Pediatrics and Neonatology (2014) xx, 1–5

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.pediatr-neonatol.com

ORIGINAL ARTICLE

Effectiveness of Vitamin A in the Prevention of Complications of Prematurity

J. Uberos*, M. Miras-Baldo, A. Jerez-Calero, E. Narbona-López

Unidad Neonatal, Servicio de Pediatría, Hospital Clínico San Cecilio, Avenida del Doctor Oloriz, 16, 18012 Granada, Spain

Received Jul 5, 2013; received in revised form Nov 5, 2013; accepted Dec 6, 2013

Key Words
bronchopulmonary dysplasia;
intraventricular hemorrhage;
retinopathy of prematurity;
sepsis;
very low birth weight infant;
vitamin A

Aim: To assess the effectiveness of vitamin A supplementation in very low birth weight (VLBW) infants to prevent complications of prematurity.
Study design: A retrospective cohort study to determine the effectiveness of vitamin A in preventing complications of prematurity in VLBW infants. Vitamin A was delivered intramuscularly at a dose of 5000 IU, three times weekly during the first 28 days of life.
Results: Of the 187 eligible VLBW infants, we excluded from the analysis (due to death or transfer to another hospital), 16 infants weighing <1000 g and 17 weighing 1000–1500 g. Sixty VLBW infants received the vitamin supplement. We observed no differences between the groups in the duration of oxygen therapy or in the risk of bronchopulmonary dysplasia. The risk of sepsis was up to three times higher among the infants who were given the vitamin A supplement.
Conclusion: Given the increased risk of sepsis in patients weighing >1000 g, the risk associated with repeated intramuscular injections of vitamin A and the modest clinical results described, we do not believe the universal administration of vitamin A to VLBW infants to be justified as prophylaxis for bronchopulmonary dysplasia.

1. Introduction

Vitamin A is a group of fat-soluble compounds involved in regulating the growth of many epithelia that are necessary for normal development of the retina and lungs.[1] Brandt et al[2] first reported that preterm infants have lower levels of plasma vitamin A than do term infants, and their findings were subsequently confirmed by other authors.[3] In an experimental mouse model, plasma levels of vitamin A have been shown to increase by the end of gestation, which would account for the low levels of plasma vitamin A in the preterm infant[4,5] and justify vitamin A supplementation in extremely low birth weight (ELBW) premature infants. However, various studies have reported that such

* Corresponding author. Unidad Neonatal, Servicio de Pediatría, Hospital Clínico San Cecilio, Avenida del Doctor Oloriz 16, 18012 Granada, Spain.
E-mail address: juberos@ugr.es (J. Uberos).

1875-9572/$36
http://dx.doi.org/10.1016/j.pedneo.2013.12.002

Table 1 Perinatal data, mean (SD), for infants given supplementary vitamin A and untreated infants.

	≤1000 g		1000–1500 g	
	Vitamin A +	Vitamin A −	Vitamin A +	Vitamin A −
Patients (No.)	19	27	41	67
Gestational age (wk)	27.9 (1.8)	28.0 (2.0)	29.1 (1.5)	29.8 (1.9)
Birth weight (g)	854 (113)	906 (103)	1224 (154)	1261 (159)
Apgar score at 5 min	6.7 (1.5)	7.8 (1.9)	7.8 (1.7)	9 (1.2)†
Female infants, *n* (%)	12 (63.1)	14 (51.8)	15 (36.6)	36 (53.7)
Small for gestational age, *n* (%)	7 (36.8)	15 (55.6)	4 (9.7)	19 (28.3)*
Maternal age (y)	30.6 (6.7)	30.2 (6.1)	31.6 (5.8)	30.5 (5.6)
Cesarean section, *n* (%)	15(78.9)	25 (92.5)	35 (85.3)	50 (74.6)
Completed courses of antenatal steroids, *n* (%)	13 (68.4.3)	26 (96.3)	25 (60.9)	34 (50.7)
Chorioamnionitis, *n* (%)	2 (10.5)	3 (11.1)	6 (14.6)	3 (4.5)

*$p < 0.05$, vitamin A + versus vitamin A −.
†$p < 0.01$, vitamin A + versus vitamin A −.
SD = standard deviation.

prophylactic supplementation can provoke complications of prematurity, such as bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH) and retinopathy of prematurity (ROP).[4,6] To prevent vitamin A deficiency in the preterm infant and avoid repeated intramuscular (IM) administration, some authors have proposed supplying vitamin A to pregnant women in areas of endemic vitamin A deficiency.[6,7]

Vitamin A administered during the first weeks of life in ELBW infants has been reported to produce a modest improvement in respiratory outcomes.[6,8] Tyson et al[4] studied a series of 800 very low birth weight (VLBW) infants and observed a significant reduction in oxygen requirement and in BPD of prematurity after the IM provision of vitamin A in the first weeks of life.

Even with plasma levels of vitamin A >30 μg/dL and serum retinol >20 μg/dL, children with BPD may have a functional deficiency of vitamin A, as a result of excessive vitamin A binding to plasma proteins. Furthermore, in infants with low levels of plasma proteins, toxic effects may occur as a result of the administration of vitamin A.[9] Values of 80 μg/dL in serum are considered normal in children and adults.[10] However, the values above which signs of toxicity may appear in VLBW infants have not been established with certainty.[11] Some authors have reported increased plasma levels of vitamin A with postnatal steroid use, which might contribute to the development of toxic effects in preterm infants treated with vitamin A.[9] Among the toxic manifestations of vitamin A are vomiting, poor tolerance, and seizures, although such outcomes are rare according to the published studies.[4]

Vitamin A is also an important factor for the development of the retina and may have a protective role against the development of ROP.[8] However, the greatest impact of vitamin A in the prevention of ROP concerns the possibility that it may reduce oxygen dependence in the preterm infant.[6]

Some authors, in clinical trial models and meta-analyses, have demonstrated the efficacy of vitamin A in the prevention of complications of prematurity, particularly ROP and BPD.[6,12] In this study we evaluate the effectiveness of vitamin A supplementation in VLBW infants in the prevention of complications of prematurity.

2. Materials and methods

A retrospective cohort study was designed and implemented in the neonatal intensive care unit (NICU) at San Cecilio University Hospital (Granada, Spain) to determine the effectiveness of vitamin A in preventing complications of prematurity in VLBW infants, during the period from January 1, 2008 to December 31, 2012. During this period, the NICU treated 187 VLBW infants, of whom 33 could not be analyzed due to death or transfer to another center for surgery. Of those analyzed, 60 were given supplemental vitamin A.

The study was approved by the Hospital Ethics Committee and informed consent was obtained from the parent or guardian of the patients for the use of their data. The use of vitamin A was approved by the Hospital Pharmacy Committee as a compassionate use drug.

We included in the study all infants weighing <1500 g at birth or with a gestational age <32 weeks. We excluded children who died in the first 4 weeks of life or 36 weeks corrected gestational age and patients transferred to other hospitals. Our hospital does not have a pediatric surgery department. Most of the transferred patients required surgical attention for enterocolitis.

The following demographic variables were obtained from the patients included in the study: birth weight, gestational age, mode of delivery, presence of chorioamnionitis, Apgar score at 5 minutes, and complete lung maturation with antepartum steroids. We recorded the elapsed days until the establishment of full enteral feeding, days of parenteral feeding, days of oxygen therapy, days of mechanical ventilation and continuous positive airway pressure (CPAP), comorbidity associated with each group, and finally, ROP and IVH.

BPD was defined according to the criteria of Jobe and Bancalari[13]: oxygen requirement >21% at 28 days of age and/or >21% positive pressure in the airway at 36 weeks corrected gestational age.

In the diagnosis of sepsis coincidence of more than one clinical and analytical criteria from the following was considered[12,14]: (1) Clinical criteria: fever or hypothermia, tachycardia or bradycardia, tachypnea or apnea, two

Please cite this article in press as: Uberos J, et al., Effectiveness of Vitamin A in the Prevention of Complications of Prematurity, Pediatrics and Neonatology (2014), http://dx.doi.org/10.1016/j.pedneo.2013.12.002

Table 2 Clinical results for infants given supplementary vitamin A and untreated infants.

	≤1000 g		1000–1500 g	
	Vitamin A +	Vitamin A −	Vitamin A +	Vitamin A −
Days in NICU	44.8 (14.0)	52.4 (22.4)	28.6 (11.2)	25.2 (17.8)
Oxygen therapy (d)	49.5 (37.6)	49.8 (30.9)	28.6 (22.1)	18.7 (18.0)*
Mechanical ventilation (d)	6 (7.8)	14.8 (20.9)	3.0 (4.2)	3.3 (6.1)
CPAP (d)	9.1 (7.7)	9.3 (7.4)	6.4 (5.9)	3.7 (4.5)*
Parenteral nutrition (d)	23.7 (11.1)	21.6 (12.2)	13.6 (7.7)	10.3 (10.1)
Full enteral nutrition (days to start of)	24.2 (11.3)	26.1 (17.4)	15.3 (8.1)	13.9 (10.8)
BPD, *n* (%)				
Mild	5 (26.3)	12 (44.4)	12 (29.3)	12 (17.9)
Moderate	6 (31.6)	6 (22.2)	5 (12.2)	4 (6)
Severe	5 (7.4)	2 (26.3)	–	–
Total	16 (84.2)	20 (74.1)	17 (41.5)	16 (23.9)
Sepsis, *n* (%)	17 (89.5)	20 (74.1)	24 (58.5)	18 (26.9)†
Retinopathy of prematurity, *n* (%)				
Degree 1	7 (17.5)	4 (6.8)	1 (5.6)	10 (38.5)*
Degree 2	0 (0)	2 (3.4)	1 (5.6)	1 (3.8)
Degree 3	0 (0)	8 (13.6)	5 (27.8)	8 (30.8)
Plus	0 (0	3 (5.1)	4 (22.2)	4 (15.4)
Intraventricular hemorrhage, *n* (%)				
Degree 1	1 (5.3)	3 (11.1)	3 (7.3)	3 (4.5)
Degree 2	2 (10.5)	1 (3.7)	1 (2.4)	6 (9.0)
Degree 3	4 (21.1)	1 (3.7)	1 (2.4)	1 (1.5)
Degree 4	0 (0)	1 (3.7)	–	–
Death, *n* (%)	4 (17.4)	10 (27.0)	0 (0)	6 (8.2)

*$p < 0.05$, vitamin A + versus vitamin A −.
†$p < 0.01$, vitamin A + versus vitamin A −.
BPD = bronchopulmonary dysplasia; CPAP = continuous positive airway pressure; NICU = neonatal intensive care unit.

measurements at intervals of 30 minutes with average blood pressure less than the 10th percentile for gestational age, abdominal distension, vomiting, poor capillary refill, or pallor. (2) Analytical criteria: C-reactive protein and procalcitonin above reference ranges for gestational age, hyperglycemia, leukocytosis, leukopenia, thrombocytopenia, thrombocytosis, and positive blood culture.

With respect to the retinopathy examination protocol for premature infants, the following inclusion conditions were applied: preterm infant birth weight <1500 g or <32 weeks gestational age.

Following the procedure proposed by Kennedy et al,[9] vitamin A was delivered IM at a dose of 5000 IU, three times weekly during the first 28 days of life. Its use is indicated in all VLBW infants who require a fraction of inspired oxygen exceeding 21% on admission. During the period of administration of vitamin A, plasma levels of vitamin A were determined by liquid chromatography at 15 days and 28 days of life.[15,16]

The statistical analysis consisted of a descriptive analysis, a comparison of the means test for independent samples, and χ^2 analysis for categorical variables.

3. Results

3.1. Perinatal results

From January 2008 to December 2012, 187 VLBW infants were treated in our NICU. We excluded from the analysis (due to death or transfer to another hospital) 16 infants weighing <1000 g and 17 infants weighing 1000–1500 g. Perinatal data and the number of deceased patients are shown in Tables 1 and 2. Among the ELBW infants, no perinatal differences were observed between the infants who received vitamin A and those who did not. Among the infants weighing >1000 g, we observed a significantly higher percentage of small-for-gestational-age infants among those who did not receive vitamin A, and among this group, the 5-minute Apgar score was slightly higher.

3.2. Need for oxygen therapy and nutrition

The ELBW infants given vitamin A supplementation received oxygen treatment for periods similar to those for the infants who did not have vitamin supplement. The need for invasive mechanical ventilation and days of CPAP were also similar. Among infants weighing >1000 g, slightly more days of oxygen treatment were needed by the group given the vitamin A supplement. With respect to the requirements of mechanical ventilation and days of CPAP, no differences were observed. During the first 2 weeks of life, the infants with BPD (data pending publication) received significantly lower energy intakes than did those without BPD. Nevertheless, we did not observe any statistically significant differences between the groups for days of parenteral nutrition or the time needed to achieve full enteral nutrition.

Please cite this article in press as: Uberos J, et al., Effectiveness of Vitamin A in the Prevention of Complications of Prematurity, Pediatrics and Neonatology (2014), http://dx.doi.org/10.1016/j.pedneo.2013.12.002

3.3. BPD and vitamin A

The rate of VLBW in our hospital is 12.8 per 1000 live births, and the rate of BPD is 0.7 per 1000 live births, with a prevalence of 59.4% among the ELBW infants and of 27.4% among those weighing >1000 g. As shown in Table 2, there were no statistically significant differences in the prevalence of BPD between the infants who were given vitamin A and those who were not [odds ratio (OR): 2.2, 95% confidence interval (CI): 0.97–5.27]. Serum levels of vitamin A were 0.33 μg/mL [standard deviation (SD): 0.26] in the patients with BPD and 0.25 μg/dL (SD: 0.14) in those with no BPD, and there were no statistically significant differences between the groups. We observed no clinical manifestations attributable to vitamin A toxicity in any of our patients.

3.4. ROP and vitamin A

The incidence of mild, moderate, and severe ROP in our hospital is 1.5, 0.3, and 1.4 per 1000 live births, respectively. Among those weighing <1000 g, ROP was no better among the infants who were given vitamin A. However, among the infants weighing >1000 g, there were fewer cases of mild ROP among those given vitamin A (OR: 0.68, 95% CI: 0.24–1.9; Table 2).

3.5. IVH

The rate of incidence of IVH, Grade I, Grade II, Grade III, and Grade IV in our hospital is 0.6, 0.7, 0.6 and 0.2 per 1000 live births, respectively. We observed no differences in the prevalence of IVH between the infants who were given vitamin A and those who were not. The OR for IVH in infants weighing <1000 g was 2.04 (95% CI: 0.55–7.5) and for those weighing >1000 g it was 0.79 (95% CI: 0.25–2.5).

3.6. Sepsis and vitamin A

There were no significant differences in death rates between the groups. However, regardless of birth weight, the risk of sepsis was up to three times higher among infants given vitamin A supplementation than among those who were not (OR: 3.8, 95% CI: 1.6–8.7). Stratifying by birth weight, there were no significant differences in the prevalence of infection among the ELBW infants (OR: 2.9, 95% CI: 0.54–16.3). In those with a birth weight >1000 g, there was a significantly higher prevalence of sepsis in the group receiving vitamin A supplementation (OR: 3.8, 95% CI: 1.7–8.7). The microorganisms in our sample related to the development of sepsis in neonates were *Staphylococcus aureus* (5.9%), *Klebsiella pneumoniae* (35.3%), *Enterobacter cloacae* (5.9%), coagulase-negative *Staphylococcus* (23.5%), *Enterococcus faecalis* (11.8%), *Enterococcus faecium* (5.9%) and *Enterobacter* (11.8%).

The statistical power post hoc for a dichotomous endpoint and two independent samples was 83%.

4. Discussion

This study reviews our results following the introduction, in April 2010, of vitamin A supplementation for VLBW infants as prophylaxis for BPD. Despite the efficacy of vitamin A in the prevention of BPD that has been demonstrated by some authors in experimental models,[8,17,18] our study obtained no better results for BPD among vitamin-A-supplemented than among untreated patients.

Some systematic reviews[8] have reported that the IM supplementation of vitamin A in VLBW infants is associated with a trend towards reduced rates of death or oxygen use at 1 month of age, with borderline statistical significance (RR: 0.93, 95% CI: 0.86–1.0). We observed no differences in the perinatal risk factors classically associated with BPD between the infants who received vitamin A and those who did not. Some authors[19,20] have reported a decrease in the prevalence of BPD in recent years. This decline has coincided with improved ventilatory techniques with guaranteed volume utilization and a more rational use of oxygen therapy,[21,22] but also with increased nutritional inputs of protein and energy, as recommended by the ESPGHAN.[23] In our sample, no differences were observed between the groups concerning the duration of parenteral feeding or days of life elapsed to achieve full enteral nutrition. Days of oxygen therapy, CPAP and noninvasive ventilation did not differ significantly between the groups.

Although several authors have shown that a 5-minute Apgar score of <7 is associated with increased neurological morbidity,[24] in the short, medium, and long term, in our sample the patients with a birth weight >1000 g who were given vitamin A had a 5-minute Apgar score of >7. Although there are statistical differences between these patients and the group that was not given vitamin A, we believe that this finding is of little clinical significance, because neither of the two groups had a low 5-minute Apgar score (<7).

Shenai et al[3] reported a trend toward decreased risk of ROP in infants receiving vitamin A supplementation, findings similar to those reported by Darlow et al,[8] who based their systematic review on Shenai et al.[3] In our sample, we only observed a decrease in Grade I ROP in the infants weighing over 1000 g who received IM vitamin A supplementation. In those weighing <1000 g, we observed a decrease in ROP, but without statistical significance.

Some studies have reported increased episodes of sepsis among patients receiving vitamin A supplementation, although the differences are not statistically significant.[4] Chabra et al[24] observed an increased frequency of infection and/or sepsis among patients receiving supplementary vitamin A. In our study, we also observed an increased risk of sepsis linked to vitamin A supplementation. Stratifying by birth weight, we observed a significantly higher prevalence of sepsis among the infants weighing >1000 g who received supplementary vitamin A.

Furthermore, vitamin A supplementation for VLBW infants is not without other risks.[9] Some authors have reported increased plasma levels of vitamin A with postnatal steroid use, which might contribute to the development of toxic effects in preterm infants treated with vitamin A. Chabra et al[24] in a retrospective study of preterm infants supplemented with 5000 IU of vitamin A delivered IM,

Please cite this article in press as: Uberos J, et al., Effectiveness of Vitamin A in the Prevention of Complications of Prematurity, Pediatrics and Neonatology (2014), http://dx.doi.org/10.1016/j.pedneo.2013.12.002

observed that few children receiving supplementary vitamin A actually had a real vitamin deficiency. Londhe et al[25] noted that the alveolar hypoplasia caused by caloric restriction in children with intrauterine growth retardation can be reversed with replenishment and retinoic acid supplementation. Consequently, our view is that supplements should only be given to ELBW infants with serum vitamin A levels below the lower limit of normality (20 μg/dL).[9]

Given the increased risk of sepsis in patients weighing >1000 g and the potential risks involved in the repeated IM administration of vitamin A, as well as the modest clinical results reported, we believe that there is no justification for the universal administration of vitamin A to newborn infants weighing <1000 g. Determining the levels of vitamin A in the first days of life can be helpful in deciding when vitamin A supplementation should be given and when it should not.

Conflicts of interest

The authors declare that there is no conflict of interest.

References

1. Spears K, Cheney C, Zerzan J. Low plasma retinol concentrations increase the risk of developing bronchopulmonary dysplasia and long-term respiratory disability in very-low-birth-weight infants. *Am J Clin Nutr* 2004;**80**:1589–94.
2. Brandt RB, Mueller DG, Schroeder JR, Guyer KE, Kirkpatrick BV, Hutcher NE, et al. Serum vitamin A in premature and term neonates. *J Pediatr* 1978;**92**:101–4.
3. Shenai JP, Kennedy KA, Chytil F, Stahlman MT. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. *J Pediatr* 1987;**111**:269–77.
4. Tyson JE, Wright LL, Oh W, Kennedy KA, Mele L, Ehrenkranz RA, et al. Vitamin A supplementation for extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. *N Engl J Med* 1999;**340**:1962–8.
5. Laughon MM, Smith PB, Bose C. Prevention of bronchopulmonary dysplasia. *Semin Fetal Neonatal Med* 2009;**14**:374–82.
6. Mactier H. Vitamin A for preterm infants; where are we now? *Semin Fetal Neonatal Med*; 2013. http://dx.doi.org/10.1016/j.siny.2013.01.004.
7. Guimarães H, Guedes MB, Rocha G, Tomé T, Albino-Teixeira A. Vitamin A in prevention of bronchopulmonary dysplasia. *Curr Pharm Des* 2012;**18**:3101–13.
8. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. *Cochrane Database Syst Rev* 2007;(4): CD000501.
9. Kennedy KA, Stoll BJ, Ehrenkranz RA, Oh W, Wright LL, Stevenson DK, et al. Vitamin A to prevent bronchopulmonary dysplasia in very-low-birth-weight infants: has the dose been too low? The NICHD Neonatal Research Network. *Early Hum Dev* 1997;**49**:19–31.
10. International Vitamin A Consultative Group (IVACG). *The safe use of vitamin A: a report of the International Vitamin A Consultative Group (IVACG)*. Washington DC: The Nutrition Foundation; 1980.
11. Wardle SP, Hughes A, Chen S, Shaw NJ. Randomised controlled trial of oral vitamin A supplementation in preterm infants to prevent chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 2001;**84**:F9–13.
12. Kovatchev BP, Farhy LS, Cao H, Griffin MP, Lake DE, Moorman JR. Sample asymmetry analysis of heart rate characteristics with application to neonatal sepsis and systemic inflammatory response syndrome. *Pediatr Res* 2003;**54**:892–8.
13. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;**163**:1723–9.
14. Griffin MP, O'Shea TM, Bissonette EA, Harrell Jr FE, Lake DE, Moorman JR. Abnormal heart rate characteristics preceding neonatal sepsis and sepsis-like illness. *Pediatr Res* 2003;**53**: 920–6.
15. Bieri JG, Tolliver TJ, Catignani GL. Simultaneous determination of alpha-tocopherol and retinol in plasma or red cells by high pressure liquid chromatography. *Am J Clin Nutr* 1979;**32**: 2143–9.
16. Underwood BA. Biochemical and histological methodologies for assessing vitamin A status in human populations. *Methods Enzymol* 1990;**190**:242–51.
17. Darlow BA, Graham PJ. Vitamin A supplementation for preventing morbidity and mortality in very low birthweight infants. *Cochrane Database Syst Rev* 2002;(4): CD000501.
18. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants. *Cochrane Database Syst Rev* 2011;(10): CD000501.
19. Pinto Cardoso G, Abily-Donval L, Chadie A, Guerrot AM, Pinquier D, Marret S, et al. Epidemiological study of very preterm infants at Rouen University Hospital: changes in mortality, morbidity, and care over 11 years. *Arch Pediatr* 2013;**20**:156–63 [Article in French].
20. Theile AR, Radmacher PG, Anschutz TW, Davis DW, Adamkin DH. Nutritional strategies and growth in extremely low birth weight infants with bronchopulmonary dysplasia over the past 10 years. *J Perinatol* 2012;**32**:117–22.
21. Bancalari E, Claure N. The evidence for non-invasive ventilation in the preterm infant. *Arch Dis Child Fetal Neonatal Ed* 2013;**98**:F98–F102.
22. Claure N, Bancalari E. Mechanical ventilatory support in preterm infants. *Minerva Pediatr* 2008;**60**:177–82.
23. ESPGHAN Committee on Nutrition, Aggett PJ, Agostoni C, Axelsson I, De Curtis M, Goulet O, et al. Feeding preterm infants after hospital discharge: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2006; **42**:596–603.
24. Chabra S, Mayock DE, Zerzan J, Bittner R, Neufeld MD, Gleason CA. Vitamin A status after prophylactic intramuscular vitamin A supplementation in extremely low birth weight infants. *Nutr Clin Pract* 2013;**28**:381–6.
25. Londhe VA, Nolen TL, Das A, Higgins RD, Tyson JE, Oh W, et al. Vitamin A supplementation in extremely low-birth-weight infants: subgroup analysis in small-for-gestational-age infants. *Am J Perinatol* 2013;**30**:771–80.

Please cite this article in press as: Uberos J, et al., Effectiveness of Vitamin A in the Prevention of Complications of Prematurity, Pediatrics and Neonatology (2014), http://dx.doi.org/10.1016/j.pedneo.2013.12.002