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Association between maternal anemia during pregnancy and risk of eczema in early childhood: A cohort study in Japan

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Abstract
Background: There is limited evidence on the association between maternal anemia during pregnancy and the risk of childhood allergic disorders, with regards to atopic eczema. The current pre-birth cohort study aimed to examine the association between maternal anemia during pregnancy and the risk of atopic eczema in Japanese 2-year-olds.
Methods: The study included 1354 Japanese mother-child pairs. Maternal anemia during pregnancy was determined based on self-reported iron treatment for anemia during pregnancy. Eczema was defined according to the criteria of the International Study of Asthma and Allergies in Childhood (ISAAC). Physician-diagnosed atopic eczema was evaluated through a questionnaire completed by the mothers.
Results: The prevalence of maternal anemia during pregnancy was 52.8%. The study found that maternal anemia during pregnancy was associated with an increased risk of physician-diagnosed atopic eczema in children; with an adjusted odds ratio of 1.79 and a 95% confidence interval of 1.04-3.17. However, there was no observed association between maternal anemia during pregnancy and the risk of eczema as defined by the ISAAC criteria.
Conclusions: Although the study relied on self-reported information, it suggested a potential positive association between maternal anemia during pregnancy and the risk of atopic eczema in children.

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Introduction

Anemia, a condition in which the number of red blood cells and their hemoglobin concentration are lower than normal, is a significant public health issue. It primarily affects young children, pregnant, and postpartum women, as well as menstruating adolescent girls and women. Iron deficiency is the most common cause of anemia, accounting for approximately 75% of cases diagnosed during pregnancy.[1] According to the World Health Organization (WHO), anemia is estimated to affect 37% of pregnant women globally. The burden of anemia is highest among poor households, particularly in developing countries.[2] In developed countries, reported prevalence values vary widely, ranging from 0% to 30%.[2]

In Japan, the prevalence of maternal anemia during pregnancy is higher than in Europe and the United States.[3-5] According to Jwa *et al.*, the rates were 4.5% in early pregnancy, 44.1% in mid-pregnancy, and 45.7% in late pregnancy.[6] In Japan, anemia is typically treated symptomatically, with healthcare providers recommending that pregnant women consume iron-rich foods.[7] This differs from the approach in other developed countries, where iron supplementation is often prescribed to prevent anemia,[7] and may be a factor contributing to the high incidence of maternal anemia during pregnancy in Japan.

Anemia during pregnancy is known to increase various risks, including cesarean delivery, preterm birth, and low birth weight.[8-12] However, there is limited evidence on the association between maternal anemia during pregnancy and the risk of childhood allergic disorders.

Compared with studies on respiratory allergic disorders, such as asthma and wheezing, there have been few studies on the association between maternal anemia or iron status during pregnancy and atopic eczema in childhood. Some contradictory results have been reported.[13-17] A UK prospective study observed an inverse association between umbilical cord iron concentration and the risk of eczema at 18–30 months of age,[15] while several other studies conducted in the UK[13,14] and Japan[16] did not show this association.

The prevalence of eczema among young children is increasing worldwide, so there is a need to accumulate evidence to prevent this disease.[18] The purpose of the present pre-birth cohort study was to examine the association between maternal anemia during pregnancy and the risk of atopic eczema among young Japanese children, using data from fetal life to 2 years of age from the Kyushu Okinawa Maternal and Child Health Study (KOMCHS).

Methods

Study population

Between April 2007 and March 2008, pregnant women were recruited for the KOMCHS, a prospective pre-birth cohort study that aimed to investigate risk and preventive factors for maternal and child health problems. Recruitment details have been previously provided.[19] Briefly, pregnant women were recruited from 423 obstetric hospitals in seven prefectures on Kyushu Island in southern Japan, with a total population of approximately 13.26 million, and in Okinawa Prefecture, an island chain in the southwest of Japan, with a total population of nearly 1.37 million.

At each obstetric hospital, pregnant women were given leaflets explaining the KOMCHS, an application form to participate in the study, and a self-addressed stamped return envelope. Pregnant women interested in joining the KOMCHS returned the application form to the data management center. Finally, 1757 pregnant women between the 5th and 39th week of pregnancy provided their written informed consent to participate in the KOMCHS and completed the baseline survey.

Among those 1757 mothers, 1590, 1527, 1430, and 1362 mother–child pairs participated in the second (at delivery), third (approximately 4 months postpartum), fourth (approximately 12 months postpartum), and fifth (approximately 24 months postpartum) surveys, respectively. Five pairs who did not participate in the fifth survey at 23–29 months postpartum were excluded, as along with three pairs due to missing study factor data, leaving data on 1354 pairs available for analysis. The ethics committees of the Faculty of Medicine at Fukuoka University and Ehime University Graduate School of Medicine approved the KOMCHS.

Measurements

At the time of each survey, study subjects completed questionnaires on lifestyle and other social conditions, such as smoking and medical history, for mothers during the baseline survey, and for both mothers and children during follow-up surveys.

The initial part of the baseline survey questionnaire gathered information on the region of residence, number of children, parental education levels, household income, and parental history of asthma, atopic eczema, and allergic rhinitis. A positive history of asthma, atopic eczema, or allergic rhinitis was recorded if a physician had diagnosed the parent with any of these allergic diseases.

The second section of the baseline survey questionnaire consisted of a semi-quantitative comprehensive dietary history questionnaire (DHQ) that assessed dietary habits over the previous month.[20,21] Estimates of dairy intake, food, energy, and selected nutrients were calculated using a computer algorithm for the DHQ based on the Standards Tables of Food Composition in Japan.[22] The second survey conducted after birth, included inquiries about the baby's sex, birthweight, and maternal smoking during pregnancy.

The questionnaire in the third survey (approximately at 4 months of age) included a question about maternal anemia during pregnancy. Maternal anemia during pregnancy was defined as a positive response to the following question: "Have you received iron treatment for anemia during pregnancy?"

The third and fourth surveys (approximately at 12 months of age) asked about breastfeeding duration and the smoking habits of the adult household members. Breastfeeding duration was defined as the period during which infants received breast milk, regardless of exclusivity. Postnatal living with at least one household smoker was defined as positive if the child had lived with at least one smoker in the third survey or the fourth survey.

The questionnaire in the fifth survey included questions on allergic disorders. Eczema in the last 12 months was defined as a positive response to the following three questions, based on the International Study of Asthma and

Allergies in Childhood (ISAAC) criteria: "Has your child ever had an itchy rash which was coming and going for at least 6 months?", "Has your child had this itchy rash at any time in the last 12 months?", and "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?" Physician-diagnosed atopic eczema was considered present if a physician had diagnosed the child as having atopic eczema at any time since birth.

Statistical analysis

The parameters selected a priori as potential confounding factors include region of residence, number of children at baseline survey, parental education levels, household income, parental history of asthma, atopic eczema, allergic rhinitis, children's birth weight and sex, breastfeeding duration, maternal active smoking during pregnancy, and postnatal living with at least one household smoker.

A multiple logistic regression analysis was conducted to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for eczema relative to maternal anemia during pregnancy. All statistical analyses were performed using the SAS software package version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Characteristics of the study subjects

The prevalence of maternal anemia during pregnancy was 52.8%. Out of the 1354 children aged 23–29 months, 229 children (16.9%) met the ISAAC criteria for eczema, and 62 (4.6%) had physician-diagnosed atopic eczema. Table 1 shows the characteristics of the study subjects. 40% of children had no older siblings. Around 45% of mothers and 55% of fathers had received 15 or more years of education. More children had parents with a history of allergic rhinitis compared to parents with a history of asthma or atopic eczema. The mean birthweight of the study subjects was 3002 g. Approximately 89% of the children were breastfed for 6 months or longer. About 8% of children were exposed to maternal smoking during pregnancy, and 44% had lived postnatally with at least one household smoker.

Maternal anemia in pregnancy and eczema risk

Table 2 presents the ORs and 95% CIs for the association between maternal anemia during pregnancy and eczema. Children whose mothers were anemic during pregnancy had a higher risk of physician-diagnosed atopic eczema until approximately 2 years of age compared with children with non-anemic pregnant mothers. After adjusting for potential confounding factors, the positive association remained statistically significant (adjusted OR = 1.79, 95% CI, 1.04–3.17). No association was observed between maternal anemia during pregnancy and the risk of eczema based on the ISAAC criteria.

A sensitivity analysis, in which we further adjusted for energy-adjusted maternal iron intake, produced results similar to those of the original analysis; further adjusted ORs (95% CI) for ISAAC criteria and physician-diagnosed atopic eczema were 0.97 (0.73–1.30) and 1.80 (1.04–3.19), respectively.

Discussion

To the best of our knowledge, this is the first epidemiological study to show that maternal anemia during pregnancy is significantly associated with an increased risk of physician-diagnosed atopic eczema in childhood.

Several previous studies have explored the association between maternal hemoglobin concentration during pregnancy or cord concentration of iron and the risk of atopic eczema in childhood.[13-17] In the Avon Longitudinal Study of Parents and Children (ALSPAC), it was found that an increasing cord concentration of iron was inversely associated with the risk of eczema in children aged 18–30 months.[15] This finding partially aligns with our present results. However, in another report using subsequent follow-up data from the ALSPAC, no association was observed between maternal hemoglobin concentration during pregnancy and the risk of eczema in children at 7 years old.[13] A birth cohort study involving 157 UK mother–child pairs also discovered that maternal serum iron status at 11 weeks of gestation or at delivery did not significantly correlate with the risk of doctor-diagnosed eczema up to 10 years of age.[14] Additionally, a large Japanese birth cohort study found no association between maternal hemoglobin or hematocrit concentrations during pregnancy and the risk of atopic eczema among children of 3 years old.[16] Our results contradicts those studies that show no association between maternal iron status and childhood atopic eczema. However, direct comparisons between our results and those of previous studies are not appropriate due to differences in exposure and outcome definitions, study populations, and analysis methods, including the adjustment of confounding factors.

Various mechanisms are involved in the pathogenesis of atopic eczema, including epidermal barrier dysfunction, genetic factors, immune dysregulation by Th2 cells, changes in the skin microbiome, and environmental triggers of inflammation.[23-27] The effects of iron deficiency during pregnancy on placental cytokine production have been reported in animals[28] and a study suggested that iron deficiency may upregulate Th2 cytokine responses and downregulate Th1 responses.[29] Although there is also evidence that contradicts this result,[30,31] maternal iron deficiency during pregnancy might affect the Th1/Th2 balance, resulting in altered immune function in the child. In the present study, the results of the further adjusted maternal iron intake during pregnancy were similar to those of the original analysis. Therefore, observed associations did not appear to be confounded by maternal iron intake during pregnancy.

A major strength of this study is the prospective study design, where subjects were followed from the fetal stage, minimizing recall bias. Additionally, we were able to control for many potential confounders.

Several limitations of this study need to be addressed. First, out of the 1757 participants in the baseline survey, only 1354 (77.1%) children were evaluated in this study. Selection bias may have occurred due to loss of follow-up

Table 1 Distribution of selected characteristics in 1354 parent–child pairs, KOMCHS, Japan.

Variable	Overall	Maternal anemia during pregnancy		*p*-value
	(*n* = 1354) No. (%) or mean ± SD	No (*n* = 639) No. (%) or mean ± SD	Yes (*n* = 715) No. (%) or mean ± SD	
Baseline characteristics				
Region of residence				0.03
Fukuoka Prefecture	783 (57.8)	359 (56.2)	424 (59.3)	
Other than Fukuoka Prefecture in Kyushu	442 (32.6)	229 (35.8)	213 (29.8)	
Okinawa Prefecture	129 (9.5)	51 (8.0)	78 (10.9)	
Number of living children				0.12
0	541 (40.0)	274 (42.9)	267 (37.3)	
1	543 (40.1)	243 (38.0)	300 (42.0)	
≥2	270 (19.9)	122 (19.1)	148 (20.7)	
Maternal education, years				0.63
<13	293 (21.6)	145 (22.7)	148 (20.7)	
13–14	455 (33.6)	209 (32.7)	246 (34.4)	
≥15	606 (44.8)	285 (44.6)	321 (44.9)	
Paternal education, years				0.02
<13	409 (30.2)	217 (34.0)	192 (26.9)	
13–14	198 (14.6)	86 (13.5)	112 (15.7)	
≥15	747 (55.2)	336 (52.6)	411 (57.5)	
Household income, yen[a]/year				0.70
<4,000,000	454 (33.5)	207 (32.4)	247 (34.6)	
4,000, 000-5,999,999	497 (36.7)	238 (37.3)	259 (36.2)	
≥6,000,000	403 (29.8)	194 (30.4)	209 (29.2)	
Maternal history of asthma	179 (13.2)	83 (13.0)	96 (13.4)	0.81
Maternal history of atopic eczema	246 (18.2)	114 (17.8)	132 (18.5)	0.77
Maternal history of allergic rhinitis	564 (41.7)	273 (42.7)	291 (40.7)	0.45
Paternal history of asthma	147 (10.9)	74 (11.6)	73 (10.2)	0.42
Paternal history of atopic eczema	133 (9.8)	61 (9.6)	72 (10.1)	0.75
Paternal history of allergic rhinitis	374 (27.6)	190 (29.7)	184 (25.7)	0.10
Characteristics of follow-up surveys				
Birth weight, mean ± SD, g	3002.3 ± 395.5	2955.5 ± 393.6	3044.1 ± 392.7	<0.0001
Male sex	646 (47.7)	310 (48.5)	336 (47.0)	0.58
Breastfeeding duration, months				0.81
<6	156 (11.5)	75 (11.7)	81 (11.3)	
≥6	1198 (88.5)	564 (88.3)	634 (88.7)	
Maternal active smoking during pregnancy	111 (8.2)	66 (10.3)	45 (6.3)	0.007
Postnatal living with at least one household smoker	601 (44.4)	291 (45.5)	310 (43.4)	0.42

[a]US$1 = ¥145.

Table 2 Crude and adjusted ORs and 95% CI for eczema according to maternal anemia during pregnancy, KOMCHS, Japan.

Maternal anemia during pregnancy	ISAAC criteria for eczema			Physician-diagnosed atopic eczema		
	Risk (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	Risk (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
No	109/639 (17.1)	1.00	1.00	21/639 (3.3)	1.00	1.00
Yes	120/715 (16.8)	0.98 (0.74–1.30)	0.97 (0.72–1.29)	41/715 (5.7)	1.79 (1.06–3.12)	1.79 (1.04–3.17)

CI = confidence interval; OR = odds ratio.
[a]Adjustment for the region of residence at baseline, number of children at baseline, maternal and paternal education levels, household income, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, infant's birth weight, infant's sex, breastfeeding duration, maternal smoking status during pregnancy, and child's passive smoking status.

or exclusion of subjects with incomplete information. Furthermore, our study subjects may not be representative of the Japanese population, as the parents' educational levels were higher than the general population.[32]

Second, the definition of maternal anemia during pregnancy was based on self-reported iron treatment for anemia. Objective measurements like hemoglobin or hematocrit concentrations, were not available. Using self-reported information may lead to misclassification due to recall bias. However, the relatively short recall period of approximately 4 months postpartum may increase the accuracy of the self-reported information.[33] Additionally, the subjects educational levels or health consciousness could impact response reliability. Misclassification of exposure was expected to be equal between children with and without atopic eczema, leading to a bias toward the null. Furthermore, factors like the severity of anemia, timing and duration of onset, and iron deficiency were not considered.

Third, the definition of physician-diagnosed atopic eczema was reliant on maternal self-report. It is possibile that some mothers may inaccurately recall the child's medical diagnosis, or that the physician's diagnosis could be incorrect. Therefore, there may have been misclassification of the outcomes under study. Additionally, the validity of using the ISAAC questionnaire for the subjects in this study is uncertain, as no validation studies have been conducted with Japanese infants and toddlers using the ISAAC criteria. A validation study of the ISAAC questionnaire comparing it to dermatologist diagnosis, found low sensitivity (37.1%) and high specificity (90.0).[34] False positives in the ISAAC were primarily due to scabies.[34] While this finding may not directly apply to our study population, it is possible that atopic eczema based on the ISAAC criteria might be overestimated. The lack of association observed with eczema based on the ISAAC could be due to non-differential outcome misclassification. Therefore, outcomes based on a physician's diagnosis might be less prone to misclassification, even if self-reported. This could explain the positive association between maternal anemia during pregnancy and the risk of childhood atopic eczema, which was only evident in the analyses based on a physician's diagnosis.

Conclusions

Our prospective study found that maternal anemia during pregnancy is associated with a higher risk of physician-diagnosed atopic eczema in children. Although there have been few studiesexamining the effects of maternal anemia during pregnancy on childhood atopic eczema, our study offers valuable evidence of this association. However, further studies with more accurate exposure measurements, including the timing of onset during each trimester and clinical data, as well as conclusive outcomes, are necessary to determine if maternal anemia during pregnancy is indeed a risk factor for childhood atopic eczema.

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Author Contributions

N.Y. was responsible for the analysis and interpretation of data and the drafting of the article. K.T. contributed to the study concept and design and data acquisition and was responsible for the data analysis and interpretation and the drafting article. Y.M. contributed to the study concept and design, data acquisition, and assisted in article preparation. All authors have read and approved the final version of the manuscript.

Disclosure

None.

Conflicts of Interest

K.T. and Y.M. were financially supported by Meiji Co., Ltd. N.Y. has no conflict of interest.

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