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Vitamin K Deficiency Embryopathy: A Phenocopy of the Warfarin Embryopathy Due to a Disorder of Embryonic Vitamin K Metabolism

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Three unrelated infants presented with radiographic punctate calcifications, nasal hypoplasia, and abnormalities of the spine. Additional anomalies included cupped ears in 2 patients and one each with Dandy-Walker malformation with hydrocephaly, congenital cataracts, and peripheral pulmonary artery stenosis. The mothers of these 3 patients had chronic conditions associated with intestinal malabsorption requiring total parenteral nutrition for varying periods of time. The underlying causes of malabsorption were celiac disease, short bowel syndrome secondary to surgical resection, and jejuno-ileal bypass, respectively. Bleeding diathesis occurred in one mother requiring vitamin K supplementation during the second and third trimesters of pregnancy. We speculate that the chondrodysplasia punctata and other abnormalities in these children were caused by an acquired maternal vitamin K deficiency manifested during early pregnancy. However, the involvement of other vitamin deficiencies cannot be excluded.

Thus, vitamin K deficiency of the embryo secondary to maternal malabsorption appears to be a third vitamin K-related mechanism leading to chondrodysplasia punctata in addition to warfarin embryopathy and epoxide reductase deficiency (pseudo-warfarin embryopathy). Am. J. Med. Genet. 72:129–134, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: epiphyseal stippling; malabsorption; chondrodysplasia punctata; pseudo-warfarin embryopathy; nasal hypoplasia; spinal malformation; Dandy-Walker malformation

INTRODUCTION

Warfarin embryopathy is characterized by radiographic punctate calcifications in the axial skeleton, proximal femoral and calcaneal regions during infancy, nasal hypoplasia, and less frequent abnormalities of the brain, eyes, and ears. It is caused by maternal exposure to anticoagulant therapy with coumarin derivatives in the first trimester of pregnancy [Hall et al., 1980]. Similar manifestations have been seen in a small number of children with congenital and persistent postnatal coagulopathy who were not exposed to coumarin derivatives during pregnancy. In these children, a defect of vitamin K epoxide reductase has been demonstrated. The condition is called pseudo-warfarin embryopathy referring to its presentation as a biochemical deficiency phenocopy of a teratogen [Pauli, 1988; Pauli et al., 1987; Pauli and Haun, 1993].

In this paper, we report 3 unrelated girls with a similar malformation pattern which may have been caused by another prenatal disturbance of vitamin K metabolism which we have termed a vitamin K deficiency embryopathy.

CLINICAL REPORTS

Patient 1

Patient 1 is the daughter of a Spanish father and Austrian mother who are not consanguineous. The family history is unremarkable. The first pregnancy of the mother ended as a third month spontaneous abortion. The product of the second pregnancy was a baby girl born at term who was small for dates (1,860 g, <3rd centile). She developed normally and is now 9 years old. Our patient is the product of the third pregnancy.

For more than 3 years before the third pregnancy, the mother had experienced indigestion and diarrhea which recurred in early pregnancy. Bleeding occurred

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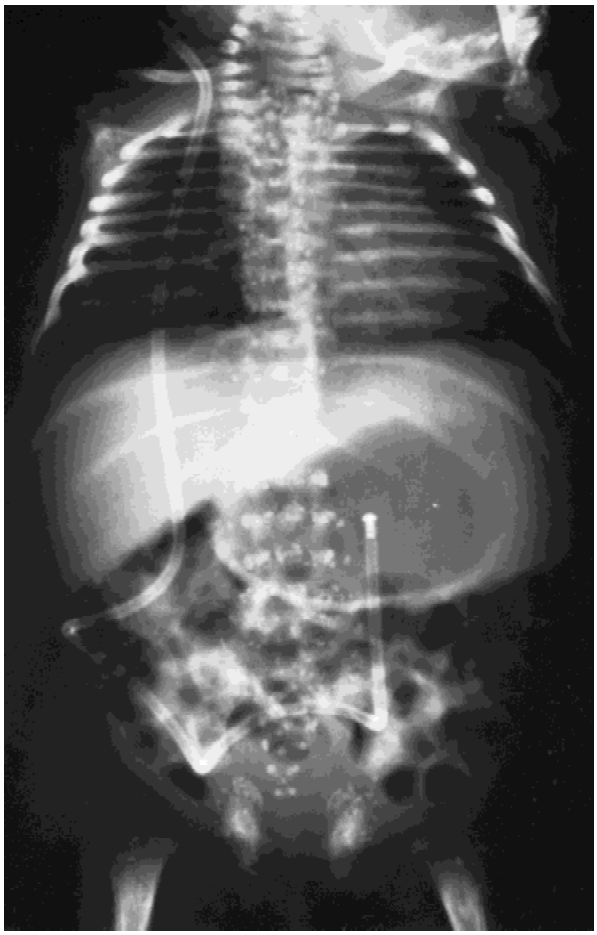

Fig. 1. Radiograph of patient 1 at age 4 weeks. Radiodense stipplings are visible adjacent to the entire vertebral column, in the sacral and coccygeal region, adjacent to the public and ischial bones and proximal femoral bone ends. There is lack of fusion of the vertebral arches from C3 to C7. The chest is short and broad and the ribs are horizontal. A right-sided ventriculoperitoneal shunt system was implanted.

in the 6th to 7th and 8th to 9th week of gestation. The diarrhea decreased, but the mother lost weight and was weak. In the 17th week of gestation total parenteral nutrition (TPN) was started, and vitamin K was supplemented in the 18th week. Celiac disease was diagnosed in the 18th week of gestation and her condition improved with dietary management within 3 weeks. However, polyhydramnios was detected by ultrasound. The mother was anemic. There was premature labor and lung maturation was induced by maternal steroid injection. Before birth, cardiotocography showed decelerations.

The patient, a girl, was born spontaneously at 35 weeks of gestation. Her weight was 1,600 g (3rd centile), length 40 cm (1 cm < 3rd centile), OFC 30.5 cm (10th centile). Hyperbilirubinemia was treated with phototherapy and exchange transfusion.

Neonatal radiographs showed punctate calcifications in the axial skeleton and spina bifida occulta of the lower cervical spine (Fig. 1). Hydrocephaly was detected at age 2 weeks and a ventriculoperitoneal shunt system was implanted. The hydrocephaly was caused by a Dandy-Walker type malformation with hypoplasia of the right cerebellar hemisphere and cystic dilatation.

During infancy, the girl developed almost complete quadriplegia at the lower cervical level with residual sensory functions. Magnetic resonance imaging (MRI) scan at 6 years showed kinking of the upper thoracic spine with stenosis of the spinal canal and compression of the spinal cord (Fig. 2).

Chromosomes were normal (46, XX). Her intellectual development was normal. She has recurrent pneumonias, bronchitis, and urinary tract infections.

When seen at age 5 8/12 years, she was a full-time wheel chair user. Her body length was 89 cm (15 cm < 3rd centile), weight 11.5 kg (3 kg < 3rd centile), OFC 49.5 cm (10–25th centile). She had a flat, short nose with anteverted nostrils and prominent chin resembling that of her father (Fig. 3). Her neck and trunk were short and her arms including fingers and nails were almost normal. Extension at both knees was limited, with the feet fixed in extension. She could not move her trunk or legs.

Patient 2

This black American girl was the first child born to nonconsanguineous parents in their 20s. The family

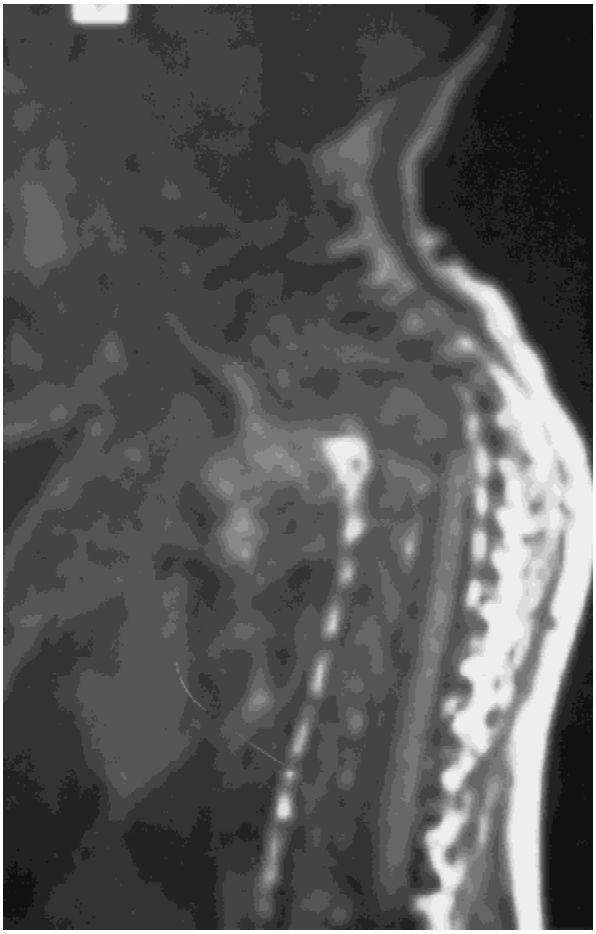

Fig. 2. MRI scan of the spine of patient 1 at age 6 years. Striking gibbus-like bending of the lower cervical and upper thoracic spine is demonstrated. There is extreme stenosis of the spinal canal with compression of the spinal cord. Only a marginal part of the cyst within the dorsal groove of the skull is seen on this film.

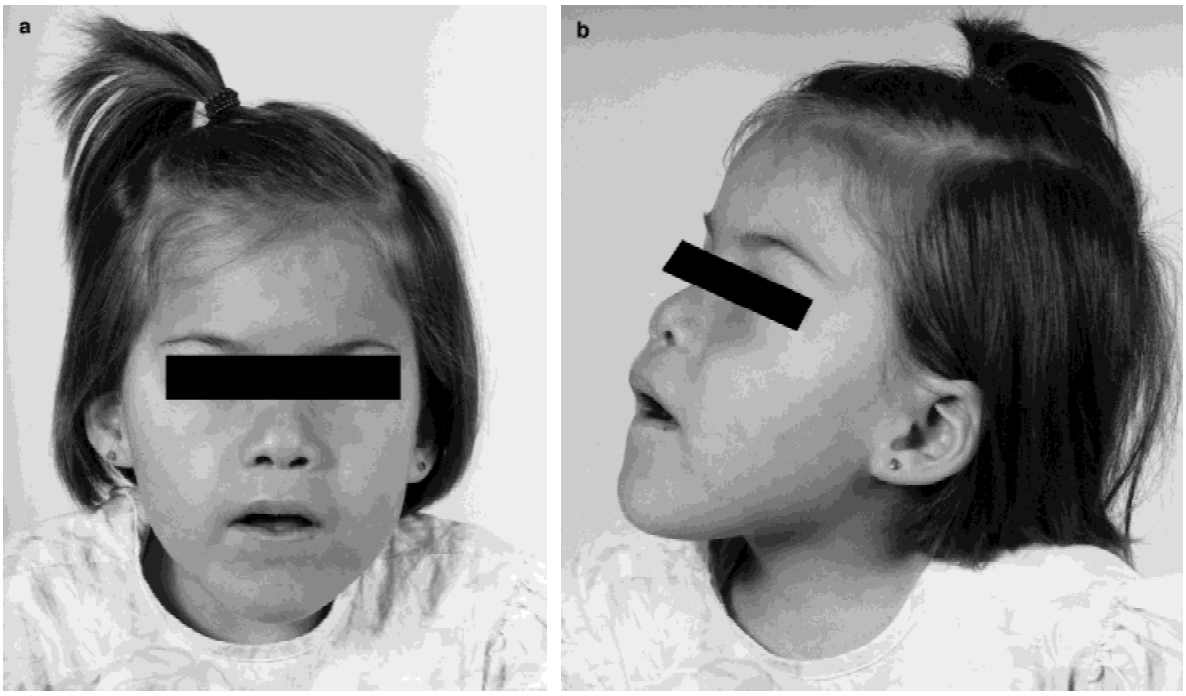

Fig. 3. Patient 1 at age 5 8/12 years. The face is flat. The nose is short with a depressed nasal bridge and anteverted nostrils. The chin is prominent (resembling her father) and the neck short.

history is not contributory. The mother underwent a small bowel tumor resection at age 13 years, resulting in short bowel syndrome necessitating total parenteral hyperalimentation through a central indwelling catheter. She tolerated some food by mouth. The mother reported that the tumor was considered benign, but her medical records could not be obtained. She reported no bleeding problems and had a normal coagulation time. During pregnancy, she was healthy and took standard prenatal vitamins for approximately 7 months, but she was unable to document when they were begun. Also unavailable was the exact amount of vitamin K received in her hyperalimentation.

The proposita was born by spontaneous vaginal vertex delivery at 37 weeks gestation and received Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The birth weight was 3,080 g (50th centile). Because of marked nasal hypoplasia, she required nasal suctioning, and had loud snoring, mild dyspnea, and intermittent duskiness usually associated with feeding. She also had small, truly low-set cupped ears and mild flattening of the occiput. There was no phalangeal or nail hypoplasia.

Radiographs showed subtle punctate ("flecks") calcifications in the laryngeal cartilage, sternum, costochondral junction, and sacrum (Fig. 4). The echocardiogram was normal. Ultrasound examination of the brain showed bilateral small (4 mm) subependymal cysts. Chromosomes were normal (46, XX). Platelet count (284,000), prothrombin time (PTT), and vitamin K and vitamin K epoxide levels (the latter two tests kindly performed by Dr. J. Suttie, Madison, Wisconsin) were within the normal range. The PTT was slightly prolonged at 42 seconds (control 25 seconds).

At follow-up at age 11 months, the length was 75.5 cm (75th centile), weight 7,960 g (10th centile), and OFC 45 cm (30th centile). Her facial appearance was similar to that in the newborn period, and neurodevelopment appeared normal. Mild scoliosis was noted. Radiographs at this time showed no punctate calcifications, but demonstrated hemivertebrae at the level of T7 and T10 resulting in thoracolumbar scoliosis. There was incomplete fusion of the posterior elements of the upper part of the sacrum, and a single irregular epiphyeal ossification center of the proximal right humerus. The mother was 28 weeks pregnant with a second child, and receiving supplemental vitamin K in the TPN. The family did not return for follow-up of either child.

Patient 3

Patient 3 was the first daughter of a 25-year-old white woman. The family history was unremarkable. Her mother had had a jejuno-ileal bypass for morbid obesity 10 years previously. The early second trimester of the pregnancy was complicated by malabsorption and anemia characterized by low hemoglobin, potassium, calcium, and serum albumin. At 24 weeks gestation, pneumonia was diagnosed, the woman was hospitalized, and TPN initiated. Ultrasound evaluation demonstrated polyhydramnios, a two-vessel umbilical cord, and growth retardation (growth consistent with 18 weeks of gestation).

The girl was born spontaneously at 34 weeks of gestation; birth weight was 885 g, length 33.5 cm, and OFC 26.8 cm (all below the 3rd centiles for 34 weeks of gestation). After birth, posterior central cataracts and optic atrophy, depressed midface, nasal hypoplasia, cupped ears, kyphosis, and short limbs were noted (Fig. 5).

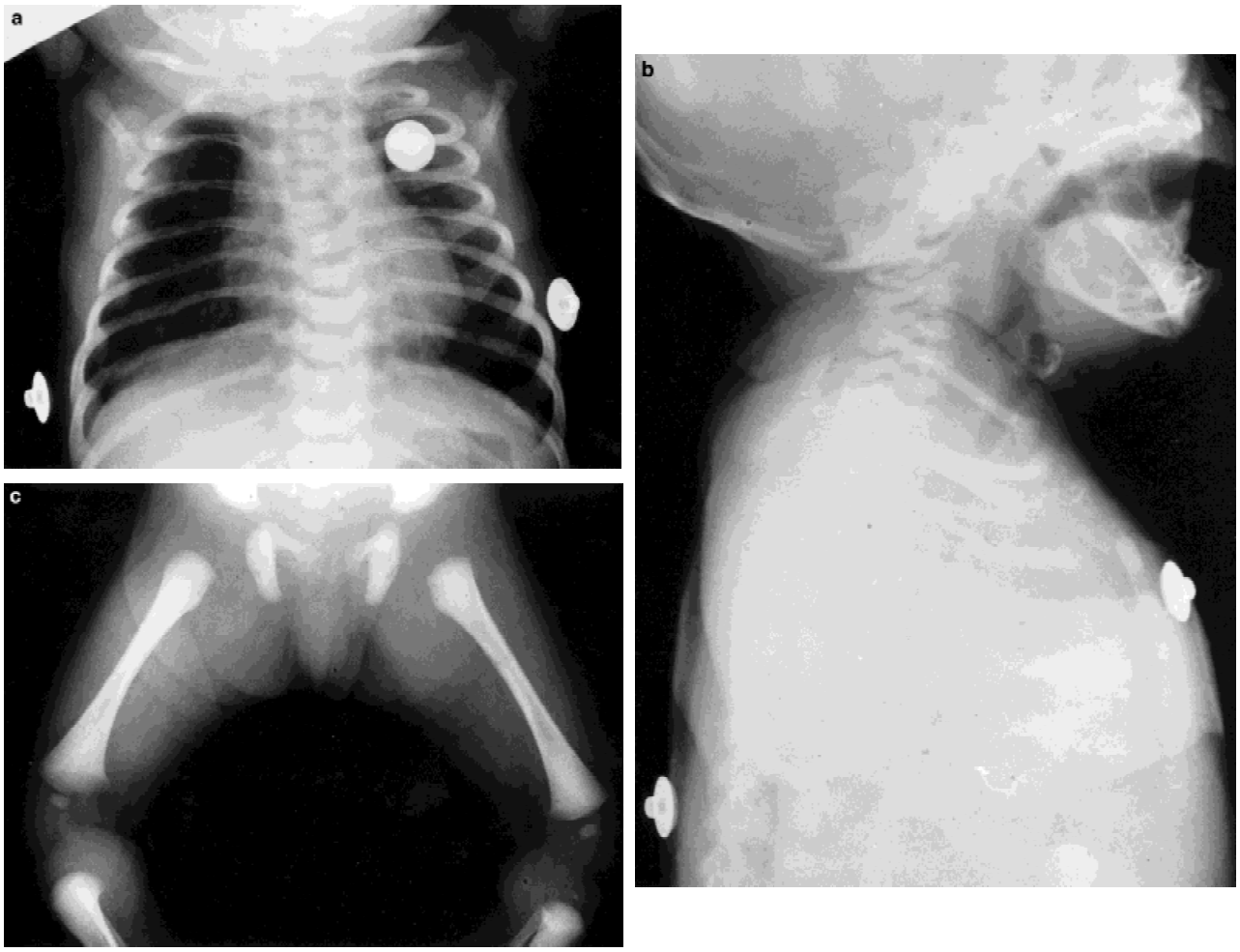

Fig. 4. Radiographs of patient 2 on the second day of life. **a:** Very pale radiodense stipplings are seen at the costochondral junction of several ribs. Note defective ossification of T-7, T-10, and mild scoliosis. **b:** Radiodensities are better demonstrated in the lateral views of the sternum and laryngeal cartilage. **c:** There are a few stipplings in the sacrum.

Radiographs documented punctate calcifications in the spinal, humeral, proximal femoral, and tarsal regions. The thoracic vertebrae and the sacrum were poorly formed, and the metacarpals and phalanges were abnormal. An echocardiogram showed increased right and left ventricular wall thickness, a thickened aortic valve, and peripheral pulmonic stenosis. A cranial computed tomography (CT) scan was normal. Platelets were low for the first 8 days of life; peroxisomal studies and karyotype analysis (46, XX) were normal. The baby remained hospitalized for 6 months. She died at home, and autopsy was denied.

Patients 2 and 3 were briefly reported in an abstract [Toriello et al., 1991].

DISCUSSION

Punctate calcifications and epiphyseal stippling refer to multiple, small radiodensities typically seen in infancy. This familiar radiographic phenotype is also described as chondrodysplasia punctata and occurs in numerous genetically heterogeneous conditions including chromosome abnormalities, mendelian gene syndromes, and teratogens, especially warfarin [Toriello et al., 1991; Wulfsberg et al., 1992]. The calcifications are usually seen in the axial skeleton, wrists, calcaneus, and epiphyses of the long bones, and were variably present in our 3 patients. They usually disappear within the first months of life and may be accompanied subsequently by abnormal bone development in the epiphyses and vertebrae. Severe spinal abnormalities leading to acute kyphosis with spinal cord compression developed in patient 1 with mild scoliosis in patient 2. Nasal hypoplasia and cataracts, other anomalies seen in chondrodysplasia punctata, were present in all 3 patients.

Pathogenetic mechanisms related to vitamin K metabolism have been postulated for both warfarin and pseudo-warfarin embryopathy. Following its intestinal absorption, vitamin K acts in its hydroxylated form as a coenzyme of a vitamin K-dependent carboxylase. This carboxylase specifically transforms protein-bound glutamic acid residues to carboxyglutamate, activating several coagulation factors, coagulation inhibitors, and proteins of the calcified tissue (Table I). Hydroxyvitamin K is oxidized to the 2,3-epoxide-vitamin K.

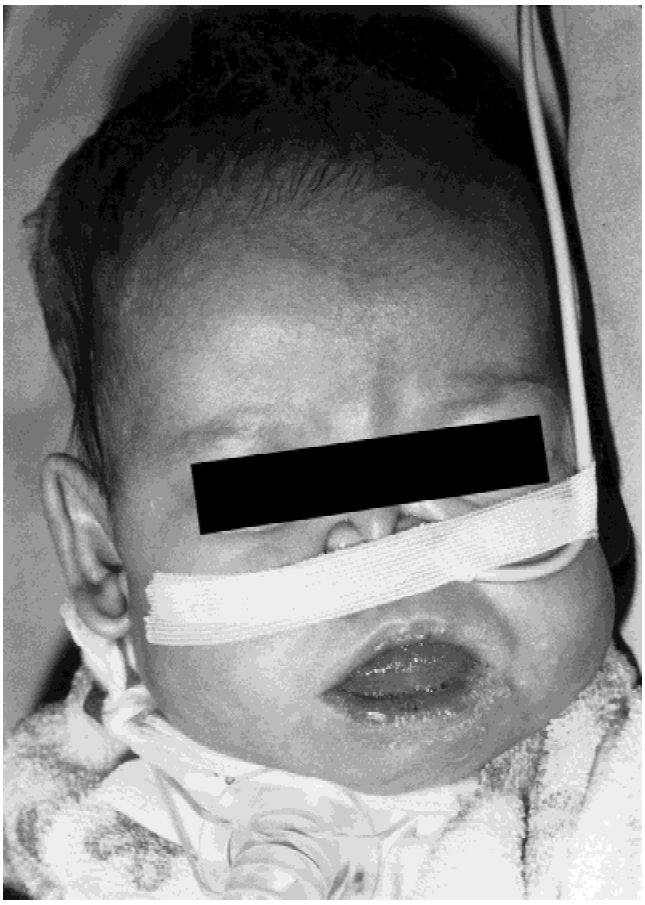

Fig. 5. Patient 3 as a newborn infant. The midface is hypoplastic, the nose flat and short with a depressed nasal bridge and alar creases. The malformed ears are cupped.

TABLE I. Vitamin K-Dependent Reactions: Carboxylation of Protein-Bound Glutamic Acid

Activation of	In
Coagulation factors II, VII, IX, and X	Liver
Coagulation inhibitor proteins C and S	Liver
Protein Z	Liver
Osteocalcin = Bone Gla-protein	Bones and others
Matrix Gla-protein	Bones and others
Plaque Gla-protein	?
Renal Gla-protein(s)	Kidneys

This molecule is recycled by a specific vitamin K epoxide reductase [Shearer, 1990; Vermeer, 1990; Vermeer and Hamulyák, 1991] (Fig. 6).

Coumarin derivatives used in oral anticoagulant therapy inhibit vitamin K epoxide reductase and prevent the recirculation of vitamin K leading to vitamin K deficiency. Maternal treatment with coumarin derivatives between the 6th and 9th week after conception may cause warfarin embryopathy [Hall et al., 1980]. The same clinical phenotype with an additional congenital, persistent coagulopathy may be caused by an inborn deficiency of the vitamin K epoxide reductase [Pauli, 1988; Pauli et al., 1987; Pauli and Haun, 1993]. Recent data indicate that high concentrations of warfarin in vitro inhibit a specific sulfatase (arylsulfatase E) whose deficiency is responsible for some cases of relatively mild chondrodysplasia punctata. This may hint to further pathogenetic aspects of vitamin K metabolism [Franco et al., 1995].

The mother of patient 1 experienced untreated celiac disease which apparently led to malabsorptive vitamin K deficiency and spontaneous bleeding which subsided after vitamin K supplementation. The mothers of patients 2 and 3 had malabsorption due to an extensive bowel resection and a jejuno-ileal bypass, respectively. In the mother of patient 3, malabsorption during preg-

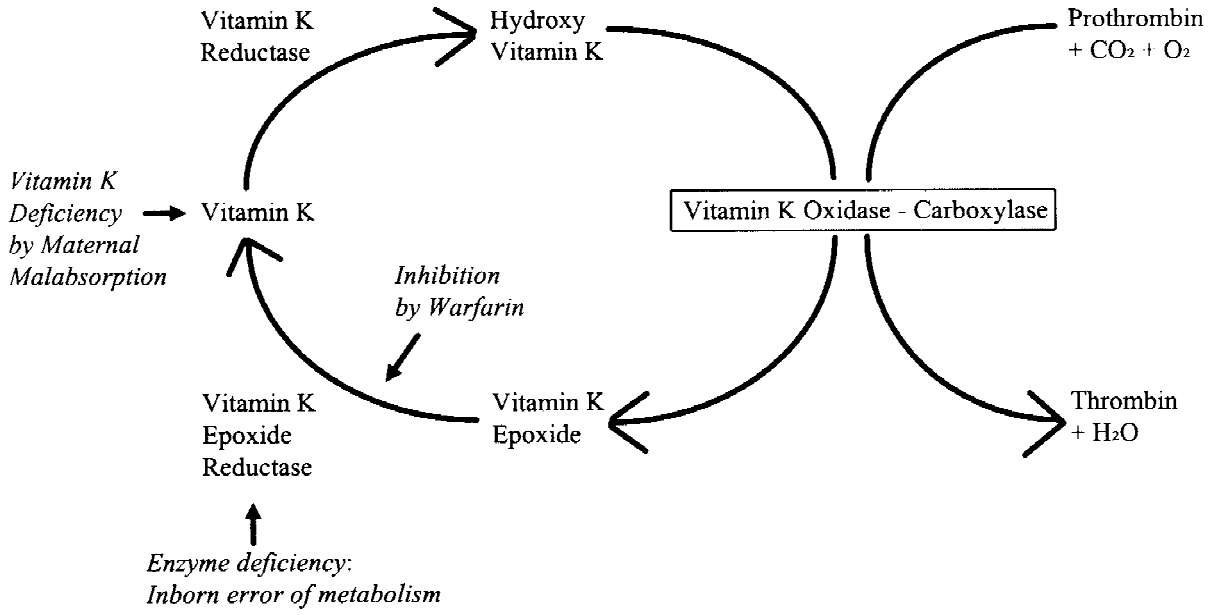

Fig. 6. Vitamin K effects and examples of their inhibition.

TABLE II. Disturbed Vitamin K Effects in the Embryonic Period

Mechanism	Disorder
Pharmacological inhibition Coumarin derivatives	Warfarin embryopathy
Embryonic enzyme deficiency Vitamin K epoxide reductase	Pseudo-warfarin embryopathy
Malabsorption/malnutrition Maternal celiac disease Crohn disease Surgical short bowel syndrome	Vitamin K deficiency embryopathy

nancy led to low hemoglobin, calcium, and albumin levels.

We propose that malabsorptive vitamin K deficiency secondary to maternal bowel disorder is a third mechanism of disturbed vitamin K metabolism in the embryonic period (Fig. 6, Table II). Untreated celiac disease, Crohn disease, and postoperative short bowel syndrome are reported now as possible causes of vitamin K malabsorption in pregnant women, but other conditions may likely exist. This hypothesis is supported by Howe and Webster [1994] who showed in rats that vitamin K deficiency during embryogenesis results in a similar phenotype including maxillonasal hypoplasia and abnormal cartilage calcification. However, other vitamin deficiencies may also be involved.

If maternal malabsorptive vitamin K deficiency can result in fetal vitamin K deficiency during a critical period in early embryonic development, then consideration should be given to a careful prenatal nutritional evaluation and possible supplementation of vitamin K. Ideally, pregnancies in women at risk should be carefully planned so that vitamin therapy can be initiated well before pregnancy is clinically recognized when intervention may be too late.

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