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Vitamin A supplementation during puerperium: systematic review

ABSTRACT

A systematic review on studies evaluating the effect of applying megadoses of vitamin A on the retinol concentrations in maternal milk and blood, as a short-term measure for preventing hypovitaminosis A, was conducted. Based on the strategy of the Brazilian Cochrane Center for randomized trials, 115 published papers were identified in PubMed. From these, through a set of inclusion/exclusion criteria, 14 articles published between 1993 and 2007 were selected. The effects of interventions with three posological regimens (200,000, 300,000 and 400,000 IU) of vitamin A were analyzed. Out of 11 experiments conducted on maternal milk, nine presented elevation of the retinol levels in comparison with the control group; out of nine that evaluated maternal blood, four showed elevation at varying times after applying megadoses of vitamin A. It was concluded that the results from administration of vitamin A at high doses were positive in 82% of the trials on maternal milk, but less notable in relation to maternal blood. No significant differences regarding the posological regimens applied were observed.

DESCRIPTORS: Vitamin A Deficiency, drug therapy. Dietary Supplements. Vitamin A. Maternal and Child Health. Review.

INTRODUCTION

The pregnancy-puerperium cycle and notably the lactation period represent a biological phase of peculiar nutritional vulnerability for women, particularly in populations with low socioeconomic conditions. This is because of the high physiological demands, behavioral and metabolic changes and frequent diseases associated with these periods. Estimates show that out of the total of 107.4 million women around the world who have children every year and live in regions at risk of vitamin A deficiency (VAD), 19.8 million (18%) present low retinol concentrations in their blood or maternal milk ($< 1.05 \mu\text{mol/l}$), and 7.2 million present concentrations that are considered deficient ($< 0.70 \mu\text{mol/l}$).³⁰

VAD leads to a disorder in how the cells of the retina function. The most known functional effect of this is transitory blindness, which has frequently been described in studies on this problem during pregnancy, especially during the third trimester of pregnancy.⁷ VAD also affects the anatomofunctional integrity of the gastrointestinal and respiratory mucosae, thereby contributing towards significantly increased morbidity-mortality due to infectious diseases.²⁷

Under these conditions, vitamin A or beta-carotene supplementation for women during the reproductive period may significantly reduce the signs and symptoms of comorbidities relating to nocturnal blindness, with a large impact on the maternal mortality statistics.^{6,8,15,29,31} In this respect, a community study by West Jr et al²⁹ (1999) among 44,646 women of reproductive age in Nepal

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showed that the risk of maternal mortality was reduced by 44%, which can be considered to be an indication of the protective effect of vitamin A supplementation during this period of the cycle of life.

Vitamin A is continually required by the fetus during pregnancy.²³ However, the fetal reserves of this micronutrient are usually low at birth. In this way, in order to maintain and accumulate normal organic levels until complementary foods supply sufficient additional quantities of vitamin A, newborns become dependent on their mothers' milk, especially the initial milk (colostrum), which is rich in vitamin A (mean of 7.0 $\mu\text{mol/l}$).³²

The mean retinol concentrations in the mature milk of women in developing countries are lower (around 1.0 $\mu\text{mol/l}$) than the levels seen among women in developed countries (mean of 2.3 $\mu\text{mol/l}$). In regions presenting poverty, the levels found in maternal milk are only enough to meet children's basic metabolic requirements, without allowing the formation of organic reserves of this vitamin.²³ Through this, infants become more susceptible to the problem.²¹

A variety of strategies have been put forward in developing countries for combating VAD during the lactation period. Among these is vitamin A supplementation with megadoses during the immediate postpartum period.³³ Theoretically, this seems to be the most effective short-term strategy. Thus, both the mother, through elevation of the levels of this micronutrient in her organism, and the child, through the maternal milk, would be benefited.²³ However, since the time of the original proposal from the World Health Organization (WHO), of 200,000 IU,³³ the posology and the beneficial effects from this strategy have still not been sufficiently evaluated.

Among the indicators for the response to maternal supplementation with megadoses of vitamin A, retinol concentrations in maternal blood and milk have been taken as the reference points.^{17,23} The main foundation for this comes from the study by Vahlquist & Nilsson²⁶ (1979).

The aim of the present study was to conduct a systematic review of studies about the effect of supplementation with megadoses of vitamin A on the retinol concentrations in maternal blood and milk.

METHODS

The Brazilian Cochrane Center's strategy for systematic reviews of randomized clinical trials was used.^a The search was conducted in the PubMed database, covering the period from 1980 to 2007, by using the following descriptors: "randomized controlled trial" [Publication

Type] OR "controlled clinical trial" [Publication Type] OR "randomized controlled trials" [MeSH Terms] OR "random allocation" [MeSH Terms] OR "double blind method" [MeSH Terms] OR "single blind method" [MeSH Terms] OR "clinical trial" [Publication Type] OR "clinical trials" [MeSH Terms] OR "(clinical* [Text Word] AND trial* [Text Word])" OR "single*" [Text Word] OR "double*" [Text Word] OR "treble*" [Text Word] OR "triple*" [Text Word] OR "placebos" [MeSH Terms] OR "placebo*" [Text Word] OR "random*" [Text Word] OR "research design" [MeSH Terms] OR "comparative study" [MeSH Terms] OR "evaluation studies" [MeSH Terms] OR "follow-up studies" [MeSH Terms] OR "prospective studies" [MeSH Terms] OR "control*" [Text Word] OR "prospectiv*" [Text Word] OR "volunteer*" [Text Word] AND "supplementation" AND "vitamin A" AND "mothers". This consultation of the database identified 115 published papers.

After reading the titles, the abstracts and, when indicated, the complete texts, articles were then selected using five inclusion criteria: 1- randomized controlled clinical trials; 2- comparison of supplementation with megadoses of vitamin A alone, in the form of retinol palmitate; 3- presence of different posological regimens (200,000 IU, 300,000 IU and 400,000 IU); 4- evaluation of the effect of supplementation on the retinol concentrations in maternal blood; and 5- evaluation of the possible effect of vitamin A supplementation on the retinol levels in maternal milk. Through these five basic criteria, the set of studies for this review was defined. The inclusion of additional requirements relating to methodological procedures would have resulted in a final list of articles numerically inadequate for the objectives of this study. There were no restrictions regarding publication year or language. Review articles and experimental studies on animals were excluded.

The 115 studies identified through the review strategy were carefully analyzed by two investigators, independently. Articles were selected when there was agreement between the two investigators and/or after arbitration by a third investigator, based on the inclusion criteria. Fourteen articles were selected in this manner.

RESULTS

Out of the 14 studies selected, seven^{3-5,10,16,19,28} evaluated a single dose of 200,000 IU, one²² evaluated the results from applying 300,000 IU, three^{9,11,24} compared applications of 200,000 IU and 400,000 IU, and another three^{1,14,34} used a megadose of 400,000 IU.

The time between delivery and vitamin A application ranged from 12 to 48 hours in six studies^{1,4,5,10,19,28} and from 12 hours up to seven to 42 days in six

^a Centro Cochrane do Brasil, Distance Learning Laboratory. Escola Paulista de Medicina. Universidade Federal de São Paulo. Systematic review and meta-analysis course [internet]. [cited 2006 Dec 28]. Available from: <http://www.virtual.epm.br/cursos/metanalise/>

others.^{3,9,11,16,22,24} Two studies^{14,34} administered the vitamin supplement 48 hours after delivery. In one study,¹⁰ the follow-up time between applying vitamin A and evaluating the response was six hours. In the other experiments reported, the experimental cases were evaluated after 45 days,^{14,34} three months,^{5,28} five to six months^{1,4,9,24} and nine months.^{3,11,16,19,22} Four of the studies were published in the 1990s and the others were published after the year 2000.

Nine^{1,3,4,5,10,16,19,22,28} of the 11 studies that analyzed the retinol levels in the maternal milk found that these levels had increased, in comparison with the baseline (starting point of the experiment) or in comparison with a control group. With regard to serum retinol responses, out of nine studies, four^{14,19,22,34} showed that elevation of vitamin A had a positive effect on the serum of the groups that were followed up.

There were variations in the procedures in relation to the times and techniques for milk collection and other differences in evaluating the baseline for vitamin A among the samples, as presented in the Table.

DISCUSSION

The fundamental question in this systematic review was whether the application of megadoses of vitamin A (200,000 IU, 300,000 IU or 400,000 IU) would be enough to assure adequate provision of this nutrient to cover the infant's basic needs during the critical period of breastfeeding (the first four to six months of life). Consequently, adequate provision of this nutrient was the primary desired outcome, while the mother's serum retinol levels were a collinear objective or co-requisite for ensuring that the first condition was met. Furthermore, the maternal-fetal biological system could resort to compensatory mechanisms favoring the fetus or infant, such as nutrient depletion in the maternal organism itself.³²

Starting from these considerations, out of the 11 studies that analyzed the retinol levels in the maternal milk, nine^{1,3,4,5,10,16,19,22,28} presented a range of degrees of increase in these levels after application of megadoses of vitamin A, while this did not occur in two studies.^{9,11} However, in one of these two cases,¹¹ the baseline retinol levels in the milk were already very high (mean= 4.34; sd= 3.01 $\mu\text{mol/l}$) one month after delivery. Thus, greater elevation might not be justifiable as an objective that is necessarily desirable. In the study by Darboe et al⁹ (2007), there is no information regarding the baseline retinol levels in the maternal milk. Thus, the outcome was limited to considering a statistical comparison between two dosages, without clarifying the final impact in relation to safe levels of retinol in the milk six months later. This was therefore a result for which the analysis could not be properly established.

Among the experiments that showed positive responses in relation to the interests of the present review, it was observed that in the study by Dimenstein et al¹⁰ (2007), the follow-up was for only six hours after administering vitamin A. This length of follow-up therefore does not fit within the perspective of effectiveness regarding the protective effect. According to the study by Azaïs-Braesco & Pascal² (2000), the process of transporting vitamin A to the liver takes around five hours. Therefore, the experiment by Dimenstein et al¹⁰ (2007) merely confirms this observation. Hence, the much earlier observation by Vahlquist & Nilsson²⁶ (1979) becomes pertinent: after consumption of foods rich in vitamin A, this nutrient may go directly from the diet to the maternal milk, without needing regulation by the liver. Thus, the effect recorded in the colostrum of the women who received supplementation might reflect an elevation of transitory nature.

On the other hand, comparative analysis on the posology of the megadoses (200,000 IU, 300,000 IU and 400,000 IU) did not enable clarification of the possible differences in the results, with regard to the expected dose-response effect of increasing loads of vitamin A. This comparison would be relevant in relation to the most recent proposal from WHO,¹⁸ which recommends application of higher doses of vitamin A (400,000 IU) as a safer strategy for preventing VAD during the breastfeeding period.²³

Among the nine studies that investigated the vitamin A status in the maternal blood,^{1,9,14,16,19,22,24,28,34} only four studies found elevated serum retinol levels in relation to baseline values.^{14,19,22,34} These results are therefore inconclusive in terms of seeking an effective and safe intervention strategy. Moreover, even if serum vitamin A levels were an important indicator, these blood levels would be of secondary importance in relation to the behavior of the retinol levels in maternal milk.

With regard to the limits of the present review, among the small set of papers selected through the systematic review screening, certain conditioning factors affecting the internal and external validity of its results persist. Thus, among the studies that used the dose of 200,000 IU that was proposed by WHO in 1997,³³ and which prospectively followed up the mothers for one month or more,^{3,4,5,16,19,28} the elevation of the retinol levels in the maternal milk lasted for periods ranging from 45 days⁵ to the sixth month after delivery.¹⁹ Furthermore, three of these experiments did not adequately clarify the technique used for maternal milk collection. The study by Bhaskaram et al⁵ (1998) did not take the time of collection into consideration and did not mention the method used or the interval between breastfeeds, thereby not distinguishing between full-breast collection and on-demand collection. Other studies did not state what method was used for milk collection,¹⁹ or which breast was used.^{3,19} With regard to the other

studies that used this dose of 200,000 IU^{4,16,28} and which standardized the milk collection technique, it can be inferred that the dose had a positive effect that lasted for around three months.

On the other hand, two points were not given proper consideration: the matter of whether exclusive breastfeeding was practiced, given the universal recommendation that this is the best choice for feeding children

Table. Supplementation with megadoses of vitamin A during the puerperium: effect on the retinol concentrations in maternal blood and milk reported in papers published between 1993 and 2007.

Vitamin A dose, author, year and country of the study	Study participants, treatment groups, time of administration and follow-up	Vitamin A status at baseline	Collection technique for maternal milk	Effect
200,000 IU				
Dimenstein et al, ¹⁰ 2007, Brazil	33 received vitamin A Application: up to 12 hours after delivery Follow-up: 6 hours	Milk: 3.88 ± 2.88 µmol/l	Time: morning Method: manual expression Breast: right or left Interval: ≤ 1 hour after last breastfeeding	Elevation of retinol (1.88 µmol/l) after 6 hours
Basu et al, ⁴ 2003, India	150 received vitamin A and 150 did not Application: 24 hours after delivery Follow-up: 6 months	Milk: Test 3.85 ± 0.2 µmol/l Control 3.92 ± 0.23 µmol/l	Time: 9:00 a.m. and 11:00 a.m. Method: manual pump Breast: both Interval: Mothers instructed not to breastfeed at the start of the morning	Elevation of retinol (0.47 µmol/l) up to 4 th month
Bahl et al, ³ 2002, Ghana, India, Peru	1491 received vitamin A and 1499 placebo Application: 18 - 42 days after delivery Follow-up: 9 months	Milk: Test 1.96 ± 1.03 µmol/l Control 1.94 ± 0.99 µmol/l	Time: 9:00 a.m. and 12:00 noon Method: manual pump Breast: one or both Interval: independent of previous breastfeeding	Elevation of retinol (0.27 µmol/l) up to 2 nd month
Vinutha et al, ²⁸ 2000, India	53 received vitamin A and 56 did not Application: up to 48 hours after delivery Follow-up: 3 months	Milk: - Blood: ^a 27% (0.35 – 0.70 µmol/l) 61% (0.73 – 1.4 µmol/l) 3% (>1.4 µmol/l)	Time: 8:30 a.m. and 12:00 noon Method: manual pump Breast: both Interval: Mothers instructed not to breastfeed at the start of the morning	Elevation of retinol in milk (0.17 µmol/l) three months after administration No effect on serum retinol
Rice et al, ¹⁷ 1999, Bangladesh	74 received vitamin A and 73 placebo Application: up to 15 days after delivery Follow-up: 9 months	Milk: Test 1.71 ± 1.34 µmol/l Control 1.51 ± 1.08 µmol/l Blood: Test 1.79 ± 0.60 µmol/L Control 1.68 ± 0.53 µmol/l MRDR: ^b Test 0.032 ± 0.006 Control 0.032 ± 0.007	Time: 8:00 a.m. and 7:00 p.m. Method: manual expression Breast: right or left Interval: independent of previous breastfeeding Time: 10:30 a.m. and 9:15 p.m. Method: manual pump Breast: entire content of left breast Interval: ≤ 2 hours after last breastfeed	Elevation of retinol in milk (0.37 µmol/l) up to 3 rd month No effect on serum retinol Lower mean MRDR (0.038 vs. 0.054) in the supplemented group up to 3 rd month
Bhaskaram & Blakrishna, ⁵ 1998, India	100 received vitamin A and 100 placebo Application: up to 24 hours after delivery Follow-up: 3 months	Milk: -	Time: 8:00 a.m. Method: not stated Breast: entire content of left breast Interval: not stated	Elevation of retinol for 45 days
Roy et al, ¹⁹ 1997, Bangladesh	25 received vitamin A and 25 did not Application: up to 24 hours after delivery Follow-up: 9 months	Milk: Test 3.20 ± 0.68 µmol/l Control 3.08 ± 0.84 µmol/l Blood: Test 1.38 ± 0.17 µmol/l Control 1.18 + 0.23 µmol/l	Time: 9:00 a.m. and 11:00 a.m. Method: not stated Breast: not stated Interval: in the middle of breastfeeding	Elevation of retinol in milk (0.33 µmol/l) up to 6 th month Elevation of serum retinol (0.26 µmol/l) up to 6 th month

To be continued

Table continuation

Vitamin A dose, author, year and country of the study	Study participants, treatment groups, time of administration and follow-up	Vitamin A status at baseline	Collection technique for maternal milk	Effect
300,000 IU				
Stoltzfus et al, ²² 1993, Indonesia	76 received vitamin A and 77 placebo Application: from 7 to 21 days after delivery Follow-up: 8 months (milk) and 6 months (blood)	Milk: Test $2.30 \pm 1.42 \mu\text{mol/l}$ Control $2.69 \pm 1.53 \mu\text{mol/l}$ Blood: Test $1.17 \pm 0.45 \mu\text{mol/l}$ Control $1.31 \pm 0.51 \mu\text{mol/l}$ RDR ^c >20%: Test 9.2% Control 4.4%	Time: 9:00 a.m. and 11:00h Method: manual pump Breast: entire content of the right or left breast Interval: >1 hour after last breastfeeding	Elevation of retinol in milk ($0.48 \mu\text{mol/l}$) up to 8 th month Elevation of serum retinol ($0.15 \mu\text{mol/l}$) up to 6 th month No effect from the RDR test
400,000 IU vs. 200,000 IU				
Idindili et al, 2007, ¹¹ Tanzania	390 received 400,000 IU split into two doses and 390 received 200,000 IU Application: up to 1 month after delivery Follow-up: 9 months	Milk: Test $4.34 \pm 3.01 \mu\text{mol/l}$ Control $4.60 \pm 3.52 \mu\text{mol/l}$	Technique not stated	No additive effect on retinol at the dose of 400,000 IU
Darboe et al, ⁹ 2007, Kenya	110 received 400,000 IU split into two doses and 110 received 200,000 IU Application: within the first week after delivery Follow-up: 6 months (milk) and 2 months (blood)	Milk: - Blood: -	Time: not stated Method: manual expression Breast: both Interval: not stated	No additive effect on retinol in milk and blood at the dose of 400,000 IU
Tchum et al, ²⁴ 2006, Ghana	85 received 400,000 IU split into two doses and 82 received 200,000 IU Application: up to 6 weeks after delivery Follow-up: 5 months	Blood: ^a $1.44 \pm 0.5 \mu\text{mol/l}$ MRDR: ^b 0.048 ± 0.037	-	No effect on serum retinol or on hepatic reserves
400,000 IU vs. placebo				
Ayah et al, ¹ 2007, Kenya	282 received vitamin A and 282 placebo Application: 24 hours after delivery Follow-up: 6 months	Milk: - Blood: ^a $0.81 \pm 0.21 \mu\text{mol/l}$	Time: not stated Method: manual expression Breast: not stated Interval: ≤ 1 hour after last breastfeed	Elevation of retinol in milk ($0.06 \mu\text{mol/l}$) up to 6 th month No effect on serum retinol
Zvandsara et al, ³⁴ 2006, Zimbabwe	7058 received vitamin A and 7052 placebo Application: up to 96 hours after delivery Follow-up: 45 days	Blood: HIV (-): $1.19 \mu\text{mol/l}$ HIV (+): $0.98 \mu\text{mol/l}$	-	Elevation of retinol ($0.44 \mu\text{mol/l}$) for 45 days in group of HIV (-) women
Malaba et al, ¹⁴ 2005, Zimbabwe	4619 received vitamin A and 4589 placebo Application: up to 96 hours after delivery Follow-up: 45 days	Blood: Test: $1.23 + 0.40 \mu\text{mol/l}$ Control: $1.14 + 0.36 \mu\text{mol/l}$	-	Elevation of retinol ($0.16 \mu\text{mol/l}$) for 45 days

^a No separation between experimental and control groups.

^b MRDR: Modified relative dose response

^c RDR: Relative dose response

during their first six months of life; and, secondarily, the baseline situation at the start of the experiment. In relation to exclusive breastfeeding, continuing this for six months implies a greater cumulative demand for

vitamin A than, for example, in the cases of mothers who give only one, two or three breastfeeds per day. Only two papers^{4,28} give consideration to this important point.

Regarding the baseline situation, out of the 11 studies that evaluated the maternal milk, four did not consider the initial situation of retinol in the milk.^{1,5,9,28} Among the nine studies that evaluated the serum retinol levels, one did not consider the initial situation.⁹ These observations give rise to three implications: a) prospective follow-up among cases that present normal or high initial values does not keep to the same pattern as among cases that already present low values at the starting point; b) the final question of the outcome is not limited to the situation of whether the vitamin A levels simply went up or down, but a question of whether, in cases of decreases or possible small increases, the retinol values might be at unsafe levels, i.e. low and deficient; c) finally, an initial biochemical evaluation would make it possible to distinguish the evolution over time of the retinol levels separately for maternal blood and milk, considering that the colostrum or the milk of the first few days naturally presents higher levels of vitamin A than the mature milk does. Seven studies provided information in this respect.^{3,4,10,11,16,19,22}

The variability of the fat content of the milk needs to be considered, given that vitamin A is carried in the lipid fraction of this food, which is subject to sampling errors because of non-standardized collection procedures. The most important source of these errors relates to the content of the breast from which the sample is removed. The fuller the breast is, the lower the fat content is.²³ Another source of variation in the fat content of the milk that might influence the vitamin A levels relates to the time of day at which the sample is taken. Thus, Ruel et al²⁰ (1997) found greater agreement for the lipid concentrations in maternal milk collected between 6:00 a.m. and 8:00 a.m. from fasting mothers and greater variation in milk collected between 12:00 noon and 2:00 p.m. and between 4:00 p.m. and 6:00 p.m. This may explain the differences between results from studies without proper homogenization of the procedures.

Among some of the studies in which the maternal serum retinol was evaluated^{16,19,28} only one¹⁹ found a statistically significant difference up to the sixth month after receiving the supplementation. Although the study by Rice et al¹⁶ (1999) did not find this effect in the blood, elevated hepatic deposition was observed among the women who received supplementation, by means of the test Modified relative dose response (MRDR) test, after three months. Vinutha et al²⁸ (2000) observed at the baseline that 27% of the women presented retinol levels that were considered low (0.35–0.70 $\mu\text{mol/l}$). In the study by Rice et al¹⁶ (1999), 54% of the women in the placebo group presented compromised hepatic reserves three months after delivery, which leads to the belief that the experimental group would have evolved to this situation if it had not received supplementation. With inadequate vitamin A status at the baseline and taking into account the homeostatic role of the reserves

in special situations like breastfeeding, it is possible that the serum levels would respond less to the use of megadoses than the levels in milk would.²⁵

In the study by Roy et al¹⁹ (1997), serum retinol levels were assayed at a baseline of up to 24 hours after delivery; while for Vinutha et al²⁸ (2000), it was up to 48 hours and, for Rice et al¹⁶ (1999), it was up to 15 days after delivery. It may be that the inflammatory process of delivery and the first few hours of the puerperium could have interfered with the serum concentrations of retinol.^{12,13} Furthermore, if the baseline level in the study by Roy et al¹⁹ (1997) was 1.38 (sd= 0.17 $\mu\text{mol/l}$), these women would probably have had relatively adequate hepatic reserves, which is not thought to have been the case in the other studies. This would explain the elevation of the retinol levels up to the sixth month after receiving the supplementation, both in the maternal milk and in the maternal blood.

With regard specifically to supplementation with 300,000 IU, only one study was identified and selected.²² In this, a persistent effect in the milk until the eighth month and in the serum levels until the sixth month was reported. However, the Relative Dose Response (RDR) test did not detect any difference in the group of women who received supplementation. The studies that compared the doses of 400,000 IU and 200,000 IU did not show any differential effect regarding the vitamin A levels in the maternal milk,^{9,11} serum or liver.²⁴ The methods used may not have been appropriate for such purposes. Regarding the absence of effects in hepatic deposits and blood, Tchum et al²⁴ (2006) reported that the percentage of women with MRDR > 0.060 diminished in all the groups and that, in the fifth month, there were no women in either group with MRDR > 0.060. These authors suggested that the dose of 400,000 IU probably increased the liver reserves more than the dose of 200,000 IU did, but that this could not be shown by means of the MRDR test, which only indicated that the vitamin A reserves were normal at all the post-treatment evaluations for each group.

Out of the studies that used the dose of 400,000 IU and evaluated the effect of supplementation on the serum retinol,^{1,14,34} and maternal milk,¹ Ayah et al¹ (2007) found differences between the groups regarding the vitamin A content of the maternal milk up to end of the follow-up in the sixth month. However, this was not seen with the serum retinol, probably because of deficiency of this micronutrient among the women at the baseline. Malaba et al¹⁴ (2005) found an effect that was maintained for 45 days and Zvandsara et al³⁴ (2006) reported a positive effect among HIV-seronegative women who received supplementation, in comparison with women with HIV. This is consistent with the known association between infectious/inflammatory processes and diminished vitamin A in the blood.²⁵

In summary, the studies using the dose recommended by WHO (200,000 IU) presented controversy regarding the duration of vitamin A coverage in the maternal milk, possibly due to the diversity of milk collection procedures. In relation to blood, different effects probably occurred in populations whose hepatic reserves were not depleted. Finally, it can be concluded that several points relating to the effectiveness of supplementation with megadoses of vitamin A among breastfeeding mothers have not been properly clarified. Thus, it is

recommended that new studies should go into greater depth with better controls, taking into account the main limitations relating to the variations in procedures that have been discussed here, in order to make inferences regarding the potential results and consequently provide the basis for recommendations for strategic actions. Such questions are particularly important in Brazil, where the application of megadoses of vitamin A after delivery has been disseminated as a potentially promising strategy for preventing VAD in the mother/child pair.

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