Effect on Infant Illness of Maternal Supplementation With 400 000 IU Vs 200 000 IU of Vitamin A

WHAT'S KNOWN ON THIS SUBJECT: Postpartum vitamin A supplementation is a strategy to combat vitamin A deficiency and seems to reduce maternal/infant morbidity and mortality. However, controversies exist regarding which dose has a greater efficacy, 200 000 IU (WHO protocol) or 400 000 IU (IVACG protocol).

WHAT THIS STUDY ADDS: In this study, postpartum maternal supplementation with 400 000 IU of vitamin A did not provide any additional beneficial effect in reducing infant morbidity compared with the standard dose of 200 000 IU.

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KEY WORDS

illness, infants, northeast Brazil, randomized clinical trial, vitamin A supplementation

ABBREVIATIONS

CI—confidence interval

IMIP—Professor Fernando Figueira Integral Medicine Institute

IVACG—International Vitamin A Consultative Group

RR—rate ratio

VAD—vitamin A deficiency

WHO—World Health Organization

abstract

BACKGROUND AND OBJECTIVE: Postpartum vitamin A supplementation is a strategy used to combat vitamin A deficiency and seems to reduce maternal/infant morbidity and mortality. However, studies have shown that a dose of 200 000 IU (World Health Organization [WHO] protocol) does not seem to provide adequate retinol levels in maternal breast milk, infant serum, and infant tissue. The objective of this study was to compare the effect of postpartum maternal supplementation with 400 000 IU (International Vitamin A Consultative Group protocol) compared with 200 000 IU of vitamin A on infant morbidity.

METHODS: This was a randomized controlled, triple-blinded clinical trial conducted at 2 public maternity hospitals in Recife in northeastern Brazil. There were 276 mother–child pairs that were allocated to 2 treatment groups: 400 000 IU or 200 000 IU of vitamin A. They were followed up for >6 months to evaluate infant morbidity.

RESULTS: Fever (rate ratio [RR]: 0.92 [95% confidence interval (CI): 0.75–1.14]), diarrhea (RR: 0.96 [95% CI: 0.72–1.28]), otitis (RR: 0.94 [95% CI: 0.48–1.85]), acute respiratory infection (RR: 1.03 [95% CI: 0.88–1.21]), the need for intravenous rehydration (RR: 2.08 [95% CI: 0.64–2.07]), and the use of antibiotic treatment (RR: 0.80 [95% CI: 0.43–1.47]) did not differ significantly between the 2 treatment groups.

CONCLUSIONS: Our findings suggest that postpartum maternal supplementation with 400 000 IU of vitamin A does not provide any additional benefits in the reduction of illness in children aged <6 months; therefore, we do not support the proposal to increase the standard vitamin A dose in the existing WHO protocol. *Pediatrics* 2012;129:e960–e966

All the authors contributed in general to the elaboration of this article; Dr Fernandes was involved in data collection, analyses, and interpretation; Ms Figueiroa participated in the statistical analysis and interpretation of the results; and Drs Grande de Arruda and Diniz were responsible for the conceptual study design, content revision, and approval of the final version of the article.

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Controlled clinical and randomized trials have described a relationship between vitamin A deficiency and increased mortality in young children from developing countries.^{1–3} However, the effects on morbidity are still controversial.^{4–6}

Various strategies have been designed to reduce vitamin A deficiency (VAD), including massive supplementation with high doses of vitamin A (200 000 IU) in the immediate postpartum period, a standard regimen recommended by the World Health Organization (WHO) in areas where VAD is a public health problem.⁷ However, a multicenter study revealed that this dose does not seem to assure adequate levels of or significant increases in retinol concentrations in maternal milk, serum, or the newborn's hepatic reserves.⁸ The International Vitamin A Consultative Group (IVACG) recommends that the postpartum dose be raised to 400 000 IU (divided into 2 doses), which is within the safe infertility interval,⁹ under the assumption that there would be benefits for both the mother (a reduced risk of clinical VAD and maternal mortality)¹⁰ and the child (consolidation of retinol reserves through vitamin A support during breastfeeding).¹¹ There are few studies that have evaluated the effectiveness of this new dosage scheme in reducing infant morbidity, and the results that have been reported are conflicting.^{12,13} Therefore, the objective of this study was to compare the effect on infant morbidity in the first 6 months of life of postpartum maternal supplementation with 400 000 IU (IVACG protocol) vs 200 000 IU (WHO protocol) of vitamin A in a maternal feeding regimen.

METHODS

Study Design

This randomized controlled, triple-blinded, hospital-based clinical trial was conducted at the maternity unit of

the Professor Fernando Figueira Integral Medicine Institute (IMIP) and the Bandeira Filho Municipal Maternity Hospital, which treat patrons of the Universal Health System and are located in Recife in northeastern Brazil. Children of both genders were followed up from birth to 6 months of age from August 2007 to June 2009.

The eligibility criteria used to select the sample population were children of women with low-obstetric risk who lived in Recife or in the metropolitan region. The exclusion criteria included children of women with mental disorders, children with severe perinatal hypoxia, and children with severe malformations or other illnesses that could make the anthropometric evaluation or breastfeeding impracticable.

Sample Population

By using a 1994 diarrhea incidence rate in the state of Pernambuco on the order of 22.5 episodes per 100 children per month,¹⁴ which was corrected for 2007 at 18 episodes per 100 children per month (Pernambuco State Health Secretary, unpublished data), the sample group sizing was calculated from an estimated incidence rate reduction of 15% for the group supplemented with 200 000 IU of vitamin A (μ_0) and 25% for the group supplemented with 400 000 IU (μ_1). A significance level of 5% (α) and a power of 90% (ν) were adopted, and the sample group size was calculated by using the following formula¹⁵: $n = [(u + \nu)^2 (\mu_1 + \mu_0)] / (\mu_1 - \mu_0)^2$. The minimum sample size for each treatment group was 94 mother–child pairs. To correct for inevitable cohort monitoring losses, 88 mother–child pairs were added.

Randomization and Dosage

All mothers received an oral, 200 000-IU vitamin A capsule in the childbirth room, following the Vitamin A Supplementation Program protocol of the Brazilian Health

Ministry (Farmanguinhos-Fiocruz, Rio de Janeiro, RJ, Brazil). The IMIP pharmacist, who was not a member of the research team, packed vitamin A and placebo capsules in separate containers and labeled the bottles in a coded form, keeping the codes in a sealed envelope throughout the study.

At 8 to 10 days after childbirth, 276 mother–child pairs were assigned, through a simple randomization process by using a random number table, into 2 treatment groups. One supplementation group received a capsule of 200 000 IU and the other received a placebo.

The vitamin A and placebo capsules were produced by Relthy Laboratories (Indaiatuba, SP, Brazil). The placebo capsules had the same consistency (soft gelatinous), vehicle, coloration (cloudy for photoprotection), and flavor as the vitamin A capsules. The vitamin A capsules were composed of retinyl palmitate with 40 mg of vitamin E added, and the placebo contained soybean oil with 40 mg of vitamin E added. The research members were only informed of the allocation of the supplementation groups after the completion of data analysis.

Data Collection and Procedures

After maternal supplementation with the second capsule (200 000 IU or placebo), the mothers were contacted by telephone to evaluate possible adverse effects related to high-dose vitamin A toxicity. No references that could be related to these adverse effects (fever, nausea, and vomiting) were mentioned to the mothers to prevent the suggestion of the studied clinical manifestations. When there was suspicion of some of these clinical signs, a research assistant was dispatched to the residence to confirm or dismiss the clinical suspicion and to evaluate the child for a bulging fontanelle.

The mother–child pairs were called monthly for follow-up over 6 months. During each call, the mothers were

extensively encouraged to breastfeed. However, those who did not breastfeed their infants were not excluded from the study and received the normal follow-up for illness in their infants (ie, follow-up was on an intention-to-treat basis).

The primary end points were clinical findings and the duration and severity of infections. Clinical signs of xerophthalmia were also measured as a secondary end point.

The children were accompanied at each clinical evaluation in the IMIP child care unit (at 8–10 days and at 1, 2, 3, 4, 5, and 6 months' postpartum). Home visits were completed 15 days after the clinical consultations to document the occurrence of morbidities.

The mothers were instructed to visit the IMIP Childcare Service for clinical revaluation when the child presented with complications in the intervals between consultations or home visits, and the nature and duration of the morbidity episodes were recorded in specific questionnaires.

The morbidity data were collected through interviews with the mother or the child's guardian by using a structured questionnaire that assessed specific information about the clinical manifestations presented by the child, such as fever, diarrhea, otitis, and signs and symptoms of acute respiratory infection. Severe clinical complications were inferred from hospitalization time, the use of venous rehydration, and the need for antibiotic therapy. All the children received an ocular surface examination by the research team nurse for any signs of xerophthalmia during the clinical consultation, and the child was examined by an ophthalmologist to confirm any suspicions (Table 1). The data collected by the research assistants were verified by supervisors at one-third of all the home visits.

Anthropometric measurements (weight, length, and cephalic perimeter) of the

TABLE 1 Definition of Illness in Infants

Events	Definition
Episode of diarrhea	≥1 d in which there were ≥3 stools of watery or loose consistency or any loose stool with blood
Fever	A rise of axillary body temperature >37.5°C for a period of ≥48 h was defined as fever
ARI	≥1 d of cough or nasal discharge or the combination of cough and difficulty breathing, fever, sore throat or in-drawing of breath into the lungs
Otitis	Characterized by the presence of earache (or persistent crying and tugging at the ears) and examination with the otoscope revealing a hyperemic, opaque bulging tympanic membrane or purulent discharge
VAD	VAD was inferred from the presence of Bitot's spot, corneal xerosis, or corneal ulcer

ARI, acute respiratory infection.

children at birth were obtained from the hospital or clinic records. Birth weight was used as an indicator in the nutritional evaluation.¹⁶

Umbilical cord blood samples from the newborns and brachial venipuncture of their mothers were obtained; the serum retinol concentrations were analyzed by using high-performance liquid chromatography,¹⁷ and the hemoglobin was analyzed by using an electronic cell counter (Sysmex SF-3000 Automated Hematology Analyzer, GMI, Inc, Ramsey, MN). The dietary consumption of vitamin A was evaluated by using a semiquantitative feeding frequency calendar. Socioeconomic and demographic variables were collected, including per capita family income, the level of maternal schooling, maternal age, and basic sanitation.¹⁸

Data Analysis

The database was built by using the Epi Info program version 6.04d (WHO/Centers for Disease Control and Prevention, Atlanta, GA), and SPSS program for Windows, version 13.1 (SPSS Inc, Chicago, IL), was used for the statistical analysis. The socioeconomic, demographic, biochemical, and anthropometric averages were compared with baseline and between the 2 treatment groups by using the Student's *t* test for unpaired data, and the Pearson χ^2 test was used for categorical variables.

For each clinical manifestation, the incidence rate calculation and comparison

between the 2 treatment groups was completed by using the EPItools library from the R.2.11.1 software (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). The confidence intervals (CIs) and *P* values were obtained through the mid-*P* value exact method. Mood's median test was used to compare diarrhea, fever, and hospitalization between the 2 treatment groups.

Ethical Aspects

The research protocol was approved by the IMIP ethics committee, under number 720/2006, in accordance with the norms for human research. The children were selected in the related maternity units after their mothers agreed to participate in the research and signed the informed consent form. The children who presented with anemia or any other morbidity during the study were directed to the study medical assistant for clinical evaluation, and their mothers were advised on the use of ferrous sulfate or specific medications for the clinical manifestations in question. Formal rules for the interruption of the clinical trial were not established.

RESULTS

Of the 276 originally enrolled mother-child pairs, 224 completed the entire study protocol. The losses occurred due to the moving away of participants from the city or to the lack of parental

authorization for the collection of blood from the child (Fig 1).

No adverse effects indicating a vitamin A toxicity reaction were reported. In addition, no child presented with signs suggestive of xerophthalmia. The characteristics of the mother–child dyads at baseline are presented in Table 2. No significant differences between the 2 treatment groups were observed in the socioeconomic, biological, biochemical, or anthropometric characteristics of the mothers and newborns.

About 30% of the mothers (from both treatment groups) had <8 years of schooling, ~30% had less than one-quarter of the per capita minimum wage, and ~20% were <20 years of age. Fifty-one percent of the children

were female, and 24.8% presented with insufficient weight at birth (<3000 g).

Fever (rate ratio [RR]: 0.92 [95% CI: 0.75–1.14]), diarrhea (RR: 0.96 [95% CI: 0.72–1.28]), otitis (0.94 [95% CI: 0.48–1.85]), and acute respiratory infection (RR: 1.03 [95% CI: 0.88–1.21]) did not differ significantly between the treatment groups. The utilization of venous rehydration (RR: 2.08 [95% CI: 0.64–2.07]) and the need to use antibiotic therapy (RR: 0.80 [95% CI: 0.43–1.47]) were also similar in the 2 treatment groups (Table 3). Similar results were also observed for diarrhea, fever, and duration of hospitalization markers ($P > .05$) (Table 4). The analysis of illness adjusted for breastfeeding (Table 5) revealed that the duration of

breastfeeding had no benefit regarding a reduction in illness.

DISCUSSION

The absence of additional benefits from the double vitamin A dose (400 000 IU) in reducing the incidence, duration, and severity of the morbidities observed in our study is supported by most of the data found in the literature.^{12,13}

However, a study completed in Tanzania,¹² in which the mothers received 400 000 IU of vitamin A and the children were supplemented at 3 different times in the first 6 months of life, revealed a reduction in the number of fever episodes in the first month of life in the group of children who were supplemented with multiple vitamin A doses (400 000 IU). However, this reduction was not observed in the subsequent months. It is important to note that although the mothers had already been supplemented in the Tanzanian study, the children also received vitamin A according to their allocation to 1 of the treatment groups, which may have influenced the possible additional beneficial effects provided by the greater vitamin A dose. An investigation with a similar method was conducted by Darboe et al¹³ in Gambia. In this study, the mothers were supplemented at childbirth with 200 000 IU of vitamin A and at 1 week after childbirth with 200 000 IU of vitamin A or a placebo. The children were supplemented at the second, third, and fourth months of life with 50 000 IU of vitamin A or a placebo and at 9 and 12 months with 100 000 IU and 200 000 IU of vitamin A, respectively. This study also did not indicate any additional positive impact on child morbidity from the 400 000 IU supplementation compared with the group who received 200 000 IU. Furthermore, the immunologic markers analyzed in this study did not present consistent evidence of any differential effect in the 2 treatment regimens. The

FIGURE 1

Consolidated Standards of Reporting Trials flowchart. RN, registered nurse.

TABLE 2 Baseline Characteristics of Mothers and Infants in Recife, Brazil, 2007–2009

Characteristic	400 000 IU Vitamin A			200 000 IU Vitamin A			<i>P</i> ^a
	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	
Newborns							
Male, <i>n</i> (%)	134	65	48.5	142	5568	47.9	.69 ^b
Weight at birth, g	134	3344	405	142	3283	373	.24
Length, cm	134	48.9	2.0	142	48.9	1.8	.86
Head circumference, cm	133	34.5	1.7	141	34.6	2.1	.70
Hemoglobin, g/dL	125	14.0	1.8	133	13.5	2.5	.44
Serum retinol, μmol/L	26	1.09	0.5	27	1.11	0.5	.93
Exclusive breastfeeding, d (median, IQ)	127	77	14–126	131	46	10–119	.14 ^c
Breastfeeding, d (median, IQ)	114	69	11–106	119	44	9–106	.16 ^c
Mothers							
Age, y	134	24.3	5.6	142	24.9	6.8	.48
Schooling, y	134	8.8	2.9	142	8.8	2.5	.86
Per capita income, \$ ^d	130	89.4	63.3	132	83.6	47.7	.38
Inadequate sanitation, ^e <i>n</i> (%)	127	28	56.0	123	22	44.0	.42 ^b
Vitamin A consumption, ^f μg (median, IQ)	69	1090	818–1648	72	1165	841–1749	.76 ^c
Serum retinol, μmol/L	106	1.6	0.7	106	1.7	0.8	.55
Hemoglobin, g/dL	121	11.6	1.7	129	11.2	1.5	.08

IQ, interquartile interval.

^a Student's *t* test for unpaired data.^b χ^2 test.^c Mann-Whitney *U* test.^d US dollar.^e Residence that did not present 1 or more of the following characteristics: domestic household water supply system, regular garbage collection, and sewage connected to the network.^f Vitamin A food consumption in micrograms of retinol.**TABLE 3** Illness Rates of Infants in Recife, Brazil, 2007–2009

Illness	400 000 IU Vitamin A		200 000 IU Vitamin A		RR ^c	95% CI	<i>P</i> ^d
	<i>n</i> ^a	Rate ^b	<i>n</i> ^a	Rate ^b			
Clinical manifestations							
Fever	185	26.0	161	24.0	0.92	0.75–1.14	.46
Diarrhea	98	13.8	89	13.3	0.96	0.72–1.28	.80
Otitis	18	2.5	16	2.4	0.94	0.48–1.85	.87
ARI	319	44.8	310	46.2	1.03	0.88–1.21	.70
Severity signals							
Venous rehydration	4	0.56	8	1.19	2.08	0.64–2.07	.23
Antibiotic therapy	24	3.37	18	2.68	0.80	0.43–1.47	.47

ARI, acute respiratory infection.

^a Number of episodes.^b Episode rate (per 100 children per month).^c Rate pattern.^d Exact mid-*P* value.**TABLE 4** Duration of Diarrhea Episodes, Febrile Illnesses, and Hospitalizations of Infants in Recife, Brazil, 2007–2009

Duration (days)	400 000 IU Vitamin A			200 000 IU Vitamin A			<i>P</i> ^a
	<i>n</i>	Median	<i>P</i> ₂₅ – <i>P</i> ₇₅ ^b	<i>n</i>	Median	<i>P</i> ₂₅ – <i>P</i> ₇₅	
Diarrhea episodes	54	4.0	2.0–8.0	50	4.0	2.0–8.2	.90
Febrile illnesses	78	4.0	2.0–8.0	89	3.0	2.0–8.0	.45
Hospitalizations	15	4.0	2.0–8.0	18	8.0	2.0–8.2	.37

^a Mood's median test.^b Percentile.

investigators also called attention to the possible adverse effects of greater vitamin A doses and the potential negative interactions with the expanded immunization program. Another study,¹⁹ in which 9208 mother–child pairs were randomized to receive either 400 000 IU of vitamin A or a placebo (mothers) and 50 000 IU of vitamin A or a placebo (children), also did not demonstrate any beneficial effects on infant mortality in the supplemented groups. This result was attributed to the mothers participating in the clinical trial having had adequate serum vitamin A concentrations and the children having had a good nutritional status. This line of reasoning could also explain the absence of additional beneficial effects in our clinical trial, considering that in our sample only 2 children presented with a low birth weight (<2500 g) and only 6.1% of the mothers presented with low serum retinol concentrations (<0.70 $\mu\text{mol/L}$). Schemes with intermediate doses were also tested in randomized clinical trials conducted in the south of India.²⁰ In these trials, mothers were supplemented with either 300 000 IU of vitamin A or a placebo during the postpartum period, and the children were supplemented in the sixth month of life with either 200 000 IU or a placebo; they also did not demonstrate any additional reduction in the episodes of diarrhea or respiratory infection.

A reasonable attempt to explain the absence of additional benefits from a greater vitamin A dose than that recommended by the standard WHO protocol could be that 200 000 IU already assures adequate vitamin A reserves. Because the action of vitamin A would already be at its maximum effect, it would offer no additional anti-infectious benefits from its stimulatory action on the immunity of these children. Therefore, an additional morbidity-reducing effect from a greater dose is not likely.

TABLE 5 Correlations Between Durations of Breastfeeding, Episodes of Diarrhea, Fever, and Hospitalization

Group	Duration of Breastfeeding Versus Duration of Episodes of Diarrhea	Duration of Breastfeeding Versus Duration of Episodes of Fever	Duration of Breastfeeding Versus Duration of Hospitalization
400 000 IU	−0.12 (0.451)	−0.10 (0.411)	−0.12 (0.451)
200 000 IU	−0.12 (0.426)	−0.15 (0.416)	−0.08 (0.518)

Data are given as *r* (Pearson coefficient).

However, a clinical trial study by Basu et al,²¹ in which 300 mothers were randomly supplemented with 200 000 IU of vitamin A, revealed a greater number and duration of diarrhea, fever, and acute respiratory infection episodes among the control group children. It must be mentioned that placebos were not used in the study by Basu et al, which may have biased it toward a greater recording of morbidity events in the unsupplemented group. In addition, supplementation offered directly to the children has shown a decrease in the duration, average evacuation frequency, and proportion of children with semiliquid

feces²² and a reduction of morbidity events in malnourished children.^{23,24}

Our results cannot be extrapolated to populations that have more severe grades of VAD. However, the results are likely to reflect the general diet and disease conditions prevailing in northeast Brazil. Moreover, it should be taken into consideration that the power of the statistical significance in the current study was limited to the outcomes diarrhea and respiratory infection. Other end points, such as ear infection and clinical signs of VAD, were beyond the scope of the study due to the low prevalence in relation to the outcome diarrhea.

CONCLUSIONS

Considering that the supplementation dosage scheme recommended by the WHO has been widely used in the northeast region of Brazil, that it has already been optimized to reach the desirable effect of reduced mortality and that we did not detect any additional beneficial effect in morbidity reduction with a greater dose of vitamin A, our results support the continuation of the standard supplementation regimen recommended by the WHO. The protocol recommends that women receive supplementation with 200 000 IU of vitamin A in the immediate postpartum period in areas in which vitamin A deficiency is considered mild to moderate, as in the ecological context studied.

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