Neonatal Vitamin A Deficiency and Its Impact on Acute Respiratory Infections among Preschool Inuit Children

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ABSTRACT

Objective: To assess if vitamin A concentration in umbilical cord blood is associated with incidence and severity of respiratory infections in preschool Inuit children from Nunavik (Québec, Canada).

Method: The medical charts of 305 children were reviewed from 0 to 5 years of age. The association between vitamin A concentration in umbilical cord plasma and the incidence rates of acute otitis media (AOM), lower respiratory tract infections (LRTIs) and hospitalization rates for LRTIs was evaluated using Poisson regression.

Results: Compared to children with vitamin A concentration ≥ 20 $\mu\text{g/dl}$, adjusted rate ratios (RR) for children below 20 $\mu\text{g/dl}$ ranged between 1.06-1.62 for AOM, 1.12-1.34 for LRTIs, and 1.09-1.43 for hospitalization for LRTIs. Most RRs were statistically significant for AOM and LRTIs, but not for hospitalization for LRTIs.

Conclusion: Neonatal vitamin A deficiency appears to be a significant risk factor for AOM and LRTIs in this population.

Key words: Vitamin A deficiency; Inuits; nutritional status; respiratory tract infections; otitis media; infant; child; risk factor

La traduction du résumé se trouve à la fin de l'article.

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Vitamin A plays a major role in growth, development and vision.^{1,2} It is well known that a deficiency in vitamin A also impairs resistance to infections, especially in early age,²⁻⁷ and many authors have identified increased rates or augmented severity of infections in vitamin A-deficient children.⁸⁻¹³ Insufficient vitamin A intake has typically been described in developing countries. However, our group recently showed that a significant proportion of Inuit infants from Nunavik (Northern Québec, Canada) was born with low blood levels of vitamin A.¹⁴

This study is the second phase of a previous study that evaluated vitamin A concentration in cord blood of newborns from three regions of the province of Québec.¹⁴ In this study, we tested the hypothesis that low neonatal vitamin A concentration was associated with higher incidence rate of acute respiratory infections, and with rates of admission for lower respiratory tract infections in Inuit children from Nunavik during their first five years of life.

MATERIAL AND METHOD

Study population and recruitment

The recruitment procedure for this study was previously described.¹⁴ In the current analysis, only participants from Nunavik were included. Briefly, between 1993-1997, pregnant women arriving for delivering at one of the two participating health centres were invited to participate. Umbilical cord blood was sampled and a postpartum interview was conducted a few days after delivery. A subgroup of mother-child pairs was also selected for a 5-year follow-up interview (n=88). The study protocol was reviewed and approved by the ethics committee of Laval University.

Medical chart review and infection incidence rate

Medical charts were reviewed by five 2nd- and 3rd-year trained medical students using a standardized questionnaire. For the present study, only acute lower respiratory tract infections (LRTIs) and acute otitis media (AOM) were targeted. Two infectious episodes affecting the same anatomic site were considered separate if there were at least 15 days between the two diagnoses and if it was not specified that the second episode was related to the first.

TABLE I

Characteristics of Participants

Characteristics	Mean Value or Percentage				
	All Participants (n=305)	<10 µg/dl (n=26)	10-14 µg/dl (n=118)	14-19 µg/dl (n=109)	≥20 µg/dl (n=52)
Children					
Gender (% male)	47.7	65.4	51.7	49.1	26.9
Gestational age (weeks)	39.1	39.0	38.8	39.1	39.8
Birthweight (g)	3503	3368	3401	3517	3779
Length (cm)	51.5	50.8	51.3	51.7	51.9
Mothers					
Age (years)	23.8	23.3	23.1	23.9	25.4
Parity	3.7	3.7	3.6	3.5	4.1

TABLE II

Incidence Rate (95% confidence interval) of Acute Respiratory Infections

Infection and Hospitalization	Incidence rate (events per 1000 child-years)	
	0-12 Months of Age	0-4 Years of Age
Acute otitis media	2141 (1939 – 2343)	1254 (1149 – 1359)
Lower respiratory tract infections	1289 (1126 – 1451)	628 (562 – 694)
Hospitalization for lower respiratory tract infections	298 (226 – 370)	110 (85 – 134)

Determination of vitamin A in cord blood

Detailed analytic method was previously described.¹⁴ Briefly, blood samples were centrifuged, frozen at 80°C and then sent to the Institut National de Santé Publique du Québec (Québec City, Canada) for vitamin A (retinol) analysis. Retinol concentration was determined by reversed-phase high-pressure liquid chromatography.

Data collection on confounding factors

Perinatal factors were documented using data from the medical charts review, and from the postpartum interview. These factors were gender, birthweight, birth length, reviewer of the medical chart, gestational age, maternal age at parturition, parity and maternal smoking during pregnancy. Data on crowding, breastfeeding, and socio-economic status (Hollingshead index) was gathered through the 5-year follow-up interview.

Statistical analyses

Poisson regression was used to evaluate the associations between the vitamin A concentration and the infection incidence rates. The main dependent variable was the number of diagnosed episodes of infection during the first five years of life, and the main independent variable was vitamin A concentration in cord blood. Potential confounding factors were tested in the model one by one, but only those influencing the RRs by more than 5%

were included in the final model. The variables included in the final multivariate model were gender and birthweight. Gestational age, smoking during pregnancy, prenatal exposure to contaminant, and reviewer of the chart were excluded from the final model. Some potential confounding factors were available only for children included in the 5-year follow-up subgroup. These factors were breastfeeding duration, crowding, and socio-economic status. None of these variables influenced the association in a significant manner and they were also excluded from the final model.

We used SAS 8.02 (Cary, NC, United States) for database management and statistical analyses. A p-value <0.05 was considered significant.

RESULTS

Participants

The first phase of this study initially included 379 children from Nunavik.¹⁴ Of these, it was impossible to get the charts of 31 (8.2%) children for various logistical reasons. Among the 348 available charts, 23 (6.6%) were incomplete, 13 (3.7%) families moved out of Nunavik during follow-up, 4 (1.1%) children died and 3 (0.9%) children were excluded because they suffered from a serious chronic disease. The final analysis included the 305 remaining children. Table I shows the characteristics for all participants according to their vitamin A concentration in cord blood.

Vitamin A concentrations

The mean vitamin A concentration in cord blood for all participants was 15.7 µg/dl, ranging from 5.5 µg/dl to 30.8 µg/dl. There were 8.5% children with <10 µg/dl, 38.7% children with 10-14 µg/dl, 35.7% children with 15-19 µg/dl, and 17.0% children with ≥20 µg/dl.

Infection incidence rates

A total of 4,846 outpatient visits that led to a diagnosis of acute respiratory infection before the age of five were identified. Incidence rates for AOM, LRTIs and hospitalization for LRTIs are shown in Table II. As expected, acute otitis media was the most frequently diagnosed infection. Incidence rates of AOM, LRTIs and hospitalizations for LRTIs were much higher in the first 12 months of life. Hospitalizations were frequent as 17.5% of outpatient visits for LRTIs led to an admission.

Vitamin A concentration and infections in the first 12 months

The association between acute respiratory infections and vitamin A concentration in cord blood is shown in Table III (first 12 months of life) and Table IV (first 5 years of life). For AOM in the first 12 months of life, compared to children in the ≥20 µg/dl group, children in vitamin A groups of <10 µg/dl, 10-14 µg/dl, and 15-19 µg/dl had RRs of 1.84 (p<0.0001), 1.24 (p=0.084), and 1.24 (p=0.080), respectively. A statistically significant negative association was also observed in the continuous model (RR = 0.88 for each 5 µg/dl increase of vitamin A concentration, p=0.005). Similar results were observed in the adjusted model.

For LRTIs, compared to children in the ≥20 µg/dl group, children in vitamin A groups of <10 µg/dl, 10-14 µg/dl, and 15-19 µg/dl had RRs of 1.13 (p=0.59), 1.33 (p=0.07), and 1.35 (p=0.06), respectively. The continuous model yielded a non-statistically significant negative association (RRs = 0.94 for each 5 µg/dl increase of vitamin A concentration, p=0.27). Results were similar in the adjusted model.

For hospitalization for LRTIs, children in lower vitamin A categories all had RRs above 1.0, but statistical significance was reached only for children 10-14 µg/dl in the unadjusted model (RR = 2.15, p=0.040). The continuous model showed a

borderline statistically significant negative association (RRs = 0.79 for each 5 µg/dl increase of vitamin A concentration, $p=0.053$).

Vitamin A concentration and infections in the first 5 years

In general, the effect-size of associations was lower when infections during the first 5 years of life were considered. However, statistical significance was reached more often due to the increased statistical power (increased number of events).

For AOM, compared to children in the ≥ 20 µg/dl group, children in vitamin A groups of <10 µg/dl, 10-14 µg/dl, and 15-19 µg/dl had RRs of 1.63 ($p<0.0001$), 1.25 ($p=0.001$), and 1.08 ($p=0.29$), respectively. A statistically significant negative association was also observed in the continuous model (RR = 0.88 for each 5 µg/dl increase of vitamin A concentration, $p<0.0001$). Similar results were observed in the adjusted model.

For LRTIs, compared to children in the ≥ 20 µg/dl group, children in vitamin A groups of <10 µg/dl, 10-14 µg/dl, and 15-19 µg/dl had RRs of 1.17 ($p=0.28$), 1.31 ($p=0.008$), and 1.34 ($p=0.004$), respectively. The continuous model yielded a statistically significant negative association (RRs = 0.92 for each 5 µg/dl increase of vitamin A concentration, $p=0.018$). Results were similar in the adjusted model, but statistical significance was lost in the adjusted continuous model ($p=0.058$).

For hospitalization for LRTIs, children in lower vitamin A categories all had RRs above 1.0, but statistical significance was reached only for children 10-14 µg/dl in the unadjusted model (RR = 1.66, $p=0.040$). The continuous model showed a negative association (RRs = 0.81 for each 5 µg/dl increase of vitamin A concentration, $p=0.018$), but the statistical significance was lost in the adjusted model ($p=0.147$).

DISCUSSION

This study was undertaken in order to document the association between neonatal vitamin A concentration and acute respiratory infections during the first five years of life in Inuit children. For the first 5 years of life, a statistically significant association between lower blood vitamin A concentration and higher incidence rate was found

TABLE III

Incidence Rate Ratio of Acute Respiratory Infections and Hospitalizations for Lower Respiratory Tract Infections According to Vitamin A Concentration in Cord Blood for 0 to 12 Months of Age

Vitamin A Concentration in Cord Blood	Incidence Rate Ratio (95 % CI)		
	AOM	LRTIs	Hospitalizations for LRTIs
Unadjusted model (n=305)			
Continuous (for each 5 µg/dl increase)	0.88 (0.81-0.97)*	0.94 (0.84-1.05)	0.79 (0.63-1.01)
Categories (µg/dl)			
<10	1.84 (1.37-2.49)**	1.13 (0.72-1.77)	1.78 (0.69-4.61)
10-14	1.24 (0.97-1.58)	1.33 (0.98-1.82)	2.15 (1.05-4.41)*
15-19	1.24 (0.97-1.59)	1.35 (0.99-1.85)	1.59 (0.76-3.35)
≥ 20	1.00 (referent)	1.00 (referent)	1.00 (referent)
Adjusted model (n=301)†			
Continuous (for each 5 µg/dl increase)	0.87 (0.79-0.95)*	0.94 (0.84-1.06)	0.84 (0.65-1.09)
Categories (µg/dl)			
<10	1.93 (1.40-2.66)**	1.14 (0.71-1.83)	1.54 (0.55-4.29)
10-14	1.30 (1.01-1.68)*	1.36 (0.98-1.91)	1.98 (0.90-4.37)
15-19	1.27 (0.99-1.65)	1.39 (1.00-1.93)	1.55 (0.70-3.46)
≥ 20	1.00 (referent)	1.00 (referent)	1.00 (referent)

AOM = acute otitis media, URTIs = upper respiratory tract infections, LRTIs = lower respiratory tract infections, CI = confidence interval.

* Statistically significant ($p<0.05$).

** Statistically significant ($p<0.0001$).

† Model adjusted for gender and birthweight.

TABLE IV

Incidence Rate Ratio of Acute Respiratory Infections and Hospitalizations for Lower Respiratory Tract Infections According to Vitamin A Concentration in Cord Blood from 0 to 4 Years of Age

Vitamin A Concentration in Cord Blood	Incidence Rate Ratio (95 % CI)		
	AOM	LRTIs	Hospitalizations for LRTIs
Unadjusted model (n=305)			
Continuous (for each 5 µg/dl increase)	0.88 (0.845-0.92)**	0.92 (0.87-0.99)*	0.81 (0.68-0.97)*
Categories (µg/dl)			
<10	1.63 (1.37-1.94)**	1.17 (0.88-1.55)	1.43 (0.74-2.77)
10-14	1.25 (1.09-1.44)*	1.31 (1.07-1.60)*	1.66 (1.02-2.68)*
15-19	1.08 (0.94-1.24)	1.34 (1.10-1.64)*	1.18 (0.71-1.96)
≥ 20	1.00 (referent)	1.00 (referent)	1.00 (referent)
Adjusted model (n=301)†			
Continuous (for each 5 µg/dl increase)	0.87 (0.83-0.92)**	0.93 (0.87-1.01)	0.87 (0.73-1.05)
Categories (µg/dl)			
<10	1.62 (1.35-1.95)**	1.12 (0.83-1.50)	1.14 (0.57-2.27)
10-14	1.25 (1.08-1.44)*	1.27 (1.03-1.56)*	1.43 (0.86-2.37)
15-19	1.06 (0.92-1.23)	1.34 (1.09-1.64)*	1.09 (0.64-1.84)
≥ 20	1.00 (referent)	1.00 (referent)	1.00 (referent)

AOM = acute otitis media, URTIs = upper respiratory tract infections, LRTIs = lower respiratory tract infections, CI = confidence interval.

* Statistically significant ($p<0.05$).

** Statistically significant ($p<0.0001$).

† Model adjusted for gender and birthweight.

for AOM and LRTIs, but not for hospitalization for LRTIs. For AOM, the association showed a dose-response pattern.

Reports of placebo-controlled prospective studies on supplementation are controversial, as some authors found that vitamin A supplementation decreased respiratory infections incidence rates^{12,15} while some did not.^{8,16-19} In observational prospective studies, vitamin A deficiency was associated with an increased rate of respiratory infections,^{9,20} but not with rate of AOM.²¹ In a cross-sectional, follow-up

and interventional trial study performed in Thailand in a population with a vitamin A deficiency similar to that of the current study, Bloem et al.¹⁰ found a dose-response relationship between respiratory diseases incidence rates in children and mild vitamin A deficiency.

It has been discussed by some authors that the effect of a deficient level of vitamin A could better be observed on the severity of infectious episodes rather than on the incidence rate.²² Indeed, an association between vitamin A level and severity

has been demonstrated in some studies,^{8,23} but not all.¹⁶ To assess the impact of deficient vitamin A level at birth on the severity of infections in our population, we examined the incidence of hospitalization for LRTIs. Although no statistically significant association was found, most RR were above 1.0 and the effect-size in both the categorical and the continuous models was greater when only LRTIs that led to an admission were considered, compared to the total rate of LRTIs. This suggests that not only the rate of LRTIs is increased in children with lower vitamin A levels, but that these episodes were also more severe. Further studies with a greater number of subjects are needed to clarify this issue.

In this study, the vitamin A status of the mother-infant pairs was extrapolated through the umbilical cord blood retinol level. It is well known that a low concentration of retinol in umbilical cord blood correlates with a maternal vitamin A-deficient state during pregnancy.²⁴⁻²⁶ Such deficiency will in turn decrease significantly the amount of vitamin A passed to the infant through breastfeeding.^{24,27} We therefore hypothesized that breastfed infants born to vitamin A-deficient mothers were exposed to insufficient level of vitamin A *in utero* and would be fed inadequate amounts of vitamin A in the early postnatal period. We also think that, for these children, the daily diet in their first years would likely be low in vitamin A, although we could not assess this aspect in our study. We therefore believe that the association between low retinol level in cord blood and increased infection rates was due to a lack of vitamin A store both in the prenatal and the postnatal period. Whether an insufficient vitamin A concentration during the fetus development impairs the functioning of the immune systems late into childhood remains to be elucidated.

Bottle-feeding, on the other hand, will provide the infant with sufficient amount of vitamin A but can increase infections rate. Bottle-feeding is not common in Nunavik as more than 70% of children in the 5-year subgroup were breastfed for more than 3 weeks (data not shown). Although breastfeeding duration was not available for all children, its inclusion in the model for the 5-year subgroup did not affect the association between vitamin A and infections rate.

Nutrition status is an important factor that can modulate the immune system. Our preliminary analyses allowed us to find that low socio-economic status and crowding, two factors that could be related to poorer nutrition, did not influence the association between vitamin A and infection rate. Nevertheless, we cannot completely rule out that part of the association between vitamin A and infection rate could be due to other nutrients deficiencies, or to a generally less healthy diet.

The parent's decision of seeking medical attention is related to many cultural and socio-economic factors, which in turn could be associated with dietary habits. A bias could therefore be introduced if the propensity to seek medical attention was associated with maternal vitamin A intakes. If this bias was present in our data, it is likely that it would be insignificant when severe symptoms were present, symptoms for which most parents would go to the clinic. It would also not be present for hospitalization. We cannot, however, exclude the possibility of such a bias, especially for AOM.

This study underlines a possible link between low vitamin A concentration at birth and acute respiratory infections in Inuit children from Nunavik. Because children from this population are burdened by a high incidence of AOM and LRTIs compared to other North-American populations, the identification of a preventable risk factor such as neonatal vitamin A deficiency is of paramount importance. Together with the first phase of this study, these results indicate that a carefully planned supplementation program should be considered in Nunavik for both pregnant women and newborns.

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RÉSUMÉ

Objectif : Évaluer si la concentration de vitamine A dans le sang de cordon ombilical est associée avec l'incidence et la sévérité des infections respiratoires chez les enfants inuits d'âge préscolaire au Nunavik (Québec, Canada).

Méthode : Les dossiers médicaux couvrant les 5 premières années de vie de 305 enfants ont été examinés. L'association entre la concentration de vitamine A dans le sang de cordon ombilical et l'incidence d'otite moyenne aiguë (OMA), d'infections des voies respiratoires inférieures (IVRI) et d'hospitalisations pour des IVRI a été évaluée à l'aide du modèle de régression de Poisson.

Résultats : Comparativement aux enfants ayant des concentrations de vitamine A ≥ 20 $\mu\text{g/dL}$, les taux d'incidences relatifs ajustés (TR) des enfants avec des concentrations < 20 $\mu\text{g/dL}$ étaient compris entre 1,06 et 1,62 pour les OMA, entre 1,12 et 1,34 pour les IVRI et entre 1,09 et 1,43 pour les hospitalisations pour des IVRI. La plupart des TR étaient statistiquement significatifs pour les OMA et les IVRI, mais pas pour les hospitalisations.

Conclusion : Une déficience néonatale en vitamine A semble être un facteur de risque significatif d'OMA et d'IVRI dans cette population.

Mots clés : déficience en vitamine A; Inuit; statut nutritionnel; infection des voies respiratoires; otite moyenne aiguë; nourrisson; enfant; facteur de risque

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