
Natural labor or not	0.873	1.047	0.594	1.846
Premature birth or not	0.827	4.367	0.000	3.388
Birth height (cm)	0.556	1.129	0.755	1.687
Birth weight (gm)	0.037	0.999	0.998	1.000
Method of feeding within 4 months of age	0.010			
Mixed feeding: breastfeeding	0.003	0.239	0.093	0.613
Formula feeding: breastfeeding	0.076	0.263	0.060	1.150
Period of exclusive breastfeeding (months)	0.151	1.061	0.979	1.151
Introduction of complementary feeding (months)	0.817	0.978	0.812	1.178

IDA were identified using logistic regression analysis, which showed that normal birth weight (OR=0.999) and mixed feeding (OR=0.239) were protective factors against the development of IDA (Table 2).

Discussion

The findings from the present study showed that premature birth, low birth weight, long exclusive breastfeeding time (>4 months old), and late adoption of complementary food (>6 months old) were risk factors for iron deficiency anemia (IDA) in infants living in Shanghai, China, between 2010–2015. However, high birth weight and mixed feeding were factors that protected infants from IDA. In 2001, data from the World Health Organisation (WHO) showed that the prevalence of IDA in infants living in industrialized and non-industrialized countries were 21.1% and 39.0%, respectively [4]. This study showed that the prevalence of IDA in infants in the Tangqiao Community in the city of Shanghai, China was 11.49%, which was slightly lower than that previously from both local and international sources. One possible reason for this discrepancy is that Pudong New District in Shanghai is an economically developed area. Also, this study only included infants living in the Tangqiao Community and did not include the infants of the transient population, which belong to a lower socio-economic class, which may underestimate the prevalence rate of IDA in this community.

During late pregnancy, the mother's body continues to transfer nutrients, including iron, to the fetus, representing a high proportion of nutrient transfer during pregnancy. Premature infants do not have enough time to receive and accumulate iron from the mother's body, lack iron reserves from birth, and are more likely to develop IDA during infancy [11]. A prospective cohort study in the Netherlands showed that late premature infants born after 32 weeks of gestation had a higher risk of IDA than term infants [12]. Recently, in 2019, Li et al. showed that in Beijing, China, premature infants had a high incidence of IDA [13]. This finding was supported by Xu et al. in 2015, who showed that premature birth was a risk factor for medium to severe IDA in infants 6–12 months old [14]. The findings from the present study showed that the percentage of premature infants in the IDA group was significantly higher than in the control group (10.67% *vs.* 1.33%; P<0.001). These data showed that premature birth was a risk factor of IDA, which is supported by studies from other countries.

A domestic survey of nutritional conditions in China in 2013 showed that infants aged 5 months to 1 year had the highest prevalence rate of IDA, with the IDA prevalence rate in male infants 38.3% and that in female infants being 34.7% [1]. In 2019, a study in Japan reported by Amano et al. showed that male infants were more likely to develop IDA than female infants [15]. However, in 2019, in Iran, Riahi et al. reported no statistically significant difference in the prevalence of IDA between male and female infants [16]. The findings from the present study showed that male infants were more likely to develop IDA than female infants (12.75% *vs.* 10.27%), but this difference did not reach statistical significance (P>0.05). Therefore, the association between gender and the incidence of IDA in infants requires further study.

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The iron reserve in the infant's body can support growth and development for approximately 3–4 months. The infant then requires a supply of iron from food after 4–6 months of age. Therefore, infants aged 6–24 months are at higher risk of developing IDA. A cross-sectional study in Bhaktapur, Nepal in 2016 showed that the prevalence of IDA in infants aged 2–6 months was 49%, whereas the prevalence rate of IDA among infants aged 7–12 months was 72% [17]. In 2015, an investigation of 300 infants with IDA aged between 0-6 years in Beijing showed that infants aged 7–12 months had a high prevalence of IDA [13]. The Nutrition Development Report of Chinese Children Aged 0–6 Years also indicated that the prevalence rate of IDA in infants aged 6–12 months was higher than in infants aged 12–24 months [1]. The findings from the present study showed that all of the infants with IDA developed anemia within 24 months after birth, and 7.33% of these cases developed IDA at less than 6 months old, 74.00% developed IDA at between 6–12 months of age, and 18.67% developed IDA at between 12–24 months of age. Therefore, the age group between 6–12 months had the highest prevalence of IDA ($P<0.01$), which was similar to the findings from previous studies. Therefore, to reduce the prevalence of infant IDA, communities should improve the investigation of infants aged between 6–12 months to identify IDA.

Although iron from breast milk can be absorbed more easily, the iron content is low. After the first four months, infants exhaust their supply of iron transferred from their mother. Infants grow quickly with a high demand for iron, and may easily develop IDA if they are still fed exclusively with breast milk. Exclusive breastfeeding is a risk factor for moderate to severe IDA among infants aged 6–12 months [14]. The longer the infant is breastfed, the worse the severity of childhood anemia [18]. In 2017, Hirata et al. in Japan showed that the infant feeding method was the most significant risk factor for IDA, followed by exclusive breastfeeding, and partial breastfeeding, with formula feeding having the lowest risk [19]. A cross-sectional study in Thailand reported that if mothers received adequate nutritional supplements, including iron, during pregnancy and lactation, exclusive breastfeeding up to 6 months should be advocated due to its substantial health benefits, particularly for anemia [20]. The American Paediatric Society suggested that term infants might take iron supplements to prevent IDA at 4 months of age [21]. The present study found that a longer period of exclusive breastfeeding (>4 months) was a risk factor for infant IDA, whereas mixed feeding was a protective factor. This finding is consistent with the findings from these previous studies. Therefore, communities should improve the guidance for infant feeding, especially regarding starting complementary feeding promptly to reduce the occurrence of IDA.

The WHO and the China Infants Food Guide suggest that complementary feeding should commence at 6 months of age [22]. One domestic study reported that infants who start receiving complementary feeding after 6 months of age had a high incidence of IDA [6]. A systematic retrospective study in Canada showed that starting complementary feeding after 4 months of age may help to reduce the incidence rate of infant IDA in breastfed infants [23]. This study showed that more infants in the IDA group started complementary feeding after 6 months of age than in the control group, and starting complementary feeding late (>6 months of age) was a risk factor for infant IDA. The findings from the present study support that starting complementary feeding of infants at 4–6 months of age may reduce the incidence of infant IDA.

In 2015, Xu et al. showed that low birth weight was a risk factor for moderate to severe IDA in infants aged 6–12 months [14]. The findings from the present study showed that low birth weight was a risk factor for infant IDA, whereas normal birth weight was a protective factor. Also, this study investigated other possible risk factors for IDA. In the 2012 study by Elalfy et al. in Egypt, of infants aged 6–24 months from a poor social background, the investigators identified that being the second-born or later birth order infant was an independent risk factor for IDA [24]. The findings from the present study showed that there was no significant difference in IDA associated with birth order ($P>0.05$). A domestic cohort study and a case-control study from Sudan found that cesarean births were associated with infant anemia [25,26]. However, the present study showed that the mode of delivery was not significantly associated with the incidence of IDA ($P>0.05$).

Previous studies have shown that the prevalence of IDA in developed countries was lower than in non-undeveloped areas. Premature infants with low birth weight, aged between 6–24 months (especially 6–12 months) and the introduction of complementary foods later than 6 months of age, are believed to contribute to IDA. The National Program of Action for Child Development in China, 2011–2020, including the strategy for Shanghai Pudong New District, indicated that during 2020, the medical standards of Pudong New District have reached those of a moderately developed country [3]. This study selected a community in Pudong New District, Shanghai, to assess the prevalence and risk factors for IDA in infants and young children in more developed regions in China. Previous studies on IDA have focused more on underdeveloped regions in China. The present study complemented these previous studies, but this study from the Shanghai Children's Health Check Record system in the Tangqiao Community Health Service Center for infants aged <24 months included the five-year (2010–2015) prevalence of IDA, which was 11.49% overall, 12.75% for male infants, and 10.27% for female infants.

This study had several limitations. A retrospective case-control study was conducted to rapidly determine the risk factors for

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IDA for infants in Shanghai, China, between 2010–2015, and to investigate the relationship between multiple risk factors and the development of IDA in infants. This study analyzed cross-sectional data and did not establish a causal relationship between the identified risk factors and IDA. Also, the study only included resident infants living in the Tangqiao community in Shanghai, and did not include the infants of the migrant population, which belong to a low socio-economic class and may have underestimated the prevalence rate of IDA in this community. Therefore, this study included a selection bias for the study population. Also, as one community was chosen with a high level of economic development and a relatively stable population in Shanghai was included for data analysis, the study might have underestimated the prevalence of anemia in the population. Also, this study included only one community and caution should be taken when extrapolating these results to the entire city of Shanghai, China, or other communities.

Conclusions

This study aimed to analyze the social determinants of iron deficiency anemia (IDA) in infants living in Shanghai, China, between 2010–2015. The study was conducted to identify factors to support community-based primary and secondary public health intervention measures to reduce IDA in infants. The introduction of an iron-fortified formula for exclusively breastfed infants at 4 months of age, starting complementary feeding promptly before 6 months of age, and improving perinatal care for pregnant women to avoid premature birth and reduce low birth weight may be effective measures to prevent IDA.

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