include a lack of public and professional awareness, limited availability of suitable supplements which omit retinol (vitamin A) and inconsistency in guidance. In 2003 NICE concluded that "vitamin D supplementation should not be offered routinely to all pregnant women".¹⁰ This view clearly conflicts with the COMA opinions cited above and was based on a meta-analysis of two randomised trials, one of which was conducted in the UK and showed important effects.⁵ The Department of Health later stressed the continued importance of offering vitamin D supplements to pregnant women, particularly those in vulnerable groups.¹¹

Some time ago a public education campaign conducted amongst at risk groups in Glasgow demonstrated effectiveness in terms of both increased uptake of supplements and a reduction in rickets,¹² but a recurring and commonly cited concern has been the lack of a suitable low cost and palatable preparation. Fortunately this has recently been rectified in the process of reforming the welfare food scheme as *Healthy Start*. A single tablet providing vitamin D (10 µg) with folic acid (400 µg) and vitamin C is now available free to pregnant or breastfeeding mothers who are eligible for *Healthy Start* benefits, and can be prescribed at low cost for those who are not.

The issue of hypovitaminosis D in pregnancy must also recognise current uncertainty about the meaning of "normal" in the context of vitamin D status. Population reference ranges are influenced by a number of biological and lifestyle influences, most importantly sunlight exposure. However, in the twenty first century "sun shy" culture of industrialised nations¹³ they may not be indicative of optimal health. Indeed 25-OHD concentrations encountered in people liberally exposed to sunlight (such as lifeguards) exceed by 5–10-fold the lower limit of "normal" (25 nmol/l) cited above.¹³ Several authorities in the United States now argue that maintenance of a 25OHD

concentration above 75–80 nmol/l is associated with improved health, citing the associated reduction in parathyroid hormone concentration and increased calcium absorption and bone mineral density.^{13 14} Interestingly, the achievement of such plasma levels through high dose supplementation (50 µg, 2000 IU vitamin D per day) in breastfeeding mothers also increases both antirachitic activity in breast milk and plasma 25OHD concentration in their infants.^{15 16} The National Diet and Nutrition Survey of British adults suggests that if such a threshold were applied to UK population data, some 80–90% would be considered at risk of deficiency.¹⁷ This is potentially therefore a population health issue of considerable importance and its significance and implications require careful thought.¹⁸ Currently the 25-OHD concentration of <25 nmol/l cited by Dijkstra *et al* as a threshold of deficiency risk remains widely adopted but may prove conservative to say the least.

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Vitamin K deficiency

Vitamin K deficiency bleeding: the readiness is all

Paul Clarke, Martin J Shearer

Perspective on the papers by Busfield *et al* and McNinch *et al* (see pages 754 and 759)

Over 10 years ago, William Hathaway described the 50-year chequered history of the association

between a neonatal bleeding disorder and vitamin K deficiency and its prevention as a splendid example of the cyclical nature of

discovery–rediscovery in medical science.¹ The lessons that should have been learnt from the extensive body of early work were reiterated in a recent lively review in this journal.² In the UK these forgotten lessons first resurfaced in a 1983 *Lancet* article entitled "Haemorrhagic disease of the newborn returns".³ Of course this rare deficiency syndrome, now more accurately termed vitamin K deficiency bleeding (VKDB), had never gone away but had merely been rediscovered at a time of a progressive trend towards exclusive breast feeding. The latter had long since been established as an important risk factor for neonatal hypoproteinaemia.⁴

The 1983 *Lancet* paper was the catalyst for three prospective 2-year surveys of VKDB bleeding in the British Isles, with the results from 1993–94 and 2001–02 studies now reported in this issue by McNinch *et al.*⁵ In an accompanying paper, the same authors present data from a 2003 survey of prophylaxis practices in the UK and review the efficacy of regimens used.⁶ These papers are timely because a new 2-year BPSU survey of VKDB commenced in October 2006. This fourth survey was precipitated by the replacement of the phytomenadione formulation, Konakion Neonatal Ampoules, by Konakion MM, which is now the only vitamin K product licensed in the UK for parenteral or oral administration. The difference between the two preparations lies in the nature of the solubilising agent. The original preparation introduced in the 1960s contained the artificial emulsifier polyethoxylated castor oil (Cremophor EL) along with the preservatives propylene glycol and, more worryingly, phenol. Although there is no hard evidence that phenol is carcinogenic in humans, there is some evidence that it is a tumour promoter in mice. The fact that newborns receiving 1 mg phytomenadione were simultaneously being injected with 5 mg of phenol was rightly highlighted as a cause for concern during the original vitamin K and cancer debate.⁷ In welcome contrast, the newer formulation, a mixed micellar (MM) solution solubilised in natural components (glycocholic acid and phosphatidylcholine), has a significantly improved safety profile and a much lower risk of serious anaphylactoid reactions.⁸

There was also an expectation that the MM preparation would be absorbed more efficiently. Although this appears true for healthy infants,⁹ it seems not to be the case for infants with cholestasis. Surveillance in Germany has shown that a 3×2-mg oral regimen of MM phytomenadione (at birth, days 3–10 and weeks 4–6) does not reduce the incidence of late VKDB compared to the Cremophor preparation; nearly all failures in the survey were infants with latent cholestasis.¹⁰ Furthermore, a UK study shows that absorption of the MM preparation is unreliable in infants with cholestatic jaundice.¹¹ The survey by Busfield *et al* reveals a variable practice of oral prophylaxis with probable under-treatment of breast-fed infants.⁶ In the light of the German data, hospitals which give fewer than 3×2-mg oral doses of Konakion MM over the first 4–6 weeks may not be protecting those breast-fed infants destined to develop cholestasis, admittedly a small number but with a very high prevalence of intracranial bleeding.

Would charging parents with administration of more frequent oral doses of vitamin K as pioneered in the Netherlands and Denmark be more effective in the British Isles? Busfield *et al* clearly think so. In its favour is the fact that the target group at risk are infants of motivated breast-feeding mothers, while a reason against it is that poor compliance at home can have a devastating outcome. The Dutch and Danish models are very different, with the Dutch preferring to give a low daily “physiological” dose and the Danes a weekly “pharmacological” dose. The Dutch experience with a 25-µg daily dose (after 1 mg orally at birth) was initially favourable with no cases of VKDB in a birth population of 439 000 infants who received the complete recommended prophylaxis,¹² but a recently published national surveillance study for the year 2005 documented six infants who developed late VKDB (one a fatal idiopathic case and five with bleeding secondary to underlying cholestatic disease).¹³ The failure to protect Dutch infants with cholestasis is reinforced by the recent revelation of the alarming incidence of late VKDB as the initial presenting feature of biliary atresia.¹⁴ A useful benchmark of the likely daily oral dose that might afford as much protection as the intramuscular (IM) route comes from our knowledge that VKDB is exceedingly rare in formula-fed infants for whom intakes are typically ~50 µg/day compared to ~1 µg/day in breast-fed infants.¹⁵ A rarely considered caveat to giving low-dose vitamin K drops is that the absorption of vitamin K, which is the most lipophilic of all the fat soluble vitamins, is greatly enhanced by taking it with foods that contain fat. This occurs by default in formula-fed infants but not necessarily when drops are administered to breast-fed infants. We believe that further consideration needs to be given to bioavailability issues and optimal timing of oral doses in breast-fed infants. That oral prophylaxis can work is demonstrated by the experience in Denmark where the introduction of an oral regime of 1 mg vitamin K given once weekly for 3 months (after 2 mg orally at birth) resulted in no cases in almost 8 years of surveillance between 1992 and 2000.¹⁶ This is impressive because about 80% of Danish infants received oral prophylaxis, 71% were still exclusively breast-fed at 3 months, and the incidence of VKDB was previously comparable to that in other European countries. It should be added in postscript that the Danes were forced to revert to IM prophylaxis in June 2000 following the abrupt withdrawal of the Cremophor preparation in that country.¹⁶

Despite the attractions of the oral alternative, when given the choice many mothers may still opt for their newborn infant to get a once-off IM injection with its virtually guaranteed protection rather than the chore and responsibility of having to administer daily or weekly “medication” for 3 months. Compliance will always be an issue with oral regimens. Even for the nationwide Danish and Dutch oral regimes, there is a paucity of compliance data with only a small survey conducted in Denmark¹⁶ and no such data available for the Netherlands.¹³

Why does single dose IM prophylaxis remain more popular than oral regimens? Injection of a single 1-mg IM dose has been practised for decades, has a proven track record in providing virtually universal long-term protection, places no onus on the parents, and entails no concerns regarding compliance. No convincing new evidence has emerged in the last 15 years to support the cancer link, particularly with respect to providing any biochemical plausibility for carcinogenicity of vitamin K1, and of course today’s MM preparation has safer excipients.⁸ Even if a suitable low-dose oral preparation were available, infants with liver disease or malabsorption will always be more likely to be protected against late VKDB by a single 1-mg IM dose at birth.

One possible concern with Konakion MM relates to the long-term effectiveness of a single IM dose and whether the new formulation has the same depot properties as advocated for the Cremophor preparation.¹⁷ To date there is only one direct comparative study. The results appear reassuring and show that serum concentrations 14 days after an IM injection of 1 mg of the MM formulation were significantly higher ($p < 0.001$) than after the same dose of the Cremophor formulation.¹⁸ Nevertheless, we still need data from its use in the field, which the new BPSU survey will provide.

Preterm infants have long been considered a higher risk group for VKDB, yet the BPSU surveys consistently show that they are not over-represented among confirmed cases. One likely reason is that they have long received excessive doses of vitamin K boluses for prophylaxis and in parenteral nutrition. Indeed, the survey of Busfield *et al* shows many units still use inappropriate “term infant” doses for their premature infants.⁶ Only recently has work been done attempting to refine doses used for preterm infants.¹⁹ However, there is a woeful dearth of published data for Konakion MM in preterm infants, even though all UK preterm infants must now receive this preparation. The ongoing need to draw up minuscule volumes of the supplied concentrated MM preparation when

dosing sustains lingering concerns about possible dosage failure in this group.

With the new BPSU survey underway, we would like to highlight some practical issues with respect to the accurate diagnosis of VKDB. Many practitioners may be unaware of the advantages of obtaining a PIVKA-II measurement to assist in VKDB diagnosis. PIVKA-II (undercarboxylated or abnormal coagulation factor II) is released into the bloodstream in the very early stages of vitamin K deficiency and with modern assays can be detected well before any changes in the prothrombin time. Hence PIVKA-II measurements are commonly used to monitor subclinical vitamin K deficiency.^{9 18 19} In overt VKDB, PIVKA-II is always present at extremely high levels and, with a half-life of ~60 h, can still be detected in samples collected days and even weeks after vitamin K and/or blood products have been given to correct coagulopathy. This singular ability to detect vitamin K deficiency retrospectively in samples unsuitable for coagulation testing (eg, serum) makes it a powerful addition to the diagnostic armoury, not least to assist differentiation of VKDB from non-accidental injury. Adoption of this single test in clinical practice and in future epidemiological studies would go a long way towards improved diagnosis of VKDB and to elimination of current doubts surrounding case definitions.

McNinch *et al* remind us that cases of VKDB are still occurring in the British Isles despite vitamin K prophylaxis being offered to all newborns. It is perturbing that parental refusal of vitamin K has become a major reason for ongoing VKDB cases.⁵ The chance of serious or fatal late VKDB in an unsupplemented, exclusively breast-feeding infant, perhaps as high as two to five cases per 10 000 births,²⁰ is a small but real risk taken by parents who refuse vitamin K prophylaxis for their newborns. We believe refusal should trigger involvement of a senior paediatrician to explore parental concerns and discuss all the available options. Infants who suffered VKDB not uncommonly feature among medicolegal cases, so meticulous documentation is imperative.

While it is heartening that the incidence of VKDB in the British Isles declined significantly between 1994 and 2002,⁵ we should reflect that in many emerging countries vitamin K prophylaxis is not routine and the incidence of VKDB is significantly higher,

even by several orders of magnitude, than in the British Isles. This is especially so in the Far East. In Vietnam the incidence of intracranial haemorrhage due to late VKDB is estimated to be higher than 1 in 1000 births.²¹ Although costs of prophylaxis may initially seem prohibitive to developing countries, there is evidence that the potential reduction in morbidity and mortality would be highly cost effective.²¹ The example of Thailand in achieving an approximate 20-fold reduction in the national incidence of VKDB from a base of around 1 per 1000 births shows that this is an achievable aim.²² Once VKDB becomes very rare, as in developed countries, the challenge is to remain vigilant. To ensure quick and accurate diagnosis we must be mindful of classic early warning signs such as bruising or bleeding and of predisposing features such as cholestasis, and consider whether cases of intracranial bleeding could be due to vitamin K deficiency: the readiness is all.^{23 24}

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