Milk and Plasma Lutein and Zeaxanthin Concentrations in Chinese Breast-Feeding Mother–Infant Dyads With Healthy Maternal Fruit and Vegetable Intake

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\textbf{ABSTRACT}

\textbf{Objectives:} While others have reported that milk from coastal Chinese women contains high levels of lutein and zeaxanthin, no research has determined the corresponding infant plasma response. Whether infant plasma levels increase commensurately provides important guidance for supplementation of these increasingly intriguing carotenoids in breast-feeding mothers and formula-fed infants.

\textbf{Methods:} Fifty-six mother–infant pairs with a maternal diet rich in eggs, green leafy vegetables, and fruit were enrolled between 6 and 16 weeks of lactation. Milk samples and blood samples from both the mother and infant were collected at entry. Maternal 3-day dietary records and a second milk sample were collected 1 to 3 weeks later.

\textbf{Results:} Mean milk lutein concentrations in samples 1 and 2 were 6.5 and 7.7 \( \mu \text{g/dL} \) (range 1–22.5 \( \mu \text{g/dL} \)), and for zeaxanthin, 1.6 and 1.7 \( \mu \text{g/dL} \) (range 1–5.9 \( \mu \text{g/dL} \)). Lutein concentrations in infant plasma (18.2 \( \mu \text{g/dL} \)) were similar to those in maternal plasma (21.6 \( \mu \text{g/dL} \)); zeaxanthin was lower than lutein in both maternal (3.1 \( \mu \text{g/dL} \)) and infant (2.9 \( \mu \text{g/dL} \)) plasma. Infant and maternal mean plasma lutein and zeaxanthin concentrations were higher than those in both milk samples 1 and 2 (lutein, 6.9 and 8.2 \( \mu \text{g/dL} \); zeaxanthin, 1.9 and 2.0 \( \mu \text{g/dL} \)). Infant plasma lutein and zeaxanthin concentrations positively correlated with those in milk sample 1 (lutein, \( r^2 = 0.15, p = 0.004 \); zeaxanthin, \( r^2 = 0.21, p < 0.001 \)).

\textbf{Conclusions:} Together, these results reveal that high milk concentrations of lutein and zeaxanthin driven by healthy maternal intakes of xanthophyll rich foods are associated with high infant plasma concentrations. These findings will be useful for determining appropriate lutein fortification strategies.

\textbf{Clinical Study.gov registration number:} NCT01669655.

\textbf{Introduction}

Human milk contains approximately 30 of the more than 50 plant-derived carotenoids consumed in the human diet (1–3). Of these, only lutein and zeaxanthin are found in the neural retina. Lutein and zeaxanthin reach particularly high concentrations in the macula to form the characteristically yellow macular pigment. Macular pigment is widely believed to protect macular photoreceptors from short-wavelength blue light and oxidative damage (1,4). Recent research has increasingly implied that lutein and zeaxanthin play a role in cognitive function in adults (5–9), and more recently in children (10,11). Both infant and adult human brain contains lutein and zeaxanthin at higher levels than those observed for other carotenoids found in human plasma (8,12).

As lutein and zeaxanthin cannot be synthesized by animals, young postnatal infants receive lutein and zeaxanthin through human milk and/or supplemented infant formula. Human milk lutein and zeaxanthin levels are known to vary widely among women (13,14), and geographical locations with substantially higher levels of both in milk samples come from China and Japan (15,16). This is attributed to high intakes of green leafy vegetables and eggs during lactation in China and Japan. However, plasma lutein and zeaxanthin levels in breast-fed infants from these countries have not been reported in a systematic manner (17). Therefore, it is not known whether infant plasma lutein and zeaxanthin concentrations are correspondingly higher in infants consuming milk with high levels of these xanthophylls. The answer to this question is important to...
establish appropriate supplementation strategies for lactating women and formula-fed infants. Understanding determinants of infant status for these carotenoids is in turn important due to the rapid rate of brain and retinal development in the infant.

To address this knowledge gap, we enrolled coastal Chinese mother–infant dyads meeting recommendations for the intake of fruits and green leafy vegetables (18,19). We report the resulting infant plasma lutein and zeaxanthin concentrations and interrelationships with maternal plasma and milk levels.

**Materials and methods**

**Ethics**

All procedures were approved by the Ethics Committee of Pediatrics Clinical Pharmacology, Fudan University. Mothers provided informed consent on their own behalf and on behalf of their infant.

**Subjects**

Fifty-six pairs of lactating mothers and their infants were recruited from Shanghai, China. Inclusion criteria were: healthy singleton full-term infant (37–42 weeks gestation), birth weight greater than 2490 g, between 6 and 16 weeks (42–112 days) of age at enrollment, exclusively breast-fed for at least 4 weeks at enrollment, and the infant’s mother voluntarily signed the informed consent form. In addition, the mothers were healthy nonsmokers, consumed at least 300 g of fruit and/or vegetables per day, including at least 100 g of dark green leafy vegetables, and confirmed her intention to continue breast-feeding for at least 1 week after enrollment. Mothers completed a food frequency questionnaire on fruit and vegetable intake the week before enrollment.

**Milk and plasma samples**

Milk was collected at enrollment and 1 week later by using a breast milk pump (Harigen, Shantou, China) or by manual expression by the mother between 1 p.m. and 6 p.m. on the day of sample collection. Milk was collected from the breast that had a longer time gap since the last feeding. Milk from one breast was completely expressed for collection. The total volume of milk was measured and the samples were kept at −80 °C until analysis.

Maternal blood samples were collected by venipuncture by a registered nurse. Infant blood samples were collected by venipuncture or by heel stick by a registered pediatric nurse. Blood samples were collected into heparin tubes (BD Vacutainer, Franklin Lakes, NJ) under red light, coagulated at room temperature for at least 30 minutes, and then centrifuged at 1500 × g for 15 minutes. Samples were stored at the Shanghai Center of Disease Control and Prevention analytical lab at −80 °C until analysis.

**Dietary intakes**

Maternal food intake was captured using a 3-day dietary diary collected for 2 weekdays and 1 weekend day. Average daily lutein plus zeaxanthin intake was estimated by matching the foods consumed with similar foods in the U.S. Department of Agriculture (USDA) National Nutrient Database (20). This was necessary since lutein and zeaxanthin concentrations were not available for Chinese foods. Song (21) provides the details of the procedure used. Average daily intake of dark green leafy vegetables, light green leafy vegetables, fruits, and eggs was also calculated.

**Xanthophyll analysis**

Milk samples were mixed with water and tetrahydrafuran, and then saponified for 30 minutes at room temperature with 5% methanolic potassium hydroxide. After saponification, the target analytes were extracted using 50 mg butylated hydroxytoluene in a mixture of 200 mL dichloromethane, 400 mL petro ether, and 400 mL hexane. The extracts were dried and reconstituted in 1 mL ethanol. Plasma samples were extracted with chloroform:methanol (2:1) and hexane. The extracts were dried and reconstituted in 100 μL ethanol.

High-performance liquid chromatography (HPLC) analysis was conducted with an Agilent 1290 Infinity HPLC system (Agilent, Santa Clara, CA) equipped with PAD detector. Briefly, a 50-μL injection volume was separated with a YMC C30 column (3 μm, 150 × 4.6 mm, YMC, Wilmington, NC) at a column temperature of 23 °C. A gradient wash procedure using methanol and methyl-tert-butyl ether was used for 50 minutes at a flow rate of 1 mL/minute according to the method of Yeum et al. (22). Echinonone was used as an internal standard.

Xanthophyll concentrations are presented as micrograms per deciliter. To convert from micrograms per deciliter to nanomoles per liter, for lutein multiply by 17.58, and for zeaxanthin multiply by 17.58.

**Validation and linearity**

The method was validated for recovery (internal standard method), repeatability, method detection limit, method quantification limit, and linearity. The linear assay range was 10–250 μg/L for both lutein and zeaxanthin. Internal standard calibration curves were applied by using the concentration of calibration standards versus the peak area ratio of target analytes and the internal standard echinenone. The linearity coefficient value R was > 0.9990 for lutein and zeaxanthin. The residual error for both compounds was < 5%, except for the lowest concentration of lutein calibration standard, which had 7.02%.

Original and spiked plasma and milk samples were tested in triplicate for 3 days. The interanalyst and day-to-day variations relative standard deviation (RSD) were below 5%. Recovery of spiked lutein or zeaxanthin from milk samples was 87% and 105%, respectively. The method quantification
limit was determined by the lowest point of calibration curve and considered the preconcentration factor during sample preparation. The determined method quantification limits were 5 μg/L (100 μL sample) for plasma samples and 10 μg/L (2 mL sample) for milk samples.

**Statistical analyses**

A sample size of 51 had 95% power to detect a probability of establishing a relationship between lutein concentration in milk and infant plasma concentrations, in the form of a linear model at significance level of 0.05. Assuming a 10% attrition rate, 56 pairs of mothers and infants were targeted for enrollment. The software nQuery Advisor 5.0 from Statistical Solutions (Saugus, MA) was used in the estimation of sample size.

A stepwise multiple linear regression model was used to detect factors associated with infant plasma lutein level. Blood lutein (total, cis, and trans) levels in breast-fed infants were introduced into the linear regression analysis as a dependent variable. Independent variables tested were lutein (total, cis, and trans) content of the mothers’ milk; maternal weight, height, and age; infant weight, length, and head circumference; infant age at enrollment, infant birth weight of infant, gestational age, infant gender, total volume of breast milk expressed, time of breast milk collection, time gap between breast milk collection and the previous time the same breast was used for feeding, and time gap between mother’s last meal and time of breast milk collection. After applying stepwise selection methods on these independent variables, the independent variables used with infant plasma versus breast milk total lutein were total lutein content of mother’s breast milk, infant age at enrollment, and gestational age. The independent variables used with infant plasma versus breast milk trans-lutein were trans-lutein content of mother’s breast milk, infant age at enrollment, and gestational age.

A simple linear regression model was also used to describe the relationship between infant plasma lutein level and the corresponding level in milk. Milk sample 1 values were used in regression analyses, as sample 1 was collected near both plasma samples and dietary records. No differences in lutein or zeaxanthin concentrations were detected near both plasma samples and dietary records. No differences were used in regression analyses, as sample 1 was collected near both plasma samples and dietary records. No differences were used in regression analyses, as sample 1 was collected near both plasma samples and dietary records.

**Results**

**Subjects and maternal diet**

The baseline characteristics of the study population are listed in Table 1. Average daily intakes of light colored vegetables, dark green leafy vegetables, fruits, and eggs are presented in Table 2 in comparison to dietary intakes previously reported for the general and lactating Chinese populations (19,23). The average lutein + zeaxanthin intake (mean ± SEM) estimated by applying the USDA database (20) was 3.3 ± 0.41 mg/day with a minimum of 0.4 and a maximum of 19.7 mg/day.

| Characteristic                      | Value       |
|------------------------------------|-------------|
| Infant race, number Chinese        | 56 (100%)   |
| Maternal race, number Chinese      | 56 (100%)   |
| Infant gender, number male         | 29 (52%)    |
| Age at enrollment, mean ± SEM (range) | 28.4 ± 0.4 (19.0, 35.0) |
| Infant, weeks                      | 9.9 ± 0.4 (6.3, 15.7) |
| Height, cm, mean ± SEM (range)     | 60.2 ± 0.3 (55.1, 66.5) |
| Infant (body length)               | 160.9 ± 0.7 (150.0, 179.8) |
| Weight, mean ± SEM (range)         | 6121 ± 117 (4400, 9800) |
| Mother, kg                         | 58 ± 1 (44, 82) |

**Milk and plasma lutein and zeaxanthin**

Mean lutein concentrations for milk samples 1 and 2 were similar (Table 3), and trans-lutein accounted for most of the lutein in milk. Mean concentrations of zeaxanthin in milk were substantially lower than those of lutein in both sample 1 and 2. Zeaxanthin levels were also highly variable between individuals.

The concentrations of lutein were similar in maternal and infant plasma (Table 3). trans-Lutein accounted for most of the lutein in plasma, and cis-lutein concentrations were correspondingly low in each of the sample types. Mean plasma concentrations of zeaxanthin were lower than those of lutein, but maternal and infant plasma concentrations of zeaxanthin were comparable, revealing the same pattern as observed for lutein (Table 3). Mean milk concentrations of both lutein and zeaxanthin were lower than those of both maternal and infant plasma samples. Levels were highly variable between individuals, but were similar for maternal and infant samples. Infants with high plasma lutein concentrations also tended to have high zeaxanthin levels (data not shown).

**Correlations between infant plasma and milk or maternal plasma lutein and zeaxanthin**

Infant plasma lutein concentration positively correlated with milk lutein concentration (Table 4). Infant plasma trans-lutein and cis-lutein also positively correlated with the concentration of the same analyte in milk; however, the slope of the relationship was directionally higher for trans- than for cis-lutein. Infant plasma zeaxanthin concentration also positively correlated with zeaxanthin level in milk with a higher slope than that of lutein.

Positive correlations were also found between infant and maternal plasma for each of the analytes. The $r^2$ values were directionally higher, but the slopes lower compared relationships with milk. Significant and positive correlations were also found between the maternal plasma concentration and milk concentration for total lutein, trans- and cis-lutein, and zeaxanthin. Interestingly, the $R^2$ values were higher than those noted for infant plasma, but the slopes were lower.

A 10-μg/dL increase in milk trans-lutein concentration led to a 7.64-μg/dL increase in infant plasma trans-lutein when infant age at enrollment and gestational age were held constant ($p = 0.001$) (data not shown). Removing outliers
However, it is not known whether infant milk lutein concentration equaled the mean in the current cohort (17). Nevertheless, as supplementation with these xanthophylls is becoming more common in both lactating mothers and formula-fed infants, this is an emerging and important question, as supplementation with these xanthophylls is becoming more common in both lactating mothers and formula-fed infants.

The current data reveal that infant plasma lutein and zeaxanthin concentrations are positively correlated with milk concentration in infants receiving breast milk with higher concentrations of lutein and zeaxanthin. The highest milk concentration of lutein in the current cohort was substantially higher than that reported in conjunction with infant plasma previously (17). We believe that plasma levels of lutein and zeaxanthin are the best practical measure of status in infants as assessment of macular pigment is generally not feasible in infants. This observation reveals the impact of an intake of lutein and zeaxanthin that can be considered healthy since the mothers studied consumed amounts of eggs, fruits, and green vegetables generally consistent with healthy guidelines (18–20).

**Table 2. Maternal Dietary Intake by Food Group Compared to Previous Research.**

| Food group                          | Current studya | Chinese general populationb | Chinese lactating mothersc |
|-------------------------------------|----------------|-----------------------------|-----------------------------|
| All vegetables (g/d)                | 283.5 ± 16.7   | 276.2                       | 295.9                       |
| Dark green leafy vegetables         | 170.0 ± 12.2   | 90.8                        | 94.7                        |
| Light-colored vegetables            | 113.6 ± 10.2   | 185.4                       | 201.2                       |
| Fruits (g/d)                        | 283.8 ± 19.8   | 45.0                        | 47.8                        |
| Eggs (g/d)                          | 74.3 ± 5.2     | 23.7                        | 35.0                        |

aAverage ± SEM (3).

bReference 18.

cReference 22.

**Table 3. Lutein and Zeaxanthin Concentrations in Human Milk and in Maternal and Infant Plasma.**

| Sample 1a | Sample 2b | Maternal | Infant |
|-----------|-----------|----------|--------|
| Lutein (µg/dL) | 6.9 ± 0.56 (1.0–22.5) | 8.2 ± 0.65 (1.0–22.4) | 21.6 ± 1.13 (7.1–44.6) | 18.5 ± 1.22 (3.7–45.8) |
| trans-Lutein (µg/dL) | 6.5 ± 0.54 (0.9–21.9) | 7.7 ± 0.61 (0.9–21.2) | 17.9 ± 0.96 (5.8–39.0) | 16.1 ± 1.08 (3.3–41.3) |
| Zeaxanthin (µg/dL) | 1.9 ± 0.14 (1.0–4.6) | 2.0 ± 0.17 (1.0–5.9) | 3.1 ± 0.16 (0.9–6.2) | 3.0 ± 0.22 (0.5–7.9) |

**Table 4. Correlations Between Infant Plasma Lutein or Zeaxanthin Concentrations and Those in Milk and Maternal Plasma.**

|                      | Infant plasma vs. milk | Infant plasma vs. maternalmilk | Maternal plasma vs. milk |
|----------------------|------------------------|-------------------------------|--------------------------|
|                      | r²         | p          | Slope        | r²         | p          | Slope        | r²         | p          | Slope        |
| Lutein               | 0.15       | 0.004      | 0.810        | 0.42       | <0.001     | 0.697        | 0.26       | <0.001     | 0.260       |
| trans-Lutein         | 0.16       | 0.002      | 0.798        | 0.43       | <0.001     | 0.736        | 0.26       | <0.001     | 0.313       |
| cis-Lutein           | 0.10       | 0.016      | 0.505        | 0.35       | <0.001     | 0.220        | 0.19       | <0.001     | 0.183       |
| Zeaxanthin           | 0.21       | <0.001     | 0.935        | 0.44       | <0.001     | 0.315        | 0.26       | <0.001     | 0.174       |

Note. Milk sample 1 was used in these correlation analyses. Milk sample 1 and the plasma samples were collected at enrollment at 6–16 weeks of lactation.

Discussion

Previous reports have revealed that infant plasma lutein and zeaxanthin levels positively correlate with milk concentrations in populations with low milk xanthophyll levels (24,25), and in a small multinational subset whose highest milk lutein concentration equaled the mean in the current cohort (17). However, it is not known whether infant plasma concentrations of lutein and zeaxanthin continue to increase when milk contains higher levels of these xanthophylls from food sources. This is an emerging and important question, as supplementation with these xanthophylls is becoming more common in both lactating mothers and formula-fed infants.

The current data reveal that infant plasma lutein and zeaxanthin concentrations are positively correlated with milk concentration in infants receiving breast milk with higher lutein intake. Interestingly, the daily lutein + zeaxanthin for the current population was lower than that in the South Korean population (26), but milk lutein concentrations were higher. We postulate that high egg intake in our population might
explain this observation. Although egg intake was not reported for the South Korean population, the high intake of eggs in the current population might have accentuated bioavailability differences, as lutein and zeaxanthin are known to be highly bioavailable from eggs as compared to spinach (27).

The current lutein + zeaxanthin intakes were also higher than those previously reported for Western countries (13,14,16,24,25). While the current study population consumed 3.3 mg lutein + zeaxanthin per day, U.S. women 19–30 years of age consume less: 0.9 mg lutein and 0.1 mg zeaxanthin per day (28). Higher intake of leafy green eggs, vegetables, and fruit compared to the U.S. population likely explains this difference (23,28,29).

As mentioned in the preceding, previous reports on milk samples that contained high concentrations of lutein did not provide corresponding infant plasma data. In contrast, reports did report infant plasma values involved substantially lower milk and plasma concentrations from U.S. breast-fed infants (24,25). Here, we report a mean infant plasma lutein concentration of 18 μg/dL, compared to 6 and 7 μg/dL reported for U.S. breast-fed infants by Mackey et al. (25) and Bettler et al. (24), respectively. These findings reveal that breast-fed infant lutein status is increased by high-lutein milk due to a maternal diet rich in eggs, fruits, and vegetables. Surprisingly, we found that infant plasma concentrations of lutein and zeaxanthin were similar to maternal plasma concentrations; previous studies did not report maternal and infant lutein concentrations. Consistent with previous reports, both maternal and infant plasma concentrations were higher than milk concentrations (16,24,25,30).

Our results reveal that the rate of increase in infant plasma lutein concentration is higher for infants receiving milk below than above the 75th percentile for milk lutein concentration. This observation suggests that the ability of infants to absorb and transport lutein might be lower at milk lutein levels above the 75th percentile of this study population. This hypothesis is supported by a comparison of Bettler et al. (24) to the current study. A relatively small cohort of 13 U.S. breast-fed infants experienced a 37-μg/dL increase in infant plasma lutein per 10-μg/dL increase in milk lutein for a milk concentration range of 0.6 to 6.1 μg/dL. This rate of increase is higher than that observed in the current study (8 μg/dL per 10 μg/dL); however, the maximum milk lutein concentration was markedly lower than that in the current study. In the current study, infants receiving milk below the 75th percentile had a regression slope (21 μg/dL per 10 μg/dL) that was closer to that reported by Bettler et al. (24). Taken together, these observations are consistent with, but do not prove, a higher absorption/transport rate in infants consuming milk containing lower concentrations of lutein.

We enrolled lactating Chinese women who reported higher daily intakes of dark green leafy vegetables and fruits than the general Chinese population (23). The green leafy vegetable intake in our study sample was also higher than the average dark-green vegetable and lutein intake of U.S. females (28,29). It is important to note, however, that the current intakes met Chinese and U.S. government recommendations for a healthy diet (18–20). Consistent with this, maternal plasma lutein concentrations in the current study were high compared to those reported by others in other populations (1,16,30). Unfortunately, the other studies cited in lactating Chinese mothers did not report maternal plasma data.

One of the weaknesses of this study was that the dietary intake of lutein and zeaxanthin were not separated. This was because lutein and zeaxanthin values for Chinese foods are not available. This obviated differential analyses of lutein and zeaxanthin intake and required us to apply values for similar Western foods. Studying lactating mothers following dietary guidelines for vegetable and fruit intake was a strength toward understanding safe intakes of lutein for infants, but it was simultaneously a weakness as the general population of lactating mothers consumes lower amounts of eggs, vegetables, and fruits. An additional weakness is that we did not assess plasma or milk lipid or plasma lipoprotein cholesterol levels. HDL has been suggested as the primary transport mechanism for lutein and zeaxanthin (31).

Conclusions

Overall, our findings reveal that infant plasma lutein and zeaxanthin are positively correlated with concentrations in milk and plasma from women with relatively high intake from healthy vegetable and fruit intake. Further, infant plasma lutein and zeaxanthin concentrations were similar to maternal concentrations. In combination with traditional infant formula safety criteria, these findings may help determine target lutein and zeaxanthin supplementation levels for breast-feeding mothers and for formula-fed infants. These questions are increasing in importance as supplementation with the xanthophylls is becoming common and research is rapidly accelerating our understanding of the roles of lutein and zeaxanthin in brain and eye function.

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Disclosure statement

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