1. Background

Newborn babies are deficient in vitamin K by comparison to older children and adults.¹ The vitamin K dependent clotting factors (2,7,9,10, protein C and protein S) are only 30-60% of normal adult levels at birth. With the exception of protein C, these levels rise to normal adult values by 3-6 months. Vitamin K does not alter these levels, instead it is required for the activation of these proteins by gamma-carboxylation. Production of undercarboxylated (abnormal) prothrombin, known as protein induced in vitamin K absence or antagonism (PIVKA II) has been used as a marker of vitamin K deficiency. Deficiency may result in bleeding in newborns and infants.

Vitamin K occurs in two forms, vitamin K₁ whose source is dietary and vitamins K₂ (menaquinones) that are produced by gut bacteria. Vitamin K₁ crosses the placenta poorly (maternal to fetal gradient, 30:1) resulting in low concentrations in the fetus. After birth vitamin K status depends on dietary intake from milk. Human breast milk contains relatively low concentrations of vitamin K₁ (1-2 micrograms/L) compared to supplemented formula milk (usually >30 micrograms/L). Hepatic menaquinones accumulate later in infancy and offer no additional protection until then. Therefore, babies exclusively breast fed, sick babies, babies slow to establish feeding and babies with cholestatic liver disease are at risk of VKDB. Without prophylaxis, the risk of VKDB is 1 in 10,000.

VKDB ²

Early VKDB, occurring on the first day of life, is rare and confined to infants born to mothers who have received medications that interfere with vitamin K metabolism. These include the anticonvulsants phenytoin, barbiturates or carbamazepam, the antitubercular drugs rifampicin or isoniazid and the vitamin K antagonist's warfarin and phenprocoumarin. It is prevented by giving vitamin K to the mother (except those that require on going anticoagulation) in the last weeks of pregnancy and ensuring a dose of IM vitamin K is given to the baby.

Classical VKDB occurs in the first week of life, often in sick babies or those slow to establish feeds. Bleeding into the brain is uncommon. It is prevented by ensuring that an early first dose of vitamin K is given by any route.

Late VKDB occurs from the first week upto 6 months, usually between 4 and 12 weeks. This form is more commonly associated with intracranial bleeds (30-50%) than classical VKDB and this can be fatal or leave permanent disability. It is almost completely confined to fully breast-fed babies. About half will have an underlying liver disease or other malabsorptive state. Late VKDB can be optimally prevented by 1mg vitamin K IM at birth or significantly reduced by repeated doses of oral vitamin K.

The challenge for any vitamin K policy, advocating the oral route, lies in its attempt to prevent late VKDB.
Over the last decade, discussions over the safety of IM vitamin K have led to much debate, but little consensus as how best to manage the risk of VKDB in the UK. However, as clinicians attempt to refine a consensus view, the department of health has produced an information leaflet for parents implying best practice. This policy attempts to incorporate this view along with current practice, current evidence and drug licensing/formulation issues.

2. Clinical and scientific controversies

- What is the best available prophylaxis?
  Vitamin K, given intramuscularly shortly after birth, is the best available prophylaxis. Oral vitamin K performs less well, in protecting against late VKDB, unless it is given daily or weekly for the first 3 months. Variations in the reported efficacy of vitamin K may be due to differences in dose, formulation, regime and compliance. Australian and American Paediatricians are advised to support intramuscular prophylaxis.

- What are the potential risks of intramuscular prophylaxis?
  An association between the early preparations of IM vitamin K and childhood cancer was suggested in 1990 and 1992. Some case control studies have supported this link, whereas other studies have not supported a significant causative relationship. Specifically, there is no increased risk of solid tumours. The data for an association with ALL has been summarised as 'inconsistent', but an increased risk has not been completely excluded. However, the current position of UK experts, is that the available data do not support an increased risk. As a result, some countries have returned to an intramuscular policy (Australia and USA).
  Other risks
  Vials of Intramuscular vitamin K may be confused with syntocinon (oxytocin) in labour suite.
  The intramuscular route should not be used if there is active bleeding.

- How can vitamin K be given?
  NICE guidance published in 2006 recommends that vitamin K should be administered IM as the most clinically and cost effective method. Should parents decline IM vitamin K, then oral vitamin K should be offered as second line. This is the guidance that NUH is following.
  It can be given by the oral route as well as the IM and IV routes. Konakion MM is the licenced product for use. When 3 oral doses of Konakion MM Paediatric were compared with an IM dose of Konakion, no significant differences in coagulation and PIVKAII production were found in the first 8 weeks of life. The main concerns with delivery by the oral route are compliance and protecting the baby with liver disease or malabsorption. It may still be too early to confidently assume that this new preparation performs as well as its predecessor, when given parenterally. Evidence for the comparable efficacy of Konakion MM Paediatric (to the previous formulation Konakion Neonatal) by the IM route, is growing.
  If it is given I.V. then further oral doses should be used when the baby is well.

The fourth BPSU study on VKDB, undertaken on cases between 2006-2008, demonstrated the sustained decrease in cases of VKDB since the implementation of vitamin K prophylaxis. Eleven cases were identified during this period, 6 of which received no vitamin K, and 2 had incomplete oral courses. The remaining 3 had IM vitamin K – but two of these babies were determined to have biliary atresia. Of the 217 UK centres included in the study, 69% recommended IM, 9% recommended oral, 21% gave a choice.

Recent audit in the QMC (2013) demonstrated that 88% of mothers were offered a choice of route of administration, 11% of mothers opted for the oral route, and 36% of mothers when asked did not know why vitamin K was recommended.

- What is the best oral regime for preventing late VKDB?
  Clearly a single oral dose of vitamin K does not protect against late VKDB. Comparable protection...
to the IM regime has been achieved by daily and weekly doses of vitamin K given for up to 3 months. Shorter regimes have been more popular, but associated with some cases of late VKDB in well breast fed babies and those with liver disease. The current licensed regime is to give 2 or 3 doses of 2mg Konakion® MM Paediatric.

3. Prevention of vitamin K deficiency bleeding in infants
Giving vitamin K after birth to all babies can reduce the risks of developing both classical and late VKDB. Intramuscular vitamin K offers the best protection.

1. Patient groups and their management
First Dose
- First Dose: Well infants of 36+6 weeks and older (Hospital or Home)
  Vitamin K prophylaxis should be discussed and decided upon antenatally.
  - Recommended: 1mg IM Konakion® MM Paediatric soon after birth.
  - Alternative: 2mg Oral Konakion® MM Paediatric, dose repeated if vomits within three hours (to be offered if IM is declined)
Midwives are able to give licensed preparations of vitamin K without medical prescription.

Konakion MM Paediatric is 2mg in 0.2ml, therefore a 1mg dose is 0.1ml

- Neonatal Alert: Infants of mothers taking medication interfering with vitamin K metabolism
  Mothers require vitamin K at the end of their pregnancy. Mothers requiring on going anticoagulation do not receive vitamin K as it counters the effect of their warfarin. The baby must have vitamin K soon after birth as 1mg IM (Konakion® MM Paediatric). In the event of significant trauma and bleeding, IV vitamin K should be given by slow intravenous injection. FFP at 10-15ml/Kg will raise the clotting factors by 10-20iu/dL and should be considered.

Subsequent Doses
- Subsequent Doses for oral prophylaxis: Breast fed babies
  - 2mg Konakion® MM Paediatric 1 week
  - 2mg Konakion® MM Paediatric 1 month
These two extra doses will be given to the mother when she is discharged, with instructions on when and how to administer them. The second dose should be given at the time of the Guthrie card blood test and supervised by the midwife. The parents give the third dose. If born at home, the midwife can arrange obtaining the vitamin K for the parents.

- Subsequent Doses for oral prophylaxis: Babies who are formula fed
  2mg Konakion® MM Paediatric 1 week
The second dose should be given at the time of the Guthrie card blood test and supervised by the midwife. A second dose has been advised since 1998.10 This theoretically covers formula fed babies who have not absorbed the first dose, have been slow to feed or less well, but have not required admission to the NNU. A second dose is recommended in the department of health leaflet for parents.9

Babies who continue to receive a mixture of formula and breast milk should receive a third dose of 2mg vitamin K (Konakion® MM Paediatric).

Table of Risk for Late VKDB

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prophylaxis</td>
<td>5-20 per 100,000 births</td>
</tr>
<tr>
<td>1x 1mg IM</td>
<td>0.3 per 100,000</td>
</tr>
<tr>
<td>1x1-2mg oral dose</td>
<td>1.5-6.5 per 100,000</td>
</tr>
<tr>
<td>3x 1mg oral doses planned (birth, 7/7 and 28/7)</td>
<td>2.5 per 100,000</td>
</tr>
</tbody>
</table>
All babies admitted to the NNU and those born preterm <36+6 weeks gestation should have IM vitamin K:

- 1 mg in those >1.5 kg (Konakion® MM Paediatric) as 0.1ml
- 0.5 mg in those <1.5 kg (Konakion® MM Paediatric) as 0.05ml

(The licensed dose for smaller babies (<2.5kg) is 0.4mg/kg - However because of the difficulty of drawing up very small volumes, we will use the more practical dosing regime above for this group of babies)

Intravenous Use

All infants with a suspected bleeding disorder should have vitamin K 1mg given by slow intravenous injection. If a baby has received IV vitamin K, then 2 further doses of oral vitamin K should be given as 2mg vitamin K (Konakion® MM Paediatric) to avoid late VKDB.

Neonatal Unit Admissions

Those infants (breast or bottle fed) who have received a single dose of IM vitamin K on the NNU do not need any further doses of oral vitamin K (even if fully breast fed) unless liver disease is diagnosed.

Consent

All parents will receive information about the need for postnatal vitamin K in the antenatal period. The use of vitamin K will be recorded in the maternal notes via the computer system.

All babies admitted to the Neonatal Unit and those born preterm will receive intramuscular vitamin K as part of their treatment. Specific parental consent is not sought but parents are informed through the babyfax system.

Vitamin K preparations

- Konakion® MM Paediatric (phytomenadione) this is a mixed micellar preparation, which is well absorbed orally. It is licensed for IM, IV and oral use. However, it is expensive, and is supplied in glass ampoules with an oral applicator. The preparation is 2mg in 0.2ml, which is a smaller volume than previously used with Konakion®. The recommended oral regime is three doses of 2mg. The information sheet dispensed with the product no longer recommends that the later doses be given by a healthcare professional. If less than 36+6 weeks the license is for IM/IV use (1mg if >2.5kg and 0.4mg/kg if <2.5kg, see above).

- Parenteral administration to premature babies <2.5kg may increase the risk of Kernicterus because of the effect of glycocholic acid (one of the excipients) in displacing bilirubin from protein binding sites.

Side effects

- “May induce haemolysis in erythrocyte G6PD deficiency or low concentrations of alphatocopherol in the blood”.15
- There are a few unconfirmed cases of anaphylaxis after IV administration of Konakion® MM Paediatric.
- Local irritation and inflammation after IM use have been reported, but thought less likely with the smaller volume.
- Kernicterus as glycocholic acid may displace bilirubin from protein binding sites.
References


5. Vitamin K: information for parents to be. www.doh.uk/vitk.htm


10. Vitamin K for newborn babies. PL/CMO/98/3

11. Joint statement and recommendations on vitamin K administration to newborn infants to prevent vitamin K deficiency bleeding in infancy. NHMRC, RACP (Paediatric division), RANZCOG, RACGP, ACM.

12. NICE guidance CG37 2006: Postnatal care: Routine postnatal care of women and their babies


VITAMIN K INFORMATION SHEET FOR PARENTS
NOTTINGHAM CITY HOSPITAL AND QUEENS MEDICAL CENTRE NOTTINGHAM

In Nottingham, we aim to give Vitamin K (also called Konakion) to all babies soon after birth to protect against a disease called vitamin K deficiency bleeding (VKDB). This is a rare bleeding disorder (5-20 per 100,000 births or 1-2 babies per year in Nottingham), which can be fatal or produce long-term disability if bleeding occurs into the brain. This disorder can be almost entirely prevented by giving Vitamin K soon after birth.

**Vitamin K prophylaxis can be given as an injection or be given into the mouth.**

The best protection is provided by the injection and many babies receive it in this way in the UK and around the world. In 1990 and 1992, some published research suggested a possible link between Vitamin K given by injection and childhood cancer, but this finding has not been conclusively supported in reviews of subsequent research studies. Australian and American Paediatricians recommend giving vitamin K as an injection.

**In Nottingham we strongly encourage all parents to agree to their babies receiving Vitamin K.**

Vitamin K by intramuscular injection offers the best protection (reduces incidence to 0.3 per 100,000 cases).

In Nottingham, recent years, Vitamin K given by mouth has been found to be consistently safe and effective (reduces incidence to 0.9 per 100,000 cases if all 3 doses of 2mg are given).

If your baby is admitted to the Neonatal Unit following birth or is born early before 36 weeks and 6 days of your pregnancy then they will receive an injection of Vitamin K, as these babies are at particular risk of developing a bleeding problem and may not absorb oral treatment. You will be advised if your baby requires any subsequent doses. In most cases the dose given immediately after birth will offer the protection required.

**Mothers of term babies are always asked to give verbal consent before their babies are given Vitamin K prior to discharge from labour suite.**

Breast feeding mothers who opt for oral treatment take home two further doses to give by mouth to their babies - at one week and one month after birth. Bottle feeding babies who receive oral Vitamin K take home only a second dose (given at 1 week). Full instructions on how to give subsequent doses at home are given before discharge.

**We strongly recommend that all babies be given Vitamin K. More information can be**
obtained from your midwife. If you have any further questions or concerns, please feel free to ask your midwife or the paediatrician.