

AMERICAN ACADEMY OF PEDIATRICS

POLICY STATEMENT

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of All Children

Committee on Fetus and Newborn

Controversies Concerning Vitamin K and the Newborn

ABSTRACT. Prevention of early vitamin K deficiency bleeding (VKDB) of the newborn, with onset at birth to 2 weeks of age (formerly known as classic hemorrhagic disease of the newborn), by oral or parenteral administration of vitamin K is accepted practice. In contrast, late VKDB, with onset from 2 to 12 weeks of age, is most effectively prevented by parenteral administration of vitamin K. Earlier concern regarding a possible causal association between parenteral vitamin K and childhood cancer has not been substantiated. This revised statement presents updated recommendations for the use of vitamin K in the prevention of early and late VKDB.

ABBREVIATION. VKDB, vitamin K deficiency bleeding.

BACKGROUND

Vitamin K deficiency may cause unexpected bleeding (0.25%–1.7% incidence) during the first week of life in previously healthy-appearing neonates (early vitamin K deficiency bleeding [VKDB] of the newborn [formerly known as classic hemorrhagic disease of the newborn]). The efficacy of neonatal vitamin K prophylaxis (oral or parenteral) in the prevention of early VKDB is firmly established. It has been the standard of care since the American Academy of Pediatrics recommended it in 1961.¹

Late VKDB, a syndrome defined as unexpected bleeding attributable to severe vitamin K deficiency in infants 2 to 12 weeks of age, occurs primarily in exclusively breastfed infants who have received no or inadequate neonatal vitamin K prophylaxis. In addition, infants who have intestinal malabsorption defects (cholestatic jaundice, cystic fibrosis, etc) may also have late VKDB. The rate of late VKDB (often manifesting as sudden central nervous system hemorrhage) ranges from 4.4 to 7.2 per 100 000 births, according to reports from Europe and Asia.^{2,3} When a single dose of oral vitamin K has been used for neonatal prophylaxis, the rate has decreased to 1.4 to 6.4 per 100 000 births. Parenteral neonatal vitamin K prophylaxis prevents the development of late VKDB in infants, with the rare exception of those with severe malabsorption syndromes.²

Oral administration of vitamin K has been shown to have efficacy similar to that of parenteral admin-

istration in the prevention of early VKDB.^{4–6} However, several countries have reported a resurgence of late VKDB coincident with policies promoting the use of orally administered prophylaxis, even with multiple-dose regimens. In a 1997 review of these experiences by Cornelissen et al,⁷ surveillance data from 4 countries revealed oral prophylaxis failures of 1.2 to 1.8 per 100 000 live births, compared with no reported cases after intramuscular administration. Newborns receiving incomplete oral prophylaxis tended to have a higher risk of developing VKDB, with rates of approximately 2 to 4 per 100 000. Small daily oral doses, as practiced in the Netherlands, may decrease the risk of late VKDB⁸ and approach the efficacy of the parenteral route; however, this needs to be better studied.

Draper and Stiller,⁹ using other data from Great Britain, have questioned the results of earlier studies of Golding et al^{10,11} that attempted to show an association between intramuscular vitamin K administration in newborns and an increased incidence of childhood cancer. Using data from the National Registry of Childhood Tumors, they estimated the cumulative incidence of childhood leukemia. Three sources of data, including the estimates from Golding et al, provided rates of intramuscular vitamin K use over the same time frame. Their analyses failed to show a correlation between increased use of intramuscular vitamin K and the incidence of childhood leukemia.

The Vitamin K Ad Hoc Task Force of the American Academy of Pediatrics¹² reviewed the reports of Golding et al and other information regarding the US experience¹³ and concluded that there was no association between the intramuscular administration of vitamin K and childhood leukemia or other cancers.

Additional studies that have since been conducted by other investigators have not supported a clinical relationship between newborn parenteral administration of vitamin K and childhood cancer. Ross and Davies¹⁴ published a review of the evidence in 2000. They found no randomized or quasi-randomized evidence of an association between parenteral vitamin K prophylaxis and cancer in childhood. Ten case-control studies were identified, of which 7 found no relationship and 3 found only a weak relationship of neonatal administration of intramuscular or intravenous vitamin K with the risk of solid childhood tumors or leukemia.

Recent research on the pathogenesis of childhood leukemia additionally weakens the plausibility of a causal relationship between parenteral administration of vitamin K and cancer. Investigations by Wiemels et al¹⁵ suggest a prenatal origin of childhood leukemia. They found an acute lymphocytic leukemia-associated gene in 12 children with newly diagnosed acute lymphocytic leukemia and postulated that an in utero chromosomal translocation event combined with a postnatal promotional event results in clinical leukemia. Although intramuscular administration of vitamin K could conceivably be a postnatal promotional event, a genetic etiologic explanation further lessens the likelihood of a clinically significant relationship between intramuscular administration of vitamin K and leukemia.

There is concern that adequate vitamin K prophylaxis be provided to the increasing numbers of newborns who are breastfed exclusively to avoid an increased risk of late VKDB with its associated intracranial hemorrhage.⁷

RECOMMENDATIONS

Because parenteral vitamin K has been shown to prevent VKDB of the newborn and young infant and the risks of cancer have been unproven, the American Academy of Pediatrics recommends the following:

1. Vitamin K₁ should be given to all newborns as a single, intramuscular dose of 0.5 to 1 mg.¹⁶
2. Additional research should be conducted on the efficacy, safety, and bioavailability of oral formulations and optimal dosing regimens of vitamin K to prevent late VKDB.
3. Health care professionals should promote awareness among families of the risks of late VKDB associated with inadequate vitamin K prophylaxis from current oral dosage regimens, particularly for newborns who are breastfed exclusively.

COMMITTEE ON FETUS AND NEWBORN, 2002–2003
 Lillian Blackmon, MD, Chairperson
 Daniel G. Batton, MD
 Edward F. Bell, MD
 William A. Engle, MD
 William P. Kanto, Jr, MD
 Gilbert I. Martin, MD
 Warren Rosenfeld, MD
 Ann R. Stark, MD

*Carol A. Miller, MD
 Past Committee Member

LIAISONS
 Keith J. Barrington, MD
 Canadian Paediatric Society

Tonse Raju, MD, DCH
 National Institutes of Health
 Laura E. Riley, MD
 American College of Obstetricians and Gynecologists
 Kay M. Tomashek, MD
 Centers for Disease Control and Prevention
 Carol Wallman, MSN, RNC, NNP
 National Association of Neonatal Nurses

STAFF
 Jim Couto, MA

*Lead author

REFERENCES

1. American Academy of Pediatrics, Committee on Nutrition. Vitamin K compounds and the water-soluble analogues: use in therapy and prophylaxis in pediatrics. *Pediatrics*. 1961;28:501–507
2. von Kreis R, Hanawa Y. Neonatal vitamin K prophylaxis. Report of Scientific and Standardization Subcommittee on Perinatal Haemostasis. *Thromb Haemost*. 1993;69:293–295
3. Motohara K, Endo F, Matsuda I. Screening for late neonatal vitamin K deficiency by acarboxyprothrombin in dried blood spots. *Arch Dis Child*. 1987;62:370–375
4. O'Connor ME, Addiego JE Jr. Use of oral vitamin K₁ to prevent hemorrhagic disease of the newborn infant. *J Pediatr*. 1986;108:616–619
5. McNinch AW, Upton C, Samuels M, et al. Plasma concentrations after oral or intramuscular vitamin K₁ in neonates. *Arch Dis Child*. 1985;60:814–818
6. Schubiger G, Gruter J, Shearer MJ. Plasma vitamin K₁ and PIVKA-II after oral administration of mixed-micellar or cremophor EL-solubilized preparations of vitamin K₁ to normal breast-fed newborns. *J Pediatr Gastroenterol Nutr*. 1997;24:280–284
7. Cornelissen M, Von Kries R, Loughnan P, Schubiger G. Prevention of vitamin K deficiency bleeding: efficacy of different multiple oral dose schedules of vitamin K. *Eur J Pediatr*. 1997;156:126–130
8. von Kries R, Hachmeister A, Gobel U. Can 3 oral 2 mg doses of vitamin K effectively prevent late vitamin K deficiency bleeding? *Eur J Pediatr*. 1999;158(suppl 3):S183–S186
9. Draper GJ, Stiller CA. Intramuscular vitamin K and childhood cancer. *BMJ*. 1992;305:709
10. Golding J, Paterson M, Kinlen LJ. Factors associated with childhood cancer in a national cohort study. *Br J Cancer*. 1990;62:304–308
11. Golding J, Greenwood R, Birmingham K, Mott M. Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *BMJ*. 1992;305:341–346
12. American Academy of Pediatrics, Vitamin K Ad Hoc Task Force. Controversies concerning vitamin K and the newborn. *Pediatrics*. 1993;91:1001–1003
13. Devesa SS, Silverman DT, Young JL Jr, et al. Cancer incidence and mortality trends among whites in the United States, 1947–84. *J Natl Cancer Inst*. 1987;79:701–770
14. Ross JA, Davies SM. Vitamin K prophylaxis and childhood cancer. *Med Pediatr Oncol*. 2000;34:434–437
15. Wiemels JL, Cazzaniga G, Daniotti M, et al. Prenatal origin of acute lymphoblastic leukaemia in children. *Lancet*. 1999;354:1499–1503
16. American Academy of Pediatrics, American College of Obstetricians and Gynecologists. *Guidelines for Perinatal Care*. 3rd ed. Washington, DC: American College of Obstetricians and Gynecologists; 1992

All policy statements from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

Controversies Concerning Vitamin K and the Newborn

Committee on Fetus and Newborn

Pediatrics 2003;112;191

DOI: 10.1542/peds.112.1.191

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/112/1/191>

References

This article cites 15 articles, 5 of which you can access for free at:
<http://pediatrics.aappublications.org/content/112/1/191#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):

Current Policy

http://www.aappublications.org/cgi/collection/current_policy

Committee on Fetus & Newborn

http://www.aappublications.org/cgi/collection/committee_on_fetus_newborn

Fetus/Newborn Infant

http://www.aappublications.org/cgi/collection/fetus:newborn_infant_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:

<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



PEDIATRICS[®]

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Controversies Concerning Vitamin K and the Newborn

Committee on Fetus and Newborn

Pediatrics 2003;112;191

DOI: 10.1542/peds.112.1.191

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/112/1/191>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2003 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN[®]

