Babies, Dioxins and Coagulation

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Hypothesis:

Due to a cocktail effect of PCBs, Dioxins, PBDEs ,HBCD, SCCPs and MCCPs in utero, secondary vitamin K deficiency is created in the fetus, leading to increased risk of hemorrhaging during delivery. Skeletal abnormalities might also be the result.

Introduction:

In the following chapters we review what is known about vitamin K deficiency, more specifically Late Hemorrhagic Disease of the Newborn (LHDN), and coagulation under which the number of thrombocytes in relation to Dioxins and PCBs.

Vitamine K metabolism before birth

Before birth the foetus is more or less protected against external injuries by the mother and its own amniotic fluid.
During development in utero, the liver starts to produce the proteins necessary for a controlled coagulation in cooperation with blood platelets, endothelium, inhibiting factors and the fibrinolytic system. Vitamin K (K is from the German Koagulation), necessary in the posttranslational carboxylation of proteins involved in the coagulation process, transforms them from an inactive into an active state. The proteins dependent on vitamin K are prothrombin = factor II, factor VII, factor IX and factor X. Other proteins are also vitamin K dependent: protein C and protein S inhibiting factors, involved in keeping the blood flowing. Des-carboxylated proteins, the so-called PIVKAs (Prothrombin In Vitamin K Absence) are functionally defective prothrombins and markers of a Vitamin K deficiency.

The enzymes that control the vitamin K cycle in the liver are species specific and there are differences between rats and humans. Vitamin K is recycled by means of reduction and oxidization. In the vitamin K cycle the vitamin is first reduced to KH2 in the presence of NADH or diaforase, and then oxidized during the carboxylation reaction, first into an epoxide and then with a coumarin sensitive epoxide-reductase into the natural vitamin K.

Problems
Enzymes of the cytochrome P 450 system, normally not active before birth, can metabolize vitamin K, probably when it is an epoxide, and the molecule is then excreted with bile.
These enzymes are normally not active before birth and are induced slowly in the first half year after birth. During pregnancy the level of vitamin K is kept low in the baby's liver and transplacental transport is not made easy, because the molecule is aggressive. Israels et al. described an effect of vitamin K on benzo(a) pyrene metabolism and in vivo DNA-adduct formation [1] .This may be important considering the association described by Golding et al. between administering intramuscular vitamin K and childhood leukaemia [2]. This is, however, controversial.

Especially during delivery, a baby is in danger should it be vitamin K deficient. However, also earlier, during

pregnancy: stillbirth and bleeding are described in babies of mothers on anticonvulsant drugs like phenobarbital, phenytoine and carbamazepine. It is known since 1957 that anti-epileptic drugs can cause bleeding in the newborn, based on a deficiency of vitamin K, resulting in a prolonged prothrombin time [3]. Severe intracranial, intrathoracic, and intraperitoneal bleeding has been reported. Subcapsular bleeding in the liver may lead to peritoneal bleeding. The mother on anti-epileptic drugs receives extra Vitamin K during the last weeks before delivery, The newborn of a mother on anti-epileptic drugs receives double dosage vitamin K after birth. Vitamin K postpartum is not always protective enough and is of course too late for antenatal haemorrhaging or bleeding occurring during delivery.
Based on this knowledge, it is plausible that phenobarbital-like PCBs may have a similar effect. In the eighties, a new phenomenon was recognised: coagulation problems, with severe intracranial haemorrhages, due to vitamin K deficiency in exclusively breastfed babies. This was later termed Late Hemorrhagic Disease of the Newborn (LHDN).

Late Hemorrhagic Disease of the Newborn

Around 1985 an increasing number of case reports of LHDN were published, and this was considered to be a new epidemic [4]. Severe brain hemorrhages were seen in babies exclusively breastfed in the first month of life and during the first year.

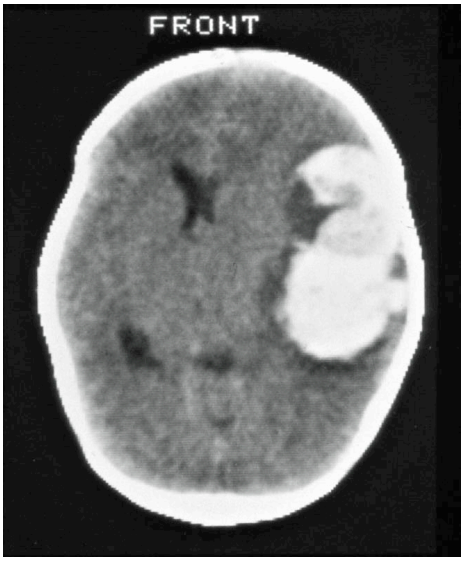

Figure 1, severe intracranial haemorrhage in 3 week-old baby due to vitamin K deficiency.

The incidence of severe bleeding was about 5-10/100.000. However, in a Dutch study, in 20 % of babies PIVKAs were found [5,6]. In 1990, a new protocol was introduced in the Netherlands, whereby the newborn was administered 1 mg vitamin K after birth and, when exclusively breastfed, each week during the first 3 months, which successfully prevents LHDN. However, the problem of a possible vitamin K deficiency before or during delivery was not tackled.

Dioxins and PCBs, vitamin K and coagulation (thrombocytes)

In rats, polychlorinated biphenyls (PCBs) and dioxins influence vitamin K metabolism [7-9]. Both are strong inducers of microsomal enzymes. A correlation between the high levels of PCBs and Dioxins in breast milk in Western Europe and vitamin K deficiency was hypothesized [10]. In 1987 a prospective study was started in the region of Amsterdam-Zaandam, looking at effects of prenatal and lactational exposure to dioxins in general, including coagulation. This mother-child cohort was studied in the neonatal period (1), at the age of 2.5 years (2), at the age of 7-12 years (3) and at the age of 14-19 years (4). In the neonatal period vitamin K was measured. Decreased thrombocyte counts in increased lactational dioxin exposed babies was seen in the neonatal period, which was still evident at 8 years of age [11,12]. A negative effect on vitamin K level at 11 weeks of age was seen in relation to the level of TCDF and 1,2,3,7,8-HxCDF in relation to PIVKA-II levels, while 1,2,3,7,8-PeCDF and 1,2,3,4,6,7,8-HpCDF were significantly correlated with Vitamin K levels [13]. There are little human data on dioxins and PCBs and coagulation factors. Recently NAHNES 2003-2004 data showed a negative effect on the number of thrombocytes, in relation to PCBs in the general population[14].

Cocktail effect

PCBs and Dioxin levels are decreasing nowadays [16] . However other chemicals than PCBs and Dioxins, are also present in breast milk now. They can be prenatally active in the liver of the fetus and may cause a synergistic cocktail effect. These are the polybrominated diphenyl ethers (PBDEs),hexabromocyclododecane (HBCD), and the short chain and medium chain chlorinated paraffins (SCCPs and MCCPs). The latter have been shown to cause vitamin K deficiency and bleeding in the offspring of rats. This is reason for concern, considering the limited regulation to protect humans[15] .

Conclusion

The vitamin K status before birth and during delivery can be compromised by chemicals inducing microsomal enzymes. The number of thrombocytes might be lowered by dioxin and dioxinlike chemicals . Antenatal and perinatal hemorrhaging can be caused by vitamin K deficiency, which may be induced by these chemicals. An additional negative effect on coagulation can be the lower number of thrombocytes caused by PCBs and Dioxins.

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