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Commentary

Vitamin K deficient bleeding and COVID-19: How are they related?

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1. Introduction

Vitamin K deficient bleeding (VKDB), especially late VKDB, is a serious problem of the neonatal period and early infancy, and appears to be undergoing a recrudescence in the United States (see later). The disorder relates to failure of administration of any (or an insufficient amount of) vitamin K shortly after birth. Late VKDB is the most serious form of VKDB, especially because of its propensity to involve the central nervous system. The reasons for the lack of neonatal vitamin K administration in recent years overlap considerably with those given for a reluctance or refusal to accept COVID-19 vaccination (see later). The following will consider briefly the clinical features of VKDB, the likely reasons for its recrudescence, the issue of refusal of vitamin K and other vaccines (including that for COVID-19), and possible approaches to address these issues.

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2. Vitamin K deficiency and bleeding in early infancy

Vitamin K is crucial to coagulation via its action as a cofactor for the carboxylation of clotting factors II (prothrombin), VII, IX and X, thereby rendering these proteins active [1]. Deficiency of these active factors leads to prolongation of both the prothrombin time and partial thromboplastin time and the propensity for bleeding. Laboratory diagnosis of VKDB is established by detection of these coagulation defects and of the presence in blood of undercarboxylated coagulation protein species (proteins induced by vitamin K absence – PIVKA), especially those related to prothrombin (PIVKA-II).

Several factors render the infant prone to vitamin K deficiency [1]. Transplacental transfer of vitamin K is not optimal, and thereby neonatal hepatic stores are limited. Vitamin K prophylaxis at birth may be either omitted (see later) or insufficient because of route of administration (e.g., single oral dose) [1, 2]. Breastfeeding is the exclusive or near-exclusive source of nutrition in VKDB syndromes and can be problematic, especially in late VKDB, because breast milk is low in vitamin K and the intestinal flora of breastfed infants produces relatively low levels of vitamin K

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[1]. Less commonly, hepatic cholestatic disease (e.g., biliary atresia, neonatal hepatitis) is present [1, 3].

3. VKDB syndromes

Three syndromes of VKDB are recognized in the neonatal /early infancy period [1]: early VKDB, with onset in the first 24 hours; classic VKDB, with onset between 1 and 7 days; and late VKDB, with peak onset between 3 weeks and 8 months. Early VKDB is related to maternal drug administration, especially antiepileptic therapy, (e.g., hydantoins, barbiturates, primidone and carbamazepine) with resulting increased degradation of vitamin K [4]. Intracranial hemorrhage (ICH) occurs in 20–25% of such infants. This disorder is now rare. Classic VKDB is characterized principally by bleeding from the gastrointestinal tract, umbilicus and circumcision site. The lack of neonatal vitamin K prophylaxis, coupled with "exclusive" breast-feeding and delayed establishment of gut flora, is important in this now very uncommon form of VKDB. ICH is rare in this form (1/127 in one series) [1]. However, classic VKDB can be associated with appreciable neonatal morbidity.

Late VKDB, the most serious form of VKDB, with onset between 3 weeks and 8 months, is characterized principally by ICH [1, 2, 5–11]. Approximately 50–75% of cases present with ICH, very often with rapid clinical evolution and severe signs (seizures and signs of increased intracranial pressure). A history of "warning" bleeding (e.g., ecchymoses) occurs in one-third or more, often for weeks before the ICH presents. The predominant loci of the ICH include subdural in 40%, parenchymal in 40%, intraventricular in 10% and subarachnoid in 10%. Combinations of sites occur commonly. Outcome reflects the severity of the lesions — approximately 15–20% have died and neurological sequelae result in 20–50%. Misdiagnosis as nonaccidental cranial trauma may occur. (Notably, retinal hemorrhages have been reported in late VKDB, albeit rarely.) [1]. Rapid diagnosis of late VKDB and prompt treatment with intravenous vitamin K can be lifesaving.

4. Why a resurgence of late VKDB?

Although difficult to quantitate on a national level, a carefully documented resurgence of late VKDB in Tennessee in 2013 is especially instructive [12, 13]. Thus, in 2013 five infants with serious late VKDB were identified over a nine-month period [12]. Of these infants, three were born in hospital and two at home. Neonatal vitamin K had been omitted in each instance, principally because of parental decline. The cluster of cases prompted a detailed CDC review of a random sampling of Tennessee hospitals and private birthing centers during the same period. The review determined that 3.4% of 3,080 infants discharged from the hospital nurseries sample and fully 28% of 218 newborns delivered in the birthing centers did not receive vitamin K prophylaxis. (The reasons for the lack of vitamin K administration and parental decline are discussed later.). It is notable in this context that a recent survey showed that, in 2017, out-of-hospital births in the U.S. accounted for 1.61% of all births [14]. This percentage translated to 62,228 infants. Both home births and birth center births increased similarly, i.e., nearly doubled during this interval. Many of these births are attended by midwives, many of whom do not have prescriptive authority for parenteral Vitamin K and/or do not routinely recommend Vitamin K administration (see later) [15].

The current overall incidences of lack of neonatal Vitamin K administration and or late VKDB in the United States is unclear. Studies in New Zealand, Australia, Canada and Great Britain suggest incidences of refusal of parental vitamin K administration at birth of 1–7% [9, 16, 17]. Estimates for the USA range from 0–3.2% of births in hospitals, 14.5% in home births and up to 31% in birthing centers [18]. The incidence of late VKDB in the absence of vitamin K at birth ranges broadly but may be as high as 8/10,000. Thus, in the USA with nearly 4,000,000 births yearly [19] and an arbitrarily estimated incidence of 2% for lack of vitamin K administration at birth, 60–70 examples of this serious example of VKDB would be expected yearly. Notably the incidence of classic VKDB is approximately 20-fold higher than that for late VKDB [18], and thus as many as 1400 of this significant, but less serious form could be expected [18]. It can be expected, as recent experience indicates (see earlier), that clusters of cases of VKDB would occur in regions with higher proportions of births at out-of-hospital sites. Moreover, since vitamin K refusal is especially prevalent in out-of-hospital births, which, as a group, constitute a rising proportion of all births in the USA, the overall prevalence of late VKDB likely is increasing. These facts indicate the importance of neonatologists ensuring that neonatal parenteral vitamin K

administration is as prevalent as possible and of pediatricians maintaining a high level of suspicion for the diagnosis of late VKDB in infants with severe ICH.

5. Reasons for refusal of vitamin K

The reasons for parental decline of vitamin K have been studied worldwide, with very similar results [15–18, 20–28]. The principal concerns generally cited are: (1) increased risk of cancer, especially childhood leukemia (not supported by available data); (2) toxicity of either vitamin K or ingredients in the preparation; (3) excessive dose of vitamin K; (4) vitamin K not needed or ineffective; (5) pain for the infant; (6) desire for "natural" birth and postnatal course; (7) distrust of pharmaceutical companies or modern medicine or both. Of particular concern, a strong correlation was noted between parental decline of vitamin K and decline of later childhood immunizations. Information cited by parents who decline vitamin K and subsequent vaccinations most often is derived from social media sources, often specifically directed at parents and expectant mothers. So-called "science" from unqualified pseudoexperts is similarly propagated. Well-intentioned midwives do not encourage or cannot prescribe parenteral vitamin K. Finally, neonatologists may be remiss in not ensuring that parents understand the importance of vitamin K administration. In one notable study in Israel, although 63% of expecting parents held academic degrees, 60–70% did not know that providing vitamin K to a newborn can prevent serious bleeding and had not yet decided whether to consent to vitamin K administration [21].

6. Relation of VKDB to coronavirus

At the time of this writing (January, 2021), vaccination to immunize individuals against COVID-19 has become available and in the coming weeks and months will become widely available. Available data indicate that the currently available vaccines are highly effective. However, a recent longitudinal study in the USA of over 8,000 adults queried between April and December 2020 showed that the percentage who stated that they were "somewhat" or "very likely" to be vaccinated declined from 74% to 56% [29]. The December values were lowest for women (51%), individuals aged 18–49 (51%), blacks (38%) and those with a high school education or less (48%). Achievement of "herd immunity" will not be possible with these levels of vaccination. Clearly, educational campaigns to increase the public's awareness of the effectiveness, safety and societal importance of COVID-19 vaccination are needed. The reasons for the reluctance to accept vaccination are complex, but *similarities with the reasons noted earlier for decline of vitamin K are emerging*.

Many of those who are skeptical about the safety or effectiveness of the COVID vaccines have expressed similar views about other vaccines. On the basis of social media monitoring, so-called "anti-vaxxers" appear to be active in introducing skepticism about the safety and efficacy of the coronavirus vaccines (Google: "coronavirus vaccine and anti-vaxxers"). This phenomenon is directly reminiscent of the role of social media in the decline of vitamin K administration. Perhaps educational campaigns by appropriate federal health agencies and relevant medical societies to increase adherence to COVID vaccination and neonatal vitamin K administration should more explicitly utilize social media to emphasize benefits and safety.

7. Conclusions

The key concluding message for the neonatologist is to emphasize to parents the benefits of parenteral vitamin K administration, the safety and the potential gravity of VKDB, especially late VKDB. Similarly, the pediatrician caring for young infants should have a high index of suspicion for late VKDB when encountering an infant with ICH. Misdiagnosis, e.g., nonaccidental trauma, will delay lifesaving therapy and lead to other unfavorable consequences. More broadly, educational programs directed not only at hospital-based caretakers but also midwives and other out-of-hospital birthing personnel should be encouraged and facilitated.

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