vitamin K:
controversy? what controversy?

By Karin Rothville DipCBEd.

For the last 40 or 50 years, it has become a generally accepted fact that vitamin K prevents haemorrhagic disease of the newborn, and routine administration of vitamin K to all newborns has been recommended.[3, 6, 21, 34, 72] This recommendation has been questioned because results released in 1990 from a study by Golding and colleagues[26] in the UK showed a two to three times increased risk of childhood cancers, especially leukaemia, in children given prophylactic drugs (usually intramuscular vitamin K) in their first week. A further study in 1992 seemed to confirm this risk.[25]

There was widespread anxiety among parents when these findings were published. Parents were, understandably, reluctant to have their baby receive a substance that could predispose it to cancer in childhood, and many health workers were also reluctant to give, without prescription, a possibly cancer-causing substance to prevent a disease that few, if any, of them had ever seen. These concerns are not the first time that vitamin K safety has been questioned. So, what is the controversy about vitamin K? And does it predispose babies to childhood cancer?

WHAT IS VITAMIN K AND WHAT DOES IT DO?

Vitamin K is a fat-soluble substance which triggers off the blood-clotting process. Blood clotting is a complex process and can be described as a sequence of three stages, requiring up to 12 different coagulation factors.[72] The liver needs vitamin K to synthesise four of these factors. Vitamin K is also needed for the formation of other proteins found in plasma, bone and kidney.[33, 58]

As with other fat-soluble vitamins, a normal flow of bile and pancreatic juice is necessary for digestion, and the presence of dietary fat, especially short-chain fatty acids, enhances absorption. Absorbed vitamin K is transported via the lymph into the systemic circulation.[58]

Normally, a significant portion (up to 55%) of absorbed vitamin K is excreted so the amount in the body is small and its turnover is rapid (about 30 hours).[58] Vitamin K is stored and re-utilised in the body for 3-4 weeks.[33]

Vitamin K is found in many foods. Leafy, dark green and deep yellow vegetables are the best sources.[58] Alfalfa[18] is a good source; and milk and dairy products, eggs, cereals, fruits and other vegetables also provide small but significant amounts. As the liver of adults contains about equal amounts of plant and animal forms of Vitamin K, it is assumed that vitamin K is produced in the intestinal tract by bacterial flora. One of the reasons given for the low levels of vitamin K in newborn babies is because their gut has not yet been colonised by the required bacteria.

Recommended daily dietary intakes of vitamin K[58]

Category	Age	Amount (μg)
Infants	0 – 1	10
Children	1 – 3	15
	4 – 6	20
	7 – 10	25
Adolescents	11 – 14	30
	15 – 18	35
Adult Male	19 – 70+	45
Adult Female	19 – 70+	35
Pregnancy		+ 10
Lactating		+ 20

The dietary requirements for vitamin K in infants and children are estimates and are based on weight and growth rates as

compared to adults. Many unsupplemented breasfed infants do not show clinical signs of vitamin K deficiency on intakes of less than 3 μg daily and the mean requirement for infants is estimated to be 5 μg daily based on weight. The higher amount of 10μg is recommended for prevention of Haemorrhagic Disease of the Newborn.[58]

WHAT IS HAEMORRHAGIC DISEASE OF THE NEWBORN?

Haemorrhagic Disease of the Newborn (HDN) is a bleeding disorder associated with low levels of vitamin K in newborn babies. It was first defined in 1894 by Townsend[69] as spontaneous external or internal bleeding occurring in newborn infants not due to trauma, accident or inherited bleeding disorders such as haemophilia. Previously, there were no generally agreed upon criteria to determine causes of haemorrhaging, so any diagnosis was based solely on the opinion of the attendant medical personnel.

Infants are born with low levels of vitamin K[23] compared to adults and this is termed 'vitamin K deficiency'. Up to 50% of babies develop this 'vitamin K deficiency', but bleeding occurs in only a fraction of these cases.[37] In most it starts after birth, becomes

progressively more severe over 48-60 hours, then spontaneously corrects itself by 72-120 hours.[9]

HDN has always been rare – in Britain where maternity units practised a selective policy of vitamin K administration, the incidence was no more than 1 in 20,000 in the years 1972-80. Estimates for late onset HDN are 4-8 per 100,000.[45] Incidence also seems to vary from country to country.

HDN is divided into three categories:

1. Early onset HDN occurs in the first 24 hours. It is very rare and mainly associated with mothers who have taken anticonvulsant, antibiotic, antituberculous or anticoagulant drugs during pregnancy.
2. Classic HDN occurs in the first week after birth. It is manifested by the oozing of blood from the intestines, the nose, the cord site and broken skin sites. Bruising at sites where there has been no trauma can also appear.
3. Late onset HDN occurs after the first week, with a peak incidence between the second and sixth weeks, and about half the cases present with intracranial bleeding (bleeding into the brain).

WHAT ARE THE RISK FACTORS FOR HDN?

There has been some debate over the years as to whether or not HDN is actually caused by vitamin K deficiency. Certainly, giving vitamin K does arrest bleeding in the majority of cases, but this does not mean that vitamin K deficiency causes HDN. One may as well say that an antibiotic deficiency causes bacterial infection. There is also no consensus as to what level of vitamin K in plasma protects against HDN. Some researchers have found no evidence of vitamin K deficiency in babies in their studies[43, 49] and other factors have also been suggested.[52, 73, 74]

Most, if no all, of the reported cases of late onset HDN have presented with problems which affect the baby's ability to absorb or utilise vitamin K.[45, 56] These include: hepatitis, cystic fibrosis, chronic diarrhoea, bile duct atresia, alpha-1-antitrypsin deficiency, coeliac disease of insufficient plasma transport capacity. Subclinical cytomegalovirus has also been implicated. Vitamin K-responsive bleeding syndrome has been well documented after antibiotic therapy, especially with cyclosporins.[33]

There are other factors which place the newborn at higher risk. These include pre-term birth (as the liver is very immature), low birth weight, instrumental or traumatic delivery, bruised or bleeding in the first few days after birth, requiring surgery or circumcision, taking inadequate feeds and breastfeeding.[33]

BREASTFEEDING – WHY IS IT A RISK?

Several authors have noted the higher incidence of HDN in solely breastfed babies.[9, 30] The incidence has been quoted as 1 in 1200.[30] Studies comparing breastmilk with formula and cow's milk have shown that breastmilk is lower in vitamin K.[22, 28, 32] Breastmilk substitutes are heavily supplemented with vitamin K, however, it is possible that, like iron, vitamin K is biologically more available to the baby from breastmilk, and so such high levels are not necessary.

Measured levels of vitamin K in breastmilk seemed to vary depending on the type of measurement used; however, they all come out lower than cow's milk. Fournier[22] and Greer[28] found levels of around 8-9μg/l, which would mean that if a baby was taking in about 500ml per day, it would be getting the recommended 3-5μg daily.

Vitamin K content and availability are greater in the hind milk because of its higher fat content and vitamin K levels are also higher in colostrum.[32] As an extra plus, breastmilk contains thromboplastin, one of the factors in blood clotting.[18]

Vitamin K levels in the breastmilk rise markedly in response to the mother eating vitamin K rich foods or taking vitamin K supplements.[29, 54] Nishiguchi found no cases of low vitamin K levels in breastfed infants whose mothers had been given supplements, as opposed to infants who had only been given 1 or 2 doses of oral vitamin K.[54]

Unrestricted access to the breast in the early days after birth is important, due to the higher levels of vitamin K in colostrum. The importance of early feeding has been recognised since the 1940's. Babies who have been fed within their first 24 hours have significantly better coagulation times than babies not fed until after 24 hours.[24]

It is essential that, to receive the full complement of vitamin K in breastmilk, the baby completely finishes one breast before being offered the other. Any practice that involves restricting either the baby's time at the breast or the number of feeds will not allow the baby to receive optimum amounts of vitamin K and will also prolong the time it takes for the baby's intestine to be colonised by friendly, vitamin K manufacturing bacteria.

<u>THE HISTORY OF VITAMIN K USE TO PREVENT HDN.</u>

The search for the cause of HDN began in 1913 when Whipple[82] postulated that a lack of prothrombin activity could be a cause of HDN. In 1929, Henrik Dam[14] noticed that chicks fed a fat-free diet suffered subcutaneous and intramuscular haemorrhages, which could be prevented if the chicks were fed seeds, cereals and green, leafy plants. Dam described the condition as a vitamin deficiency and named the deficient vitamin 'vitamin K', from the Danish word 'koagulation'.

Research in 1937[8] found that prothrombin times in normal neonates were between 30-60% adult levels, falling to 15-30% on day two, and then gradually rising again until about day 10. This research led to the continuing belief that these low levels in the newborn are a deficiency and need to be corrected.

In 1939, vitamin K_1 was isolated from alfalfa by Dam, for which he later received the Nobel Prize, along with Edward Doisy, who isolated vitamin K_2.[45] Further research in 1939 by Waddell and Guerry[81] found that low plasma prothrombin levels could be elevated by the administration of oral vitamin K.

Armed with this 'proof' that vitamin K deficiency caused HDN, vitamin K was synthesised and various trials were commenced

to ascertain which was the most effective amount and route to use in prophylaxis.

It is difficult for us to assess these trials nowadays as they were mostly neither double blind nor well controlled. The dosage of vitamin K given, the route of administration and the time of administration all varied. In many cases, the conclusions did not seem to match the results.[72]

Some of the studies assessed the effect on neonatal vitamin K levels if the mother was given vitamin K during labour.[72] Results varied, with the effectiveness of the vitamin K given depending on how soon the woman gave birth and the dosage given. More recent studies have shown increases in cord blood levels where mothers were supplemented antenatally with vitamin K.[1, 66] Two showed a significant difference between the supplemented and unsupplemented groups and found that the effect of prenatal vitamin K persisted until the fifth day after birth.[1]

Because of the variations in results from these early studies, further research focussed on treating the baby after birth. One particular study done in 1942[31] was intended to determine the minimal effective

oral dose of Synkavite (K_3), a water-soluble synthetic form of vitamin K. The results showed that very small daily doses were effective and that a dose of 5μg daily would probably prevent the development of HDN, except in early onset cases. The study also found that 1.25mg was effective in lowering an excessively high prothrombin time to normal. However, the author admitted that several workers found prothrombin deficiencies in babies with no abnormal bleeding.

By 1950, most maternity units had a policy of giving infants oral vitamin K (usually Synkavite) immediately after birth.[70] This prevented the fall in prothrombin levels that occurred in the first few days and, presumably, the risk of excessive bleeding. This risk was higher in male babies because of routine circumcision, and, indeed, vitamin K proved to be of great clinical value in preventing post-circumcision bleeding.[75]

Then, in the mid-1950's, reports of increased jaundice and kernicterus (brain damage caused by high bilirubin levels) associated with vitamin K prophylaxis began circulating. Reviews of maternity units found that some were giving Synkavite in doses exceeding 50mg.[70] It was established that high doses of Synkavite caused haemolysis (destruction of red blood cells) and high serum bilirubin levels.[48]

Researchers and medical professionals queried the safety aspects of vitamin K, and there were many conflicting reports on the appropriate dosages. Some researchers queried the need for vitamin K at all, quoting results from studies that showed no difference in prothrombin times or vitamin K plasma levels between babies that bled and babies that didn't.[72]

Eventually, a newer preparation, intramuscular vitamin K1 (phytomenadione), was developed and approved for use, solely on the grounds that it appeared to cause less haemolysis. Phytomenadione (trade names Konakion (Roche) or Aquamephyton (Merck, Sharpe & Dohme)) is a synthetic petrochemical derived from 2-methyl 1,4-naptha-quinone in a polyethoxylated castor oil base.[18] In the US, polysorbate-80 is used as a base instead of polyethoxylated castor oil.[15]

In spite there being no long term trials of these preparations, the American Academy of Pediatrics recommended that phytomenadione be administered prophylactically to all newborn babies.[72] The use of oral vitamin K preparations fell out of favour in the USA and the 'safer' intramuscular route became the route of choice.

In Britain, after the jaundice scare of the1950's, many maternity units began to practice a selective policy, giving vitamin K only to babies at risk of haemorrhaging. McNinch reported in 1980 that less than half the maternity units in the UK gave vitamin K to all newborns.[47] Some of these babies were given oral prophylaxis and some were given intramuscular prophylaxis.

In Germany, almost all newborn infants who required medical care and instrumental deliveries were given intramuscular vitamin K, and some healthy newborns also received it.[76] Records have not always been kept in New Zealand hospitals, so it is impossible to say whether or not vitamin K was given routinely and by which route.[17]

Although vitamin K use seemed to prevent most cases of HDN, there was still controversy. Not everyone believed vitamin K deficiency was the cause of HDN. In 1977, van Doorm et al [52, 73, 74] suggested that HDN could be caused by a heparin-like inhibitor in the newborn and he concluded that babies given their first feed soon after birth do not have a vitamin K deficiency. Other researchers agreed with van Doorn.[49] In 1980, Malia et al[43] could find no evidence of vitamin K deficiency in babies in their study and concluded that low levels of vitamin K dependent clotting factors were due to the immature liver. The authors of these studies questioned whether vitamin K prophylaxis was really necessary for healthy newborns.

Then, starting in November 1980, there was a cluster of six cases of HDN in Britain, all within 17 months.[46] Half of these cases were classic HDN, the other half were a new manifestation of HDN – late onset.

LATE ONSET HDN

Late onset HDN was first reported in 1977.[5] It mainly occurs in breastfed infants and to ¾ of cases have an underlying liver disorder or malabsorption syndrome,[15]

rather than insufficient dietary intake of vitamin K. This means the liver cannot adequately synthesise blood clotting factors or store adequate amounts of vitamin K. Liver function cannot be easily diagnosed at birth without a range of invasive tests and thus there exists an unknown risk of haemorrhaging.

Many factors contribute to poor liver function, including hepatitis, cystic fibrosis, antibiotic therapy, biliary atresia, alpha-1-antitrypsin deficiency, a-beta-lipoproteinaemia, coeliac disease, chronic diarrhoea and exposure to pharmacologic agents such as anticonvulsants, rifampin, isoniazid cephalosporins and coumarin compounds[33] When tested, most of the reported cases of late onset HDN had hepatitis, liver malfunction or enzyme

deficiencies.[6, 35, 51, 80]

Birkbeck[6] believes there are two processes at work – low levels of prothrombin and vitamin K-dependent clotting factors VII, IX and X at birth, and a further fall in these in the neonatal period. In his view the initial low levels are not due to vitamin K deficiency as levels of 2 other non-vitamin K-dependent factors, XI and XII are also often reduced. Thus, the situation at birth may be simply due to hepatic immaturity.

Birkbeck[6] also reports that HDN is almost unknown in central Africa and he suggests an environmental mechanism as the cause. Associated with this, a discussion paper from the University of Amsterdam[42] raises the idea that by-products of our industrial society such as PCBs, PCDDs and PCDFs are the cause of late onset HDN. These chemicals can induce enzymes in the liver which cause liver damage and prolong prothrombin time. Although overseas studies have reported contamination of breastmilk by these pollutants, a NZ Department of Health study on breastmilk reported that levels of these contaminants were at the lower end of the scale.[7] The Health Department is currently conducting another study to see if levels have changed over the past few years.

There seems to be a seasonal variance, with most cases of late onset HDN occurring in the warmer months.[6] It has been suggested that the mother could have contracted a viral infection during pregnancy in the colder months and this has crossed the placenta. Since viruses have an affinity for the liver and mucous membranes, they can affect intestinal absorption and liver function.[67]

Another suggested cause of late onset HDN includes use of the food antioxidant BHT (butylated hydroxytoluene), which has produced vitamin K deficiency.[68] BHT is present in many processed foods, including margarine. Our Western diets consist of a lot of processed food, and to reduce fat intakes, margarine is recommended rather than butter. The polyunsaturated fat in margarine is an inhibitor of vitamin K absorption.[68] Both of these factors could have an effect on the amount of vitamin K available to pass through to the baby. A high level of vitamin K in the mother's blood is necessary to ensure adequate transplacental transfer of vitamin K.[9, 33] It is important for the baby to have adequate stores of vitamin K in its liver at birth to prevent bleeding until its feeding and gut flora are established.

Of the six cases of HDN in Britain in 1980-1982, all were breastfed and none had received vitamin K at birth.[46] Two of the cases were in the high-risk group – one was born by caesarean section and had an epileptic mother treated with phenytoin, and the other had an alcoholic mother who had taken anti-depressants – and obviously should have received vitamin K at birth.

These cases prompted a call for the re-introduction of routine prophylaxis. Many opposed the idea of unnecessarily injecting otherwise healthy babies so studies[40, 47, 55, 79] were therefore conducted to determine whether oral vitamin K was as effective as intramuscular. It was also proposed that oral vitamin K would be more cost-effective and thus better suited for use in Third World countries.[55] Results of these studies varied. Some showed that oral vitamin K was effective in preventing classic haemorrhagic disease but not as effective as intramuscular vitamin K in preventing late onset HDN.[47, 55, 78] Others found oral as effective, especially a 10 year study conducted on 38,000 infants in Sweden where no cases of HDN were observed over that period.[40] Tripp and McNinch reported no cases in 25,000 babies in their maternity

unit where only those at risk were given intramuscular prophylaxis and the rest oral prophylaxis.[70]

In spite of these findings that oral vitamin K prophylaxis was not effective in preventing late onset HDN, it continued to be used in British maternity units, especially for low risk infants.

RISKS OF VITAMIN K PROPHYLAXIS

Konakion ampoules contain phenol, propylene glycol[38] and polyethoxylated castor oil as a non-ionic surfactant. Studies in animals given polyethoxylated castor oil have shown a severe anaphylactic reaction associated with histamine release. Strong circumstantial evidence implicates polyethoxylated castor oil in similar reactions in humans. Polyethoxylated castor oil, when given to patients over a period of several days, can also produce abnormal lipoprotein electrophoretic patterns, alterations in blood viscosity and erythrocyte aggregation (red blood cell clumping). Individuals sensitive to this base are contraindicated from using Konakion. New Ethicals Compendium also warns that the use of Konakion can cause jaundice and kernicterus in infants.[53] Other listed side effects include flushing, sweating, cyanosis, a sense of chest constriction, and peripheral vascular collapse. Local cutaneous and subcutaneous changes may occur in areas of repeated intramuscular injections.

This synthetic, injectable vitamin K formulation was never subjected to a randomised, controlled trial. In new drugs that are to be used for prophylaxis, the usual risk/benefit analysis does not apply, since the individual is not ill. The ethical principle of non-maleficence (primum non nocere – first do no harm) applies and the trials must thus be larger in order to identify any previously unrecognised side effects.[65] Since this did not happen, nor was there any long term follow up, we actually have little idea of the effects of this drug on newborn babies.

The risks of injecting vitamin K into a newborn baby are nerve or muscle damage as the preparation must be injected deeply into the muscle, not subcutaneously under the skin. There is also the documented risk of injecting the baby with the syntocinon intended for the mother.[30, 70] As stated in the product information,[53] infants can suffer from jaundice or kernicterus (brain damage from a build-up of bile pigments in the brain) from Konakion. Infants who have the enzyme deficiency G6PD (glucose 6 phosphate dehydrogenase) are at particular risk from vitamin K.[30] The other risk factor is the possible increased chance of childhood cancer.

THE LINK BETWEEN CHILDHOOD CANCER AND INTRAMUSCULAR VITAMIN K

In 1970, a national cohort study of 16,193 infants born in one week in April was begun in Britain.[26] This study was to test

hypotheses about childhood cancers and their associated factors. Thirty-three of the children had developed cancer by age 10 and were compared with 99 control children, matched on maternal age, parity and social class. One of the unlooked-for risk factors was the administration of prophylactic drugssuch as vitamin K in the first week after birth – a nearly three-fold risk. This association fitted no prior hypothesis and the authors recommended that their finding be tested in another series of cases.

The authors of the study approached Roche, the manufacturers of Konakion, for funding for a further trial to examine the findings more closely. Roche was not interested until, a few months later, the media reported the results of the study and that vitamin K given to babies might cause childhood cancer. Roche then decided to fund a new study.[27]

The new study[25] was a case-control study of 195 children with cancer born at either of two hospitals in Bristol, England, compared with 588 healthy children also born at these hospitals. One hospital predominantly gave vitamin K orally and the other intramuscularly. The authors found a nearly two-fold risk of leukaemia in children who had received intramuscular vitamin K.

These findings were extremely worrying. Golding calculated that the extra cases of leukaemia caused by vitamin K injection could be as many as 980 in the UK alone.[25] These results were supported by reports of the potential carcinogenicity of vitamin K from Israels et al, who suggested that low vitamin K levels in the newborn protect

against the risk of mutations during a period of rapid cell growth and division.[39] Pizer et al did not find any association between the route of vitamin K administration and mutations in cells but concluded that his study was too small to show any real effect.[62] Another study reported no increase in abnormalities in newborn infants, but, with only 12 infants, the study was too small to show any real effect.[10] It is worth noting that after an intramuscular dose of vitamin K, the baby's plasma levels are almost 9000 times the normal adult levels.[47] It has also been suggested that the cancer-causing agent could be a metabolite, N-epoxide, or some other component of the solution other than vitamin K itself.[15]

Golding's study was criticised by many. One of the reasons was that the authors had to make assumptions for some cases, as the information on vitamin K administration was not clearly recorded. In spite of this, expert epidemiologists considered that the results were plausible and so could not be lightly dismissed.[15] Further studies were proposed to answer the question of cancer and vitamin K.

In 1993, results from three retrospective studies on vitamin K and childhood cancer were published. The studies were done in the USA, Denmark and Sweden.[41, 57, 19] These studies, although large, did not confirm the association between intramuscular vitamin K and childhood cancer. One of the studies not only showed no association between IM vitamin K and childhood cancer, it also showed no association between maternal smoking and childhood cancer, a finding totally at odds with the results from many other studies.[19] The other two studies were also not comparable to the British study. One because of differences in type of vitamin K given[41] and the other because of the use of birth cohorts with differing regimens of vitamin K usage.[57]

Because of the design flaws in these studies, there was still a need for further case-control studies. Results from two were published in 1996.[2, 77] They had carefully matched controls and more accurate information on whether vitamin K had been given or not, and by which route. One of the studies[2] reported no association between intramuscular vitamin K and childhood cancer and the other[77] found a risk of leukaemia, but only when cases were compared with local controls (i.e. from the same hospital) and not with controls randomly selected from the whole area under study. This, although suggestive, was not followed up but dismissed as a chance finding related to multiple testing.

The suggestion was then put forward that, as these studies had failed to show a definite association between intramuscular vitamin K and childhood cancers, worries about any potential cancer risk should be abandoned.[83]

At that time, four more studies on vitamin K and cancer were in progress.[44, 59, 60, 61] The results from these four studies were published in 1998. Two of them failed to confirm any increased risk of childhood cancers.[44 61] One of the other studies showed a twofold risk of acute lymphoblastic leukaemia among 1-6 year olds,[59] the other showed a significant risk for all cancers.[60]

So, the jury is still out on whether there is an increased risk of childhood leukaemia with the intramuscular form of vitamin K. Some recommend that intramuscular vitamin K should still be used, as the risk of leukaemia "seems more hypothetical than real".[76] Others believe that public confidence in IM vitamin K has been severely shaken and will be difficult to restore fully. They recommend an oral regimen similar to that used in the Netherlands of 25μg daily, given by the mother. This would avoid the grossly unphysiological peaks of vitamin K from both the IM route and the present oral route.[71]

ORAL VITAMIN K VS INTRAMUSCULAR

The two main problems with giving vitamin K orally are that there is no licensed oral formulation, meaning that babies receive the intramuscular form orally, and that compliance with three oral doses is poor as many doctors and midwives are reluctant to give an unlicensed formula.[13] The use of unlicensed preparations may theoretically expose professionals to litigation in the event of prophylactic failure or unforeseen adverse events.[2]

Roche, the manufacturers of Konakion, state that they do not recommend the

administration of Konakion solution orally.[63] Their reasons are:

- that they have no clinical studies to support oral use,
- phenol, which has been reported to be an irritant to newborns mouths, is used as a preservative,
- the variability in the production of bile salts in newborns may affect absorption,
- that Konakion given orally has a small association with anaphylactic reactions.

The preparation was also unpleasant to taste and babies were inclined to spit it out[82] or to vomit it back up. Only about half of an orally administered dose is absorbed.[47] Even so, the plasma concentrations in babies who were given oral vitamin K reached 300 times the adult levels, before dropping off slightly after about 24 hours.[47]

After the publication of Golding's studies, further trials were done on oral vitamin K prophylaxis and whether it gave longer term protection. In 1992, Cornelissen[11] found plasma vitamin K concentrations were higher in the group given IM vitamin K than the oral group, but blood coagulability, activities of factors VII, X and PIVKA-II concentrations showed no differences. By 3 months follow-up, vitamin K levels had dropped in both groups but more in the oral group. He suggests that neither give long term protection. One would assume that babies should be producing their own vitamin K by 3 months and, if not, what other mechanism could be hindering this process.

Von Kries et al[78] studied repeated oral vitamin K prophylaxis in Germany, with 3x 1 mg doses and found that it was not as effective as a 1mg intramuscular dose at birth. Another study by Cornelissen et al[12] reported on the effectiveness of differing regimens of oral vitamin K in four different countries – the Netherlands, Germany, Switzerland and Australia (two differing regimes). In the Netherlands, babies are given 25 μg daily oral vitamin K for 3 months with I mg given at birth either orally for healthy newborns or intramuscularly for unwell babies. In Germany, the regime is 3 x 1 mg oral doses as was also the case in Australia from 1993 to 1994. In Switzerland 2 oral doses of a new 'mixed-micellar' oral vitamin K is given. The Netherlands had the lowest failure rate – 0 per 100,000. In Australia, where the regime was changed in 1994 from oral to IM, the failure rate was 1.5 per 100,000 for oral and 0.9 per 100,000 for IM, showing that 3 oral doses are less effective at preventing late onset HDN than one IM dose of vitamin K. Even if Roche are persuaded to bring the mixed-micellar preparation into New Zealand, results from Switzerland (failure rate of 1.2 per 100,000)[12] show that further study needs to be done on the most effective timing of the doses.

If New Zealand parents wish their baby to receive oral vitamin K, the recommended regimen is for 3 x 1mg doses, 1 at birth, 1 at 5 days and 1 at 6 weeks.[6, 20] It is up to parents to ensure that their baby receives all 3 doses if they choose this form of prophylaxis.

CONCLUSION

It would seem an anachronism that babies are born with a deficiency of such an essential vitamin and require supplementation. In fact, although there have been many studies on differing aspects of vitamin K prophylaxis, there has only been one[39] on the possible reasons for and the advantages (if any) of the physiological levels of vitamin K in newborns.

The risks of prophylaxis for the majority of babies who are at low risk of HDN are also not understood. As plasma vitamin K levels in newborns reach 300 times normal adult levels for oral and almost 9000 times for IM vitamin K[47], some research needs to be done on the effects this may have. Studies have shown that physiological levels of vitamin K maintain a careful balance between coagulation and anti-coagulation and we have no idea what the effects of upsetting that delicate balance would be.

The number of children currently developing cancer during childhood is much higher than the number developing a life threatening or permanently disabling problem as a result of late onset HDN. The risk of childhood cancer is estimated to be 1.4 per 1000, from the 1970 British cohort. If IM vitamin K caused cancer, there would be 100 extra cases of cancer per case of

HDN prevented.[16] This could mean that giving IM vitamin K to every baby would be doing more harm than good.[36]

The decision rests on parents' shoulders – the link between intramuscular vitamin K and childhood cancer has not been definitively proved, nor has it been completely disproved. It may be that an oral regimen as suggested by Tripp and McNinch[71] could be the answer to the dilemma. If this is the case, then Roche needs to be lobbied to make the European preparations available in New Zealand. In the meantime, the choice is between no vitamin K, with the mother being aware of her dietary intake of vitamin K, an oral regimen or the intramuscular formulation.

BIBLIOGRAPHY

1. Anai T, Hirota Y, Yoshimatsu J et al. Can prenatal vitamin K_1 supplementation replace prophylaxis at birth? Obst Gynec 1993;81:251-4.
2. Ansell P, Bull D and Roman E. Childhood leukaemia and intramuscular vitamin K: findings from a case-control study. BMJ 1996;313(7051):204-5.
3. Barton J, McNinch A. and Tripp J. Oral vitamin K prophylaxis and frequency of late vitamin K deficiency bleeding (letter). Lancet 1994 343(8906):1168.
4. Barton J, Tripp J. and McNinch A. Neonatal vitamin K prophylaxis in the British Isles: current practice and trends. BMJ 1995; 310(6980):632-3.
5. Bhanchet P, Tuchinda S, Hathirat P et al. A bleeding syndrome in infants due to acquired prothrombin complex deficiency. Clin Pediatr 1977;16:992 in, Hathaway W. New insights on vitamin K. Hematol Oncol Clin North Am 1987;1(3):367-379.
6. Birkbeck J. Vitamin K prophylaxis in the newborn: a position statement of the Nutrition Committee of the Paediatric Society of New Zealand. NZMJ 1988;101:421-2.
7. Birkbeck J. Despite the contamination breastmilk remains the best. NZ Doctor July 1990.
8. Brinkhous K, Smith H and Warner D. Plasma prothrombin level in normal infancy and in hemorrhagic disease of the newborn. Am J Med. Sci 1937;193:475-479 in, Ruby C. Vitamin K prophylaxis: a historical perspective. MIDIRS;7:3.
9. Clarkson P and James A. Parenteral vitamin K1: the effective prophylaxis against haemorrhagic disease for all newborn infants. NZMJ 14 March 1990.
10. Cornelissen M, Smeets D, Merkx G et al. Analysis of chromosome aberrations and sister chromatid exchanges in peripheral blood lymphocytes of newborns after vitamin K prophylaxis at birth. Pediatr Res 1991;30:550-3.
11. Cornelissen EAM, Kollée LAA, DeAbreu RA et al. Effects of oral and intramuscular vitamin K prophylaxis on vitamin K, PIVKA-II, and clotting factors in breastfed infants. Arch Dis Child 1992;67:1250-54.
12. Cornelissen M, von Kries R, Loughnan P et al. Prevention of vitamin K deficiency bleeding: efficacy of different multiple oral dose schedules of vitamin K. Eur J Ped 1997;156(1):126-30.
13. Croucher C. and Azzopandi D. Compliance with recommendations for giving vitamin K to newborn infants. BMJ 1994;308(6933):894-895.
14. Dam H, Dyggve H, Larsen H and Plum P. The relationship of vitamin K deficiency to hemorrhagic disease of the newborn. Adv Pediatr 1952;5:129-153 (abstract).
15. Darlow B. Vitamin K deficiency haemorrhage: dilemmas over prophylaxis continue. NZ Practice Nurse February 1995:35-37.
16. Darlow B. and Nobbs P. The neonatal vitamin K debate: IM vs. oral: two views. New Ethicals May 1993:11-18.
17. Dockerty J, Broadbent R and McNoe B. New Zealand hospital records insufficient for vitamin K study. NZMJ 10 May 1995.
18. Donley J. Vitamin K in relation to haemorrhagic disease of the newborn. NZCOM Journal December 1992.

19. Ekelund H, Finnstrom O, Gunnarskog I. et al. Administration of vitamin K to newborn infants and childhood cancer. BMJ 1993;307(6896):89-91.
20. Fetus and Newborn Committee of the Paediatric Society of New Zealand. 1992. Vitamin K administration in the newborn.
21. Foetus and Newborn Society, Canadian Pediatric Society. The use of vitamin K in the perinatal period. Canad MAJ 1988;139:127-130.
22. Fournier B, Sann L, Guillaumont M and Leclerq M. Variations of phylloquinone concentrations in human milk at various stages of lactation and in cow's milk at various seasons. Am J Clin Nutr 187;45:551-8.
23. Garrow D, Chisholm M. and Radford M. Vitamin K and thrombotest values in full term infants. Arch Dis Child 1986;61:349-51.
24. Göbel U, Sonnenschein-Kosenow S, Petrich C and von Voss H. (Letter). Lancet 1977;i:187-8.
25. Golding J, Greenwood R, Birmingham K. et al. Childhood cancer, intramuscular vitamin K and pethidine given during labour. BMJ 1992;305 (6849):341-6.
26. Golding J, Paterson M and Kinlen L. Factors associated with childhood cancer in a national cohort study. Brit. J Cancer 1990;62:304-8.
27. Greenwood R. Vitamin K and childhood cancer. MIDIRS 1994;4(3):258-9.
28. Greer F, Marshall S, Cherry J and Suttie J. Vitamin K status of lactating mothers, human milk, and breast-feeding infants. Pediatrics 1991;88(4);751-6.
29. Greer F, Marshall S, Foley A et al. Improving the vitamin K status of breastfeeding infants with maternal vitamin K supplements. Pediatrics 1997;99(1);88-92.
30. Hall M. and Pairaudeau P. The routine use of vitamin K in the newborn. Midwifery 1987;3(4):170-7.
31. Hardwicke S. et al. Studies on the minimal effective dose of a water-soluble vitamin K substitute in the prevention of hypoprothrombinemia in the newborn infant. J Pediatr 1944;24:259-269 (abstract).
32. Haroon Y, Shearer M, Rahim S et al. The content of phylloquinone (vitamin k_1) in human milk, cow's milk and infant formula foods determined by high performance liquid chromatography. J Nutr 1982;112:1105-17.
33. Hathaway W. New insights on Vitamin K. Hematol Oncol Clin North Am 1987;1(3):367-379.
34. Henderson-Smart, D. Giving vitamin K to newborn infants: a therapeutic dilemma. MJA 1996;165:414-5.
35. Heron P, Cull A., Bourchier D and Lees H. Avoidable hazard to New Zealand children: case reports of haemorrhagic disease of the newborn. NZMJ 1988;101:507-8.
36. Hey, Edmund. Vitamin K – the debate continues. MIDIRS 1998;8(2):234-6.
37. Hilgartner, M. Vitamin K and the newborn. New Eng J Med 1993;329(13):957-8.
38. Hull D. Vitamin K and childhood cancer. BMJ 1992;305:326-7.
39. Israels I, Friesen E., Jansen A. and Israels E. Vitamin K1 increases sister chromatid exchange in vitro in human leukocytes and in vivo in fetal sheep cells: a possible role for 'vitamin K deficiency' in the fetus. Pediatr Res 1991;30:550-3.
40. Jorgensen F, Fielding P, Vinther S et al. Vitamin K to neonates. Peroral versus intramuscular administration. Acta Pediatr Scand 1991;80(3):304-7.
41. Klebanoff M, Read J, Mills J. et al. The risk of childhood cancer after neonatal exposure to vitamin K. New Eng J Med. 1993;329(13):905-8.
42. Koppe J, Pluim E and Olie K. Breastmilk, PCBs, dioxins and vitamin K deficiency: discussion paper. J Royal Soc. Medicine 1989;82:416-419 in, Donley, Joan. Vitamin K in relation to haemorrhagic disease of the newborn. NZCOM Journal Dec 1992.
43. Malia R, Preston F and Mitchell V. Evidence against vitamin K deficiency in normal neonates. Thromb Haemost 1980;44:159.
44. McKinney P, Juszczak E, Findlay E, Smith K. Case-control study of childhood leukaemia and cancer in Scotland: findings for neonatal intramuscular vitamin K. BMJ 1998;316:173-7.
45. McNinch A and Tripp J. Haemorrhagic disease of the newborn in the British Isles: a two year prospective study. BMJ 1991;303(6810):1105-1109.
46. McNinch A, Orme R and Tripp J. Haemorrhagic disease of the newborn returns. Lancet 1983;i:1089-90 (abstract).
47. McNinch A, Upton C, Samuels M et al. Plasma concentrations after oral or intramuscular vitamin K1 in neonates. Arch Dis Child 1985;60:814-818.
48. Meyer T and Angus J. The effect of large doses of Synkavit in the newborn. Arch Dis Child 1956;31: 212-5 in, Ruby, C. Vitamin K: a historical perspective. MIDIRS 1997;7(3):362-4.
49. Mori P, Bisogni C, Odino S et al. (letter). Lancet 1977;ii:188.
50. Motohara K, Endo F and Matsuda I. Screening for late neonatal vitamin K deficiency by acarboxyprothrombin in dried blood spots. Arch Dis Child 1987;62:370-375.
51. Motz R. Late haemothorax after oral vitamin K. NZMJ 11 November 1992:459.
52. Muller A., van Doorm J and Hemker H. Heparin-like inhibitor of blood coagulation in normal newborn. Nature 1977;267:616-7.
53. New Ethicals Compendium; 3c: 303-304.
54. Nishiguchi T, Saga K, Sumimoto K. et al. Vitamin K prophylaxis to prevent neonatal vitamin K deficient intracranial haemorrhage in Shizuoka prefecture. Brit J Obstet Gynec 1996;103 (11):1078-84.
55. O'Connor M. and Addiego J. Use of oral vitamin K1 to prevent hemorrhagic disease of the newborn infant. J Pediatr 1986;108:616-9.
56. O'Connor M, Livingstone D, Hannah J. and Wilkins D. Vitamin K deficiency and breastfeeding. Am J Dis Child 1983;137:601-2
57. Olsen J, Hertz H, Blinkenberg K. et al. Vitamin K regimens and incidence of childhood cancer in Denmark. BMJ 1994;308(6933):895-6 in, Greenwood, R. Vitamin K and childhood cancer. MIDIRS 1994;4(3):258-260
58. Olson J. Recommended dietary intakes (RDI) of vitamin K in humans. Am J Clin Nutr 1987;45:687-92.
59. Parker L, Cole M, Craft A, Hey E. Neonatal vitamin K administration and childhood cancer in the north of England: retrospective case-control study. BMJ 1998;316:189-93.

60. Passmore S, Draper G, BrownbillP, Kroll M. Case-control studies of relation between childhood cancer and neonatal vitamin K administration: retrospective case-control study. BMJ 1998;316:178-84.
61. Passmore S, Draper G, BrownbillP, Kroll M. Ecological studies of relation between hospital policies on neonatal vitamin K administration and subsequent occurrence of childhood cancer. BMJ 1998;316:184-9
62. Pizer B, Boyse J, Hunt L. and Mott M. Neonatal vitamin K administration and in vivo somatic mutation. Mutat Res 1995;347:135-9.
63. Roche Products Ltd. Position statement re: Konakion injection given orally.
64. Roche Products Ltd. New oral vitamin K formulation for newborns (press release). Welwyn Garden City, 30 Aug 1996.
65. Ruby Christine. Vitamin K prophylaxis: a historical perspective. MIDIRS 1997;7(3):362-4.
66. Shearer M. et al. Plasma vitamin K1 in mothers and their newborn babies. Lancet 1982:460-3 in, Hathaway, W. New insights on vitamin K. Hematol Oncol Clin North Am 1987;1(3):367-379.
67. Stevenson, J. The vitamin K conundrum. Maternity Alliance Action Newsletter July/August 1992.
68. Suzuki H, Nakao T and Hiraga K. Vitamin K deficiency in male rats fed diets containing butylated hydroxytoluene (BHT). Toxicol Appl Pharmacol 1979;50:261-6 in, Birkbeck J. Vitamin K prophylaxis in the newborn: a position statement of the Nutrition Committee of the Paediatric Society of New Zealand. NZMJ 1988;101:421-2.
69. Townsend C. The hemorrhagic disease of the newborn. Arch Pediatr 1894;11:559-562 in, Birkbeck J. Vitamin K prophylaxis in the newborn: a position statement of the Nutrition Committee of the Paediatric Society of New Zealand. NZMJ 1988;101:421-2.
70. Tripp J. and McNinch A. Haemorrhagic disease and vitamin K. Arch Dis Child 1987;62:436-7.
71. Tripp J and McNinch A. The vitamin K debacle: cut the Gordian knot but first do no harm. Arch Dis Child 1998;79:295-299.
72. Vail, B. Vitamin K prophylaxis and hemorrhagic disease of the newborn. ICEA Review 1985;9(3).
73. Van Doorm J and Hemker H. Vitamin K deficiency in the newborn (letter). Lancet 1977;ii:708-9.
74. Van Doorm J, Muller A. and Hemker, H. Heparin-like inhibitor, not vitamin-K deficiency, in the newborn (letter). Lancet 1977;i:852-3.
75. Vietti T, Murphy T, James J and Pritchard J. Observations on the prophylactic use of vitamin K in the newborn. J Pediatr 1960;56(3);343-6 (abstract).
76. Von Kries R. Neonatal vitamin K prophylaxis: the Gordian knot still awaits untying. BMJ 1998;316 (7126):161.
77. Von Kries R, Göbel U, Hachmeister A. et al. Vitamin K and childhood cancer: a population based case-control study in Lower Saxony, Germany. BMJ 1996;313(7051):199-203.
78. Von Kries R, Hachmeister A and Göbel U. Repeated oral vitamin K prophylaxis in West Germany: acceptance and efficacy. BMJ 1995;310 (6987):1097-8.
79. Von Kries R, Kreppel S, Becker A, Tangermann R and Göbel U. Acarboxyprothrombin activity after oral prophylactic vitamin K. Arch Dis Child 1987;62: 938-40.
80. Von Kries R, Shearer M and Göbel U. Vitamin K in infancy. Eur J Pediatr 1988;147:106-12.
81. Waddell W. and Guerry D. The role of vitamin K in the etiology, prevention and treatment of hemorrhage in the newborn infant. J Ped 1939;15:802 in, Ruby, C. Vitamin K prophylaxis: a historical perspective. MIDIRS 1997;7(3):362-4.
82. Whipple G. Hemorrhagic disease; antithrombin and prothrombin factors. Arch Intern Med. 1913;12:637-641 in, Birkbeck, J. Vitamin K prophylaxis in the newborn: a position statement of the Nutrition Committee of the Paediatric Society of New Zealand. NZMJ 1988;101:421-2.
83. Zipursky A. Vitamin K at birth. BMJ 1994;313(1051):179-180.