Risk Factors of Acquired Prothrombin Complex Deficiency Syndrome: A Case-Control Study

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Background: *Idiopathic vitamin K deficiency in infancy or acquired prothrombin complex deficiency (APCD) is a serious bleeding disorders in infants. It leads to a high mortality rate and permanent neurological sequele among the survivors. A low vitamin K intake by infants is suggested to have a major role in the pathogenesis. To reduce the incidence of this syndrome, its risk factors have to be identified.*
Objective: *To determine the risk factors of the acquired prothrombin complex deficiency syndrome in the early infantile period.*
Material and Method: *A case-control study was conducted in 20 cases and 60 age- and sex-matched controls who were admitted to the Queen Sirikit National Institute of Child Health in Bangkok during August 1991 to August 1993. Feeding type, maternal history of herb-liquor extracts (herbal medicine) use and no history of vitamin K1 prophylactics at birth were identified to be risk factors of the syndrome. All subjects were fed by breast milk with or without formula milk. None of the subjects fed by formula milk were in the case group (Chi-square for trend = 14.77, p = 0.001).*
Rusults: *The rate of a maternal history of herb-liquor extracts use in the case group was significantly higher than that of the control group (p = 0.03). Vitamin K2MK4 level in breast milk obtained from the mothers of the infants with maternal history of herb-liquor extracts use was lower than that obtained from the mothers of the infants without maternal history of herb-liquor extracts use (p = 0.03). No infant with history of intramuscular K1 prophylactics was in the case group. Three out of eight infants with history of oral vitamin K1 regimen were cases. Although vitamin K1 and K2MK4 level in breast milk obtained from the cases' mothers were significantly lower than that obtained from the controls' mothers (p = 0.015 and p = 0.003 respectively), there was an overlapping of vitamin K levels among these two groups.*
Conclusion: *This study demonstrated that vitamin K in breast milk has a main role in the pathogenesis of this disease. Herb-liquor extracts may be a cause of the APCD syndrome. Intramuscular vitamin K1 prophylactics should be routinely given to all newborn babies who will receive breast feeding. Effectiveness of oral vitamin K1 prophylactics regimen must be studied urgently.*

Keywords: *Acquired prothrombin complex deficiency syndrome, Vitamin K, Risk factors, Thailand*

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Idiopathic vitamin K deficiency in infancy or acquired prothrombin complex deficiency (APCD) syndrome is a serious bleeding disorder in the early infantile period that was first described in 1966[1]. Since 1966, this bleeding disorder has been reported from many parts of the world including North America, Europe, Australia and Asia[2-20]. The majority of the cases reported in literature have been in Japan and Thailand. The APCD syndrome is one of the most serious diseases affecting infants. It leads to a high

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mortality rate and permanent neurological sequelae among the survivors[1-20]. A high incidence of this syndrome in Thailand (35.5 per 100,000 live births) makes this disorder a public health problem for the nation[2].

Available data at present suggests that a low vitamin K intake by infants is responsible for the disorder[21,22]. However, some patients who had been given vitamin K prophylactics at birth were reported[3,7,16,17]. Infant fed with breast milk that was found to have a much lower level of vitamin K than formula milk[8,23-26], had a higher risk of APCD syndrome[3-5,8,20,27]. A high percentage of having a maternal history of herb-liquor extracts (herbal medicine) intake and diet restrictions among patients with APCD syndrome were reported from Thailand[2,3,5,20,28]. Coumarin was found in some herb-liquor extracts and has been hypothesized as a possible causative factor in this disorder[5,28,29]. However, coumarin could not be detected in plasma or breast milk obtained from mothers who took herb-liquor extracts[28].

Although low vitamin K is considered to have a major role in the pathogenesis of the APCD syndrome, we know little about other factors involved in the pathogenesis. Moreover, to reduce the incidence of this syndrome, its risk factors have to be identified. Therefore, we conducted a case-control study to determine risk factors of the APCD syndrome among Thai infants admitted to the Queen Sirikit National Institute of Child Health in Bangkok.

Material and Method

Twenty infants aged between 2 weeks and 3 months, who were admitted to the Queen Sirikit National Institute of Child Health from August 1991 to August 1993 and diagnosed as having acquired prothrombin complex deficiency syndrome (APCD), were recruited for the study. These cases were diagnosed as having APCD by evidence of having bleeding disorder, venous clotting time longer than 15 minutes[30], abnormal prothrombin time (PT) [31], abnormal partial thromboplastin time (PTT)[32], normal thrombin time (TT)[33], the low activities of factors II, VII, IX, X[34-36] and normal platelet number. Seasonal pattern of admission, clinical manifestation and outcome of these patients was collected. Coagulogram on admission including PT[31], PTT[32], TT[33] and the activities of factors II, VII, IX, X(34, 35) were studied. For each case, three infants who were admitted during the same period and were age- ($\pm$ 2 weeks) and sex- matched were recruited as controls. Subjects with any evidence of liver impairment, diarrhea for more than three days or having received antibiotics in the last seven days were excluded from the study.

Information on the subjects and their mothers was obtained to identify risk factors of the APCD syndrome in this population including types of feeding (breast feeding only, breast plus formula milk feeding or formula milk feeding only), a history of vitamin K prophylactics, nutritional status of infants and their body weight, a history of blood transfusion, a history of drug use, a history of herb-liquor extracts intake by mothers, a history of maternal diet restriction, a history of abnormality during pregnancy and a family history of bleeding disorders.

Breast milk samples, obtained from the mothers who were breast feeding the subjects, were deep frozen (below -20 Celsius), kept in a pack of dried ice and sent to the University of Occupational and Environmental Health in Japan for analysis. Vitamin K1, K2MK4 and K2MK7 levels in the milk were analyzed by the method reported by Shino[36].

Chi-square test, Chi square for trend[37] and Student's unpaired t-test were used for statistical analysis. Odds ratio and its 95% confidence intervals[38] of risk factors were calculated. SPSS-PC+ program was used for statistical analysis.

Results

Twenty cases and 60 age- and sex-matched controls were recruited. Mean age of cases and controls were 43.6 $\pm$ 13.5 days (range 21-73) and 46.8 $\pm$ 14.5 days (range 26-82) days respectively. Seventy percent of subjects were male. (Table 1) No seasonal variation of admitted cases was found (6, 7 and 7 cases were admitted in summer, rainy season and winter respectively). Common clinical manifestations on admission of these APCD cases were convulsion and drowsiness (95%), anemia (85%) and fever (50%). Nineteen cases (95%) had intracranial bleeding including subdural hematoma, intracerebral hemorrhage, intraventricular hemorrhage and subarachnoid hemorrhage. Two cases (10%) had gastrointestinal tract bleeding. Only 10% of the cases had cutaneous bleeding (skin and oral cavity) (45%) had completely recovered. Permanent neurological handicaps including hemiparesis, microcephaly, convulsive disorders, spasticity and hydrocephalus were found in nine cases (45%). Two cases were intrahospital dead. Prothrombin time, partial thromboplastin time, thrombin time and the activities of factors II, VII, IX, X on admission were abnormal in cases only (Table 2).

Table 1. Characteristics of subjects and vitamin K level obtained from breast milk of their mother

	Case (n = 20)	Control (n = 60)
Mean age ± SD (days)	43.6 ± 13.5	46.8 ± 14.5
Mean weight ± SD (grams)	4,172 ± 790	4,283 ± 700
Malnutrition (%)		
First degree	9 (45)	19 (32)
Second degree	2 (10)	7 (12)
Maternal diet restriction - n (%)	11 (55)	26 (43)
Herb-liquer extracts - n (%)	17 (85)	35 (58)
Mean volume ± SD - ml	979.7 ± 1237.6*	632.3 ± 939.6**
Feeding type - n (%)		
Breast feeding only	14 (70)	18 (30)
Breast + formula feeding	6 (30)	15 (25)
Formula feeding only	-	27 (45)
Vitamin K1 prophylaxis - n (%)		
No	15 (75)	23 (38)
Oral route	5 (25)	3 (5)
Intramuscular injection	-	34 (57)
Vitamin K1 level in maternal breast milk		
Mean ± SD - nanograms/ml	0.87 ± 0.8	1.60 ± 1.3
Vitamin K2MK4 level in maternal breast milk		
Mean ± SD - nanograms/ml	0.50 ±0.5	1.08 ±0.8

* denominator = 17
** denominator = 35

Table 2. Results of coagulogram on admission of cases and controls

	Case		Control		
	Mean ± SD	Range	Mean ± SD	Range	p-value
Prothrombin time (sec)	196.1 ± 148.4	25.5-540.0	12.7 ± 0.7	11.5-15.4	<0.001
Partial thromboplastin time (sec)	264.3 ± 145.2	71.0-570.0	41.6 ± 10.6	32.0-54.6	<0.001
Thrombin time (sec)	9.0 ± 1.5	6.2-12.0	9.3 ± 2.1	5.6-15	>0.05
Activity of factor II (%)*	1.1 ± 2.3	<0.001-7.3	67.1 ± 11.5	39.9-99.8	<0.001
Activity of factor VII (%)*	5.9 ± 6.7	0.7-23.3	89.6 ± 18.7	52.3-163.2	<0.001
Activity of factor IX (%)*	2.9 ± 4.5	0.05-13.3	49.7 ± 22	16.0-113.7	<0.001
Activity of factor X (%)*	4.5 ± 5.4	0.07-20.8	93.3 ± 20.8	47.1-141.3	<0.001

The cases had slightly lower weight on admission than the controls. Eleven cases (55%) and twenty-six controls (43%) were classified as having malnutrition. (Table 1) There was no evidence of malnutrition in all of the subjects' mothers. There was no history of blood transfusion, history of abnormality during pregnancy or family history of bleeding disorders in all of the subjects. Common drugs used during pregnancy were paracetamol, vitamins and antihistamines. Apart from vitamin K1 prophylactics, 32% of cases and 28% of controls received some common cold remedies before admission. No evidence of medication, which could affect coagulation such as warfarin, phenytoin, phenobarbital or aspirin, was found.

Cases had higher rate of maternal history of postpartum herb-liquor extracts intake than controls (Chi-square = 4.69, p = 0.03). The difference in a history of maternal diet restriction between cases and controls was not statistically significant. Seventy percent of cases (n =14) were fed by breast milk only, 30% (n = 6) by both breast and formula milk and none by formula

milk only. Thirty percent of controls (n = 18) were fed by breast milk only, 25% (n = 15) by both breast and formula milk and 45% (n = 27) by formula milk only. Chi-square about trend and chi square for trend on types of feeding were 15.14 (p = 0.0005) and 14.77 (p < 0.001) respectively. Five cases (25%) had been given oral vitamin K1 at birth. None of the cases received intramuscular vitamin K1. Three cases (5%) and thirty-four infants (57%) in the control group received received oral and intramuscular vitamin K1 prophylactics at birth respectively. There was a statistically significant difference in the history of vitamin K1 prophylactics between the cases and controls (Chi-square = 21.58, p = 0.0000). Odds ratios and their 95% confidential interval of these factors are shown in Table 3.

Vitamin K1 level in breast milk obtained from the mothers of cases and controls were 0.89 ± 0.8 and 1.62 ± 1.3 nanogram/mL respectively. Vitamin K2MK4 level in breast milk obtained from the mothers of cases and controls were 0.53 ± 0.5 and 1.09 ± 0.8 nanogram/mL respectively. The difference of vitamin level between cases and controls was statistically significant (p = 0.015 for vitamin K1; p = 0.003 for vitamin K2MK4) (Table 1). Vitamin K2MK7 levels in all samples were lower than 0.1. Vitamin K2MK4 levels in breast milk obtained from subjects with a history of maternal herb-liquor extracts use were lower than those obtained from subjects without a history maternal herb-liquor extracts use (p = 0.03). There was no statistical difference in vitamin K1 levels among these two groups. There was no significant effect from maternal diet restriction on vitamin level in breast milk. When 1 and 0.5 nanograms per milliliter of vitamin K1 and K2MK4 level respectively were used as cut-off levels, the odds ratios for having APCD among those having low vitamin level were significantly high (Table 3).

Discussion

Infants with APCD syndrome in the present study had typically clinical manifestations and outcomes[1-19]. All of them had abnormal coagulogram which confirmed the diagnosis of the APCD syndrome. None of the controls had abnormal coagulogram (Table 2). Therefore, there were no misclassified cases in the present study.

This case-control study demonstrated some univariate factors including feeding type, vitamin K1 prophylactics, maternal history of herb-liquor extracts intake, vitamin K1 and vitamin K2MK4 level in breast milk. Feeding type is a strong risk factor suggested by the fact that none of the cases took formula milk. Moreover, linear trend of relation between types of feeding and disease is demonstrated by the chi square for trend analysis. It implies that the main cause of the disease should relate to breast milk.

Although there were some infants in the case group who had a history of vitamin K1 prophylactics at birth, all of them received the oral regimen. Three out of five subjects who had been given oral vitamin K1 prophylactics were cases while none of subjects who had been given intramuscular regimen were. The oral regimen has been used in Thailand since 1984[39]. Efficacy of this regimen was tested both in Thailand and aboard[39-43]. However, there were reports of sixteen infants who had been given oral vitamin K1 prophylactics at birth and developed the APCD syndrome[44]. Although there were reports of unrecognized bile duct paucity and liver diseases as causes of late vitamin K-deficiency bleeding after oral vitamin K prophylaxis[45,46], our study suggested an ineffectiveness of the oral route regimen. This might partly explain the finding of Pansatiankul BJ and colleague that the incidence of the APCD syndrome increased

Table 3. Odds ratio and 95% confident interval of factors included in this study

Factors	Odds ratio	95% CI
Feeding type:		
Breast + formula milk against breast milk	1.94	0.60-6.31
Vitamin K1 prophylaxis		
Oral route against no prophylaxis	0.39	0.21-0.87
Any route against no prophylaxis	4.83	1.55-15.06
Postpartum herb-liquor extracts intake	4.05	2.05-7.98
Maternal diet restriction	1.60	0.58-4.42
Malnutrition status of infants	1.60	0.58-4.42
Vitamin K1 level in maternal breast milk (< 1 nanograms/ml)	4.08	1.24-13.43
Vitamin K2MK4 level in maternal breast milk (< 0.5 nanograms/ml)	4.95	1.50-16.38

after routine use of oral vitamin K1 prophylactic was implicated by the Ministry of Public Health of Thailand[19]. Regurgitation of oral vitamin K1 solution after administration, improper storage or improper administration may be responsible factors in its ineffectiveness. Further study about effectiveness of the oral prophylactic regimen must be urgently done[47]. Meanwhile, routine prophylactics by the intramuscular prophylactic regimen should be recommended. Findings from this study suggested that, at least, newborns who take breast milk (with or without formula milk) should be given prophylactics routinely.

Use of herb-liquor extracts and restriction on diet during postpartum period are common practice in Thailand. It is believed that herb-liquor extracts are useful for the health of mothers during early postpartum period. There are reports about high prevalence of using herb-liquor extracts and diet restriction among mothers of infants with the APCD syndrome in Thailand[2-5]. From this study, association of these two factors and the syndrome was demonstrated. This finding confirmed previous finding of Pansatiankul BJ and colleague[20]. Vitamin K2MK4 levels in breast milk obtained from mothers who had used herb-liquor extracts were lower than vitamin K2MK4 levels in breast milk obtained from mothers who had not used herb-liquor extracts. Moreover, dicumarol, one of the coumarin anticoagulant, has been found in alcoholic herb elixirs[29]. Thus, herb-liquor extracts may have a role in the pathogenesis of the disease. Coumarin, alcohol or other substances in herb-liquor extracts may affect the level of vitamin K2MK4 in breast milk[5]. The responsible substance and the mechanism should be investigated further.

The vitamin K2MK7 in all samples obtained either from cases or controls were lower than 0.1 suggests that it may not be a factor in pathogenesis. The vitamin K1 and K2MK4 levels in breast milk obtained from the mothers of the controls were significantly higher than that of cases. Infants who were only fed by formula milk, which contains much higher vitamin K than breast milk[48], were free from disease. This supports the key role of low vitamin K level in breast milk in pathogenesis of the APCD syndrome[49,50].

Conclusion

The type of feeding, intramuscular vitamin K1 prophylactics, use of herb-liquor extracts and level of vitamin K (K1 and K2MK4) in breast milk are all factors relating to the APCD syndrome. Low levels of vitamin K1 and K2MK4 in breast milk are the key factor in the pathogenesis. Intramuscular vitamin K1 prophylactics should be recommended for routine use in the newborn who will be fed with breast milk instead of an oral regimen. Effectiveness of oral vitamin K1 prophylactics must be urgently studied. Herb-liquor extracts may have a role in the pathogenesis of this syndrome. Avoiding the use of these extracts may reduce the incidence of the APCD syndrome among Thai infants.

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References

1. Bhanchet P, Bhamarapravati N, Bukkavesa S, Tuchinda S. A new bleeding syndrome in Thai infants. Acquired prothrombin complex sufficiency. The XI Congress of the International Society of Haematology; Sydney, Australia, August 1966:20.
2. Ungchusak K, Tishyadhigama S, Choprapawon C, Sawadiwutipong W, Varintarawat S. Incidence of idiopathic vitamin K deficiency in infants: a national, hospital based, survey in Thailand, 1983. J Med Assoc Thai 1988; 71: 417-21.
3. Pansationkul BJ, Ratnasiri B. Acquired prothrombin complex deficiency syndrome: 10 years experience at Children's hospital. Bull Dept Med Serv 1992; 17: 485-92.
4. Bhanchet P, Tuchinda S, Hathirat P, Visudhiphan P, Bhamaraphavati N, Bukkavesa S. A bleeding syndrome in infants due to acquired prothrombin complex deficiency: a survey of 93 affected infants. Clin Pediatr 1977; 16: 992-8.
5. Mitrakul C, Tinakorn P, Rodpengsangkaha P. Spontaneous subdural hemorrhage in infants beyond the neonatal period. J Trop Pediatr Environ Child Health 1977; 23: 226-35.
6. Chan MC, Boon WH. Late haemorrhagic disease of Singapore infants. J Singapore Paediatr Soc 1967; 9: 72-81.
7. Chaou WT, Chou ML, Eitzman DV. Intracranial hemorrhage and vitamin K deficiency in early infancy. J Pediatr 1984; 105: 880-4.
8. Motohara K, Matsukura M, Matsuda I, Iribe K, Ikeda T, Kondo Y, et al. Severe vitamin K deficiency in breast-fed infants. J Pediatr 1984; 105: 943-5.

9. Lovric VA, Jones RF. The haemorrhagic syndrome of early childhood. Australas Ann Med 1967; 16: 173-5.
10. Nammacher MA, Willemin M, Hartmann JR, Gaston LW. Vitamin K deficiency in infants beyond the neonatal period. J Pediatr 1970; 76: 549-54.
11. Taj-Eldin S, al Nouri L, Fakri O. Haemorrhagic diathesis in children associated with vitamin K deficiency. J Clin Pathol 1967; 20: 252-6.
12. Forbes D. Delayed presentation of haemorrhagic disease of the newborn. Med J Aust 1983; 2: 136-8.
13. Dremsek PA, Sacher M. Life-threatening hemorrhage caused by vitamin K deficiency in breast-fed infants. Wien Klin Wochenschr 1987; 99: 314-6.
14. Deberdt P, Courpotin C, Papouin M, Lasfargues G. Acute anemia caused by hemoperitoneum disclosing hemorrhagic disease of the newborn. Arch Fr Pediatr 1988; 45: 47-8.
15. Behrmann BA, Chan WK, Finer NN. Resurgence of hemorrhagic disease of the newborn: a report of three cases. CMAJ 1985; 133: 884-5.
16. Vitamin K deficiency causing infantile intracranial haemorrhage after the neonatal period. Lancet 1983; 1: 1439-40.
17. Hanawa Y, Maki M, Murata B, Matsuyama E, Yamamoto Y, Nagao T, et al. The second nationwide survey in Japan of vitamin K deficiency in infancy. Eur J Pediatr 1988; 147: 472-7.
18. Nakayama K, Ikeda I, Shirahata S, et al. Bleeding due to vitamin K deficiency. Iji-shimpo 1981; 2996: 22. (in Japanese)
19. Pansatiankul BJ, Isranurug S, Ungchusak K, Thanasophon Y, Sunakorn P. Incidence of acquired prothrombin complex deficiency and the status of vitamin K administration in infants in Thailand. Bull Dept Med Serv 1989; 14: 761-70.
20. Pansatiankul BJ, Ruengsuwan S, Lektrakul J. Risk factors of bleeding diathesis secondary to low prothrombin complex level in infants: a preliminary report. Southeast Asian J Trop Med Public Health 1993; 24(Suppl 1): 121-6.
21. Bhanchet-Isarangkura P. The pathogenesis of acquired prothrombin complex deficiency syndrome (APCD syndrome) in infants. Southeast Asian J Trop Med Public Health 1979; 10: 350-2.
22. Isarangkura PB. Idiopathic vitamin K deficiency in infancy (acquired prothrombin complex deficiency syndrome). J Pediatr Obstet Gynaecol 1984; 10: 5-11.
23. Haroon Y, Shearer MJ, Rahim S, Gunn WG, McEnery G, Barkhan P. The content of phylloquinone (vitamin K1) in human milk, cows' milk and infant formula foods determined by high-performance liquid chromatography. J Nutr 1982; 112: 1105-17.
24. Fournier B, Sann L, Guillaumont M, Leclercq M. Variations of phylloquinone concentration in human milk at various stages of lactation and in cow's milk at various seasons. Am J Clin Nutr 1987; 45: 551-8.
25. Canfield LM, Martin GS, Sugimoto K. Vitamin K in human milk. In: Suttie JW, editor. Current advances in vitamin K research. New York: Elsevier; 1988: 499-504.
26. von Kries R, Shearer M, McCarthy PT, Haug M, Harzer G, Gobel U. Vitamin K1 content of maternal milk: influence of the stage of lactation, lipid composition, and vitamin K1 supplements given to the mother. Pediatr Res 1987; 22: 513-7.
27. Isarangkura PB, Mahadandana C, Panstienkul B, Nakayama K, Tsijkimoto I, Yamamoto Y, et al. Vitamin K level in maternal breast milk of infants with acquired prothrombin complex deficiency syndrome. Southeast Asian J Trop Med Public Health 1983; 14: 275-6.
28. Santawanpas S, Bhanchet-Isarangkura P, Tontisirin K, Mahasandana C. The possibility of the native alcoholic drugs as etiological factor of the acquired prothrombin complex deficiency syndrome. Southeast Asian J Trop Med Public Health 1980; 11: 367-70.
29. Pansatiankul BJ, Mekmanee R. Dicumarol content in alcoholic herb elixirs: one of the factors at risk induced IVKD-I. Southeast Asian J Trop Med Public Health 1993; 24 Suppl 1: 201-3.
30. Lee RI, White PD. A clinical study of the coagulation time of blood. Am J Med Sci 1913; 145: 503.
31. Tocantins LM. Estimation of prothrombin by the one stage method of Quick. In: Tocantins LM, editor. The coagulation of blood. New York: Grune and Stratton; 1955: 98-100.
32. Proctor RR, Rapaport SI. The partial thromboplastin time with kaolin: a simple screening test for first stage plasma clotting factor deficiencies. Am J Clin Path 1961; 36: 212-9.
33. Jim RTS. A case study of the plasma thrombin time. J Lab Clin Med 1975; 50: 45-60.
34. Bachman F, Duckert F, Koller F. The Stuart-Prower assay and its clinical significance. Diath Haemorrh 1958; 2: 24-38.
35. Biggs R, Eveling J, Richard G. The assay of antihaemophilic globulin activity. Br J Haematol 1955; 1: 20-6.

36. Shino M. Determination of endogenous vitamin K (phylloquinone and menaquinone-n) in plasma by high-performance liquid chromatography using platinum oxide catalyst reduction and fluorescence detection. Analyst 1988; 113: 393-7.
37. Bland M. An introduction to medical statistics. Oxford: Oxford Medical Publications; 1990: 248-51.
38. Schlesselman JJ. Case-control studies: design, conduct, analysis. New York: Oxford University Press; 1982.
39. Isarangkura PB, Bintadish P, Tejavej A, Siripoonya P, Chulajata R, Green GM, et al. Vitamin K prophylaxis in the neonate by the oral route and its significance in reducing infant mortality and morbidity. J Med Assoc Thai 1986; 69(Suppl 2): 56-61.
40. Motohara K, Endo F, Matsuda I. Vitamin K deficiency in breast-fed infants at one month of age. J Pediatr Gastroenterol Nutr 1986; 5: 931-3.
41. O'Connor ME, Addiego JE Jr. Use of oral vitamin K1 to prevent hemorrhagic disease of the newborn infant. J Pediatr 1986; 108: 616-9.
42. von Kries R, Kreppel S, Becker A, Tangermann R, Gobel U. Acarboxyprothrombin concentration [corrected] after oral prophylactic vitamin K. Arch Dis Child 1987; 62: 938-40.
43. McNinch AW, Upton C, Samuels M, Shearer MJ, McCarthy P, Tripp JH, et al. Plasma concentrations after oral or intramuscular vitamin K1 in neonates. Arch Dis Child 1985; 60: 814-8.
44. Chuansumrit A, Mahasandana C. Situation of acquired prothronbin complex deficiency in Thailand. Bangkok: Chaicharoen LTD.; 1990: 13. (in Thai)
45. Humpl T, Bruhl K, Brzezinska R, Hafner G, Coerdt W, Shearer MJ. Fatal late vitamin K-deficiency bleeding after oral vitamin K prophylaxis secondary to unrecognized bile duct paucity. J Pediatr Gastroenterol Nutr 1999; 29: 594-7.
46. Wariyar U, Hilton S, Pagan J, Tin W, Hey E. Six years' experience of prophylactic oral vitamin K. Arch Dis Child Fetal Neonatal Ed 2000; 82: F64-8.
47. von Kries R. Oral versus intramuscular phytomenadione: safety and efficacy compared. Drug Saf 1999; 21: 1-6.
48. Haroon Y, Shearer MJ, Rahim S, Gunn WG, McEnery G, Barkhan P. The content of phylloquinone (vitamin K1) in human milk, cows' milk and infant formula foods determined by high-performance liquid chromatography. J Nutr 1982; 112: 1105-17.
49. Shearer MJ, Rahim S, Barkhan P, Stimmler L. Plasma vitamin K1 in mothers and their newborn babies. Lancet 1982; 2: 460-3.
50. Greer FR, Marshall S, Cherry J, Suttie JW. Vitamin K status of lactating mothers, human milk, and breast-feeding infants. Pediatrics 1991; 88: 751-6.

ปัจจัยเสี่ยงของ acquired prothrombin complex deficiency syndrome: การศึกษาชนิด case-control

บุญเชียร ปานเสถียรกุล, สุทธิชัย จิตะพันธ์กุล

บทนำ: *Acquired prothrombin complex deficiency (APCD) เป็นภาวะเลือดออกผิดปกติที่รุนแรงในทารก ซึ่งจะทำให้อัตราตายและความพิการทางสมองของทารกที่มีเลือดออกเหล่านี้สูง การได้รับอาหารที่มีวิตามินเคต่ำน่าจะเป็นปัจจัยหลักที่ทำให้เกิดกลุ่มอาการนี้ การที่จะลดอุบัติการณ์ของกลุ่มอาการนี้จำเป็นต้องศึกษาหาปัจจัยเสี่ยงที่ทำให้มีprothrombin complex ลดลง*

วัตถุประสงค์: *ศึกษาปัจจัยเสี่ยงของทารกที่มีภาวะเลือดออกจากการมี prothrombin complex ต่ำ*

วัสดุและวิธีการ: *ผู้วิจัยได้ทำการศึกษาชนิด Case-control เพื่อค้นหาปัจจัยเสี่ยงของกลุ่มอาการ acquired prothrombin complex deficiency (APCD) ในเด็กแรกคลอดที่เป็นผู้ป่วยกลุ่มอาการ APCD จำนวน 20 รายที่เป็นกลุ่มศึกษา และเด็กแรกคลอดที่เป็นกลุ่มควบคุมจำนวน 60 ราย ณ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี กรุงเทพมหานคร ระหว่างเดือน สิงหาคม พ.ศ. 2534 ถึง สิงหาคม พ.ศ. 2536*

ผลการศึกษา: *พบว่า รูปแบบการให้นม ประวัติการใช้ยาดองเหล้า และการไม่ได้รับการป้องกันด้วยวิตามินเค เป็นปัจจัยเสี่ยงของกลุ่มอาการ APCD เด็กทารกทุกรายที่เข้าร่วมการศึกษาได้รับนมแม่แต่มีเด็กทารกในกลุ่มควบคุมบางรายที่ได้รับนมผง (formula milk) ร่วมด้วย ในขณะที่ไม่มีเด็กทารกในกลุ่มศึกษาที่ได้รับนมผงเลย (p = 0.001) อัตราของประวัติการใช้ยาดองเหล้าของมารดาในกลุ่มศึกษาสูงกว่าที่พบในมารดาของกลุ่มควบคุมอย่างมีนัยสำคัญ (ค่า p = 0.03) ระดับวิตามิน K2MK4 ในน้ำนมที่ได้จากมารดาที่มีประวัติการใช้ยาดองเหล้าต่ำกว่าที่พบในมารดาที่ไม่มีประวัติได้รับยาดองเหล้า (p = 0.03) และไม่พบว่าทารกในกลุ่มศึกษารายใดเลยที่ได้รับการป้องกันด้วยวิตามินเคชนิดฉีดเข้ากล้าม ทารกทั้งหมดที่มีประวัติได้รับการป้องกันด้วยวิตามินเคทางปากจำนวน 8 ราย อยู่ในกลุ่มศึกษา 3 ราย ถึงแม้ว่าระดับวิตามินเคหนึ่ง (K1) และระดับวิตามิน K2MK4 ในน้ำนมที่ได้จากมารดาของกลุ่มศึกษามีระดับต่ำกว่าที่ตรวจวัดได้จากมารดาในกลุ่มควบคุม (p = 0.015 และ 0.03ตามลำดับ) ผลการศึกษานี้แสดงถึงบทบาทสำคัญของวิตามินเคในน้ำนมในกลไกการเกิดโรคนี้ และแสดงว่ายาดองเหล้าอาจเป็นสาเหตุหนึ่งของการเกิดโรค*

สรุป: *ทารกแรกคลอดทุกคนที่ดื่มน้ำนมแม่ควรได้รับการป้องกันด้วยวิตามินเคชนิดฉีดเข้ากล้ามและประสิทธิผลของการใช้วิตามินเคทางปากในการป้องกันควรได้รับการศึกษาต่อไป*