Policies for giving babies vitamin K prophylactically at birth have been dictated, over the last 60 years, more by what manufacturers decided on commercial grounds to put on the market, than by any informed understanding of what babies actually need, or how it can most easily be given. By a pure fluke a 1 mg IM dose, designed to prevent early vitamin deficiency bleeding (“haemorrhagic disease of the newborn”) has been found to protect against late deficiency bleeding—a condition unrecognised at the time this policy took hold. Alternative strategies for oral prophylaxis are now opening up (see pp 109 and 113), but these are also, at the moment, dictated more by what the manufacturers choose to provide than by what would make for ease of delivery either in poor countries, or in the developed world.

Vitamin K is a fat soluble vitamin, and the development of a suitable commercial formulation for clinical use has long presented something of a challenge. Indeed, when it was first shown in 1939 that treatment with vitamin K could abolish symptomatic prothrombin deficiency in the first week of life, babies were generally given menadione, a water soluble analogue. A paper in the Lancet in 1944 generated widespread interest. It showed a five fold reduction in death from haemorrhage 2–8 days after birth when all babies were given 1 mg of oral menadione at delivery in Göteborg, Sweden, in 1940. A similar policy was soon widely adopted elsewhere even though many were unable to replicate these findings. The argument, as Ethel Dunham put it in 1948, was that “since the vitamin does no harm and may do good, it is probably best to give it to all premature infants immediately after birth”.

When this did not stop some babies from developing a bleeding tendency, or dying with an intraventricular haemorrhage, physicians started using larger and larger doses. Prothrombin levels are always relatively low at birth by adult standards, and remain so for some time, and it was (wrongly) thought that the low level seen at birth, and not just the further postdelivery drop, must be due to relative fetal vitamin K deficiency. By 1953 came a first report that high dose use could cause haemolytic anaemia, and by 1956 it had been established that this could, in turn, cause severe jaundice and even death from kernicterus after unbound bilirubin entered the brain. The dose administered was cut back after that but, within five years, the water soluble product (Synkavit®) was starting to be replaced by the natural, fat soluble, plant form of vitamin K (phyloquinone; vitamin K1). This product did not seem to cause haemolysis, and it is this product that has dominated the market in Europe and North America ever since, although menaquinone-4 (a member of the K2 series) remains the main product still used in Japan.

Routine prophylaxis soon became the norm for every baby (not just every preterm baby) in some countries. Intramuscular prophylaxis also became the route universally adopted, mainly because manufacturers never got round to licensing a product for oral use. It also became routine to give a 1 mg injection, even though this was a thousand times more than the dose of menadione needed each day, and 10 times the dose used in the only controlled trial of clinical efficacy ever conducted. Reluctance to advocate universal use persisted however, especially in the UK where most of the cases of kernicterus due to excessive dosage had been reported. There was also growing uncertainty as to just how common the condition really was. As a result it became increasingly common to only treat babies considered “at risk”—mostly preterm babies and babies having an operative delivery (a policy that gained increased credence and spread even more widely as a result of an influential editorial in the Lancet in 1978).

Spontaneous bleeding, in the absence of trauma, was seldom seen during the next decade, either in units that opted for universal or for selective prophylaxis, and those cases that did occur were quickly spotted and controlled. Most presented with dark melaena stools, bloody vomit, nose bleed, blood stained urine, or bleeding from the umbilical stump, two to six days after birth. Circumcision before seven days brought many cases to light in cultures where this ritual remained common. Presentation was much the same in countries where prophylaxis is not generally available, although here the babies risked death from blood loss. Then another paper appeared in the Lancet describing a resurgence of the condition in the UK not just in the first week of life but also in older babies. These were healthy children with a generalised bleeding tendency that responded promptly to treatment with vitamin K but where, typically, no abnormality had been suspected until there was a catastrophic intracerebral bleed two to 10 weeks after birth. It soon became clear that such problems were only being seen in breast fed babies who had never had even a few “complementary” feeds of bottle milk, and who had never received intramuscular vitamin K. Quite rapidly the previous policy of selective prophylaxis gave way to a policy of universal prophylaxis—the same policy as that long advocated in north America—although a growing number of units...
Vitamin K remains less clearly defined. It was nearly twice as common as late bleeding in breast fed babies offered no prophylaxis in the UK in 1988–89, and three times as common in a recent Malaysian study. It has also become clear that oral prophylaxis can be as reliable as intramuscular prophylaxis (for further evidence relating to this statement see the web site: www.bmjpp.co.uk/books/neonatalformulary/chapters/vkitch2comment.htm). What matters here is not so much the total dose given as the need for the dose regime to allow for the fact that natural body stores are low and turnover is rapid (a realisation that reinforces the suggestion that the solitary large intramuscular dose traditionally given at birth functions as a low release “deposit” or store). Even parents of breast fed babies might be reassured that the recommended dose is limited (1 μg/kg), and the turnover time is only 1–2 days. Low dose daily “drops” would be the most physiological option, but no commercial company has yet shown an interest in such a product.

Recent studies have certainly not provided any support for the belief that vitamin deficiency bleeding is commoner in preterm babies. Although prothrombin levels are lower than in term babies at birth, giving vitamin K does not cause a rise. Neither is bleeding commoner in babies undergoing operative delivery. However babies who are not fed at birth are certainly at increased risk, since all have low vitamin K stores at delivery, and milk provides their only source of vitamin K until bacterial activity in the gut starts to provide a secondary source. Bottle fed babies are at almost no risk because almost all these milks are artificially fortified. The babies of mothers on some anticonvulsants are also at risk, but such bleeding can occur at any time in the first 2–3 days of life. 

Further studies have also been done into the suggestion that intramuscular prophylaxis could be associated with a higher incidence of cancer in later childhood. The most informative of these were six studies that compared such children with others, matched both for date and either place or hospital of birth, who never developed cancer. A pooled analysis of these data, commissioned by the UK Department of Health in 1998, finally appeared last year: 2431 children developing cancer before 15 were compared fresh with 6338 controls matched for sex and year (but not place) of birth. The result analysis confirms that solid tumours are certainly no commoner in children given intramuscular vitamin K at birth. The situation with regard to childhood leukaemia is less clear and, since almost every baby now gets prophylaxis in some form or other, is unlikely to be clarified by the collection of further data. The increased risk, if real, is small (unadjusted odds ratio 1.25; 95% CI 1.06 to 1.46), and could be due to the fact that those selected for prophylaxis (because of prematurity, operative delivery or the like) were already more at risk of later cancer for some unknown reason. Interpretation also depends on whether you believe that staff followed unit policy with regard to prophylaxis, as they claim, even where there is no proof of this in those records that do still exist (for further evidence relating to this statement see above website commentary). It has certainly proved difficult to prove that no risk exists. Only a controlled trial could ever resolve the residual uncertainty, and this would have to be quite unrealistically large.

For nearly 40 years now clinicians have been using a fat soluble form of vitamin K (phytomenadione) dispersed in a polyethoxylated oil or in polysorbate 80 with either propylene glycol (Konakion®) or benzyl alcohol (AquaMEPHYTON®), and giving this product uneventfully at birth to prevent vitamin K deficiency bleeding. However intravenous use in adults has occasionally been associated with severe anaphylaxis, possibly due to the polyethoxylated castor oil triggering histamine release. As a result, Roche finally brought out a new colloidal product, solubilised with lecithin and a bile salt (glycocholic acid), in 1996, and started to phase out their former..
product. Little was known about the new mixed micellar product (Konakion MM®) when it first became available, but it did seem to be better absorbed when given by mouth.1 2 Roche therefore sought and obtained a licence for oral use in Europe. However, it only has a license for the prevention of “haemorrhagic disease of the newborn.”

Roche have now established, with some precision, the earlier European product it replaced, even though it had been awarded a licence for oral use in Europe. However, it only has a license for the prevention of “haemorrhagic disease of the newborn.”

Both these risks can be virtually eliminated by given a single 1 mg intramuscular “depot” injection of vitamin K, or by giving the baby 0.25 mg orally once a week for the first three months of life. Indeed, the only babies not protected by four 1 mg (or three 2 mg) oral doses of “Synkavit” in the newborn.


The manufacturers have been resisting calls for an oral product (Konakion MM®) when it first became available, but it did seem to be better absorbed when given by mouth.1 2 Roche therefore sought and obtained a licence for oral use in Europe. However, it only has a license for the prevention of “haemorrhagic disease of the newborn.”

CONCLUSION

So what have we learnt in the last 64 years? That babies have very limited reserves of vitamin K at birth, and that some will soon bleed if a continuing intake is not guaranteed. We also know that a few “supplements” of cows milk or formula milk can suffice to restock those reserves, and that is really no case for giving the healthy, artificially fed, baby further supplementation, either by injection or by mouth, other than administrative convenience. Babies who are not fed, and a very small number of fully breast fed babies, will develop symptomatic deficiency. Without prophylaxis the risk of early thrombocytopenia: Pediatr 1958; 21: 397–542.

Manufacturers have been resisting calls for an oral product for more than 40 years. Children’s needs carry little clout with the pharmaceutical industry. One product licensed for oral use (Konakion MM®) did finally reach Europe (but not north America) in 1996. Two papers in this issue of Fetal and Neonatal now tell us that it does not perform any better than the earlier European product it replaced, even though it costs only twice as much, and has not been presented in a way that allowed parents to administer the right dose of vitamin K. Children in the third world still await the arrival of a simple generic product that they can afford. Much the same is true for vitamin D and folate acid. Available commercial products cost a hundred times more than the basic cost of their one active ingredient. Those whose original research (unfunded by any commercial organisation) gave us a scientific understanding of how these vitamins work, would be shocked to discover that they still remain, after half a century, beyond the financial reach of most of the world’s women and children.

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