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Randomized control trials

The effect of vitamin A supplementation with 400 000 IU *vs* 200 000 IU on retinol concentrations in the breast milk: A randomized clinical trial

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SUMMARY

Background & aims: The vitamin A nutritional status is marginal for most of the newborns, and the prevention of that deficiency is promoted by breastfeeding. The Ministry of Health of Brazil established the National Vitamin A Supplementation Program, giving mega-doses of this nutrient to women right after delivery, in order to provide adequate vitamin A content in the breast milk and The International Vitamin A Consultative Group has supported the recommendation, to supplement with 400 000 IU of VA immediately after delivery.

This study compares retinol concentrations in breast milk (colostrum, 2 and 4 months) from mothers supplemented during immediate postpartum with 400 000 IU *versus* 200 000 IU of vitamin A.

Methods: A randomized, controlled, triple-blind trial, conducted in two public maternities in Recife, Northeast Brazil. Two hundred and ten mothers were recruited and allocated into two treatment groups: 400 000 IU or 200 000 IU of Vitamin A and monitored for 4 months.

Results: There was no significant difference between retinol concentrations in breast milk between treatment groups (400 000 IU vs 200 000 IU) in the studied period: 2 months ($p = 0.790$) and 4 months ($p = 0.279$), although a progressive reduction of concentrations throughout the study was observed in both treatment groups, 400 000 IU ($p < 0.0001$) and 200 000 IU ($p < 0.0001$).

Conclusions: The absence of an additional effect of a higher dosage justifies the 200 000 IU supplementation, according to the World Health Organization.

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1. Introduction

Vitamin A (VA) is an essential nutrient for the visual system, growth, epithelial integrity, production of red blood cells, immunity and reproduction. The human body cannot synthesize this nutrient, therefore it should be exogenously provided. When a dietary intake is chronically low, there will be vitamin A deficiency (VAD) [1].

The VA nutritional status is marginal for most of the newborns, and the prevention of that deficiency is promoted by breastfeeding, which presumes that food contains appropriate retinol concentrations [2].

Breast milk (BM) is considered the most important source of vitamin A to provide adequate the newborn's liver store, being a great protective factor against VAD up to two years of age – a period of higher level of vulnerability to the state of deficiency [3]. However, variations of nutritional components of the human milk depend on the lactation stage, period of feeding, the mother's nutrition, the mother's age, the child's gestational age, and other individual and selective aspects of the nursing mother [4].

The Ministry of Health of Brazil established the National Vitamin A Supplementation Program. This program seek to reduce and

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control VAD in children by giving mega-doses of VA to children from 6 to 59 months of age, and to women right after delivery, in order to provide appropriate VA content in the BM.

Pospartum VA supplementation would be a safe intervention to the child, as far as the potential of teratogenic risks, and would offer the advantage of preventing occasional side effects of toxic conditions, when VA is directly given to the newborn [5].

The International Vitamin A Consultative Group (IVACG) has supported the recommendation, to supplement with 400 000 IU of VA immediately after delivery, fractionated in two doses with at least one 24-h interval between them [6], as an alternative strategy to supplementing with the 200,000 IU suggested by the World Health Organization, considering the hypothesis that a greater dose of vitamin A would lead to higher levels and would increase the exhaustion point of retinol concentrations in the breast milk. However, the additional benefit resulting from a higher dose of vitamin A has not yet been thoroughly tested.

This study was intended to determine if the 400 000 IU supplementation with retinol palmitate, immediately after delivery, promotes an additional effect in the concentrations of retinol in the human milk, when compared to the 200 000 IU supplementation.

2. Materials and Methods

2.1. Study design, period and location

This was a randomized, controlled, triple blind and hospital-based clinical trial performed using data from the research titled: "Impact of maternal supplementation with double mega dose of Vitamin A in the postpartum on the nutritional status of vitamin A and iron in the mother-child binomial and in the growth and morbidity of infants under 6 months of age under breastfeeding", including 312 women from 13 to 42 years of age, in the period from August 2007 to June 2009, recruited in the government-owned maternity hospitals *Maternidade Bandeira Filho* and *Instituto de Medicina Integral Prof. Fernando Figueira* - IMIP, located in the city of Recife, Northeast Brazil. Parts of the results have been published previously [7–9].

2.2. Eligibility of participants

Mother-child pairs were selected if they presented low obstetric risk, single and at-term pregnancy (gestational age $\geq$37 weeks). Exclusion criteria were women with mental disorders, children presenting acute perinatal hipoxia, malformation and/or other disease that would compromise development and growth and not allow anthropometric measurement or breastfeeding (malabsorption syndrome, cardiopathy, metabolic syndrome, and cleft palate).

2.3. Selection of participants

The pregnant women were selected at the time of their hospital admission. After being aware of the purposes of the research, those who agreed to be part of it signed an Informed Consent. When under 18 years, consent was signed by a legally responsible person.

2.4. Randomization and follow-up

Each nursing mother was given a 200 000 IU oral capsule of VA when they were still in the delivery room, as prescribed by the protocol of the National Vitamin A Program of the Brazilian Ministry of Health (Farmanguinhos/FIOCRUZ, Rio de Janeiro, RJ – Brazil). Due to the national coverage of this protocol, it became impossible to have a placebo group. Between the 8th and the 10th day after delivery, an individual randomization of the sample was done in two treatment groups to respectively receive 200 000 IU of VA or placebo, using a random number table generated by software EPI INFO, version 6.04d (WHO/CDC, Atlanta, GE, USA). Both dispensation and random number table generated was done by research nurse.

All women were monitored to determine the presence of possible side effects related to VA toxicity over the period of three days after supplementation. No hint about the expected side effects was given to the mothers, to prevent them from being suggested about some of the clinical conditions being researched.

The VA capsules and the placebo were packed in separate recipients and code-labeled by the IMIP Pharmacist, who was not part of the research study. The randomization codes were kept secret throughout the study, and were only disclosed after the completion of the data analysis.

The flowchart containing the selection of participants, randomization and follow-up is shown in Fig. 1.

2.4.1. Group details

Group 1 – received one 200 000 IU (retinol palmitate) capsule + 40 mg of vitamin E orally immediately after delivery and, 10 days after delivery, the second 200 000 IU (retinol palmitate) capsule + 40 mg of vitamin E were given.

Group 2 – received one 200 000 IU (retinol palmitate) capsule + 40 mg of vitamin E orally immediately after delivery and, 10 days after delivery, the second "placebo" capsule containing 40 mg of vitamin E diluted in soybean oil were given.

Both VA and placebo capsules were prepared in identical size, shape, color (turbid for photoprotection) and flavor by *Relthy Laboratórios* (Indubatuba, SP-Brazil).

The mothers were followed up every month, during the first four months after delivery, at the IMIP ambulatory. During the visits in the 2nd and 4th months after delivery, the BM was collected at IMIP's Human Milk Bank and Center for the Promotion of Breastfeeding. The nursing mothers who were not exclusively breastfeeding were not excluded from the research, and were still followed up and assessed based on the study design, that is, in terms of "intention to treat".

The puerperal women who had VA deficiency or any other morbidity during the research were referred to the research assistant Doctor to be clinically assessed, and were guided as to the use of specific medications for the clinical picture they presented. No formal rules were established for the discontinuation of the clinical trial.

3. Evaluation techniques and methods.

3.1. Primary outcome

3.1.1. Retinol in the BM

The BM was collected at immediately after delivery (colostrum) and in the 2nd and 4th month after delivery, by a properly trained assistant. The process consisted of the collection of BM from one single (right) breast that had not been used to breastfeed for at least 3 h. As soon as mother and baby were together, the mother offered this breast for fifteen minutes. After that time, the baby was taken from the right breast, the left breast was offered, and the content left in the right breast was obtained by an electric pump for twenty minutes and stored in previously sterilized glass recipients. The tubes were stored, protected from the light exposure and kept refrigerated at −20 °C for further tests.

Milk sample analyses were conducted in the period of two months. The retinol content in the BM was determined by High Performance Liquid Chromatography (HPLC) using the method

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