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Metabolism of Vitamin K dependent factors in mothers and their newborn infants

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1 Introduction

Vitamin K was discovered in 1929 by DAM of Freiburg University when he was conducting research of fetometabolism in chickens. One of the chicks developed symptoms suggestive of scurvy, but which were not cured by administering vitamin C. After experimenting with several factors DAM finally found that the scorbutic symptoms could be cured by supplementing food with clover leaves. The following year in 1930, he found another factor in food which had the effect of preventing bleeding and thus named it "Koagulations vitamin" (Vitamin K).

It is now known that there are seven types of Vitamin K ranging from K1 to K7. Those which exist in nature are vitamin K1 and vitamin K2. It is also known that the main source of vitamin K for the living body is from food and enterobacteria. The main source of Vitamin K1 from food is green vegetables, while Vitamin K2 is found in enterobacteria.

Recently Martius and others have proved that vitamin K1 is converted to vitamin K2 within the living organism. It has therefore been concluded that vitamin K2 is the form most prevalent in nature. In this paper, we emphasize the importance of vitamin K to the mother and baby during the perinatal period and report the following three studies:

a. Hepaplastin test values in the last stage of pregnancy.
b. The correlation between maternal and neonatal Hepaplastin test values.
c. Transplacental passage of vitamin K.

2 Identification of the vitamin K dependant factor in the pregnant woman using the Hepaplastin test

Vitamin K dependent coagulation factors all produced in the liver include prothrombin (factor II), factor III, factor IX and factor X. During the latter half of pregnancy all coagulation factors with the exception of factor XIII increase by about 1.5 to 2 times (figure 1).

Observations of the changes in the mean values of vitamin K dependant factors were made using the Hepaplastin test (HPT). The HPT is a freeze-drying test devies to measure and control the change of factors produced in the liver which has factor II (prothrombin), VII (proconvertin) and X (Stuart Prower factor) i. e., vitamin K.

The HPT study was performed on 65 normal pregnant women who were attending the Obsteric and Gynaecology Department of Hokkaido University Hospital or other referral hospitals. The subjects were in the third to tenth lunar month of pregnany. Blood drawn from the antecubital vein was tested. About 4.5 ml of blood was required and mixed with 0.5 ml of 3.8 percent Sodium Citrate. The results of the test are as shown in figure 2. The clearly indicate that the HPT value is 1.6 to 1.7 times higher than that of normal non-pregnant people.

The pattern of the increase of vitamin K dependant factors in pregnancy was also shown. In the course of this study when measuring prothrombin activity to evaluate the activity of vitamin K dependant factors, we found that the thrombotest method could not be used without

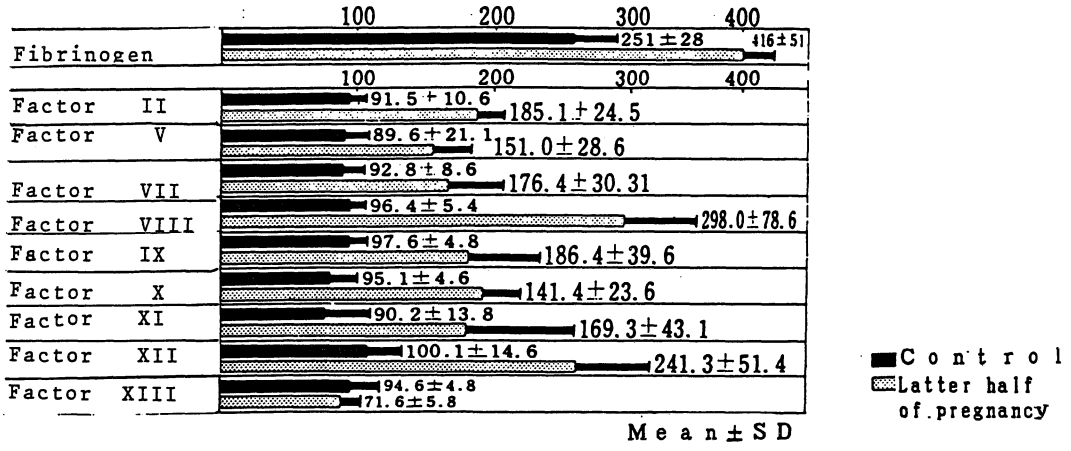
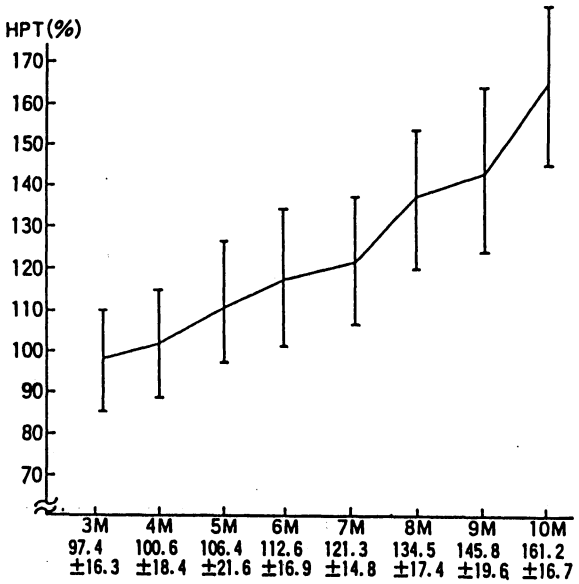


Figure 1. Changes in several blood coagulation factors in the latter half of pregnancy.



HPT value during different stages of pregnancy.

Stage of Pregnancy	HPT Value in percentage
At 3 months	97.4 ± 16.3
At 5 months	106.4 ± 21.6
At 7 months	121.3 ± 14.8
At 8 months	134.5 ± 17.4
At 9 months	145.8 ± 19.6
At 10 months	161.2 ± 16.7

Figure 2. Changes in the values of the Hepaplastin-Test during pregnancy.

further dilution, as the activity was > 100%. One further advantage of the HPT was the ability to measure vitamin K activity in an undiluted sample.

The results show that increase of vitamin K dependant factors is one of the reasons for the hypercoagulability found in pregnancy. We were also able to demonstrate the changes in the endogenous coagulation system during the course of pregnancy.

3 Correlation between maternal and neonatal HPT values

Recently much attention has been paid to intracranial bleeding in infants resulting from vitamin K deficiency. It was noted that in spite of prophylaxis with vitamin K administration intracranial haemorrhage still occured especially in breastfed infants. It has therefore been postulated that lack of vitamin K in mother's milk might predispose to neonatal intracranial haemorrhage.

The obstetrics and gynaecology haematology study group conducted studies on the relationship between the mother's HPT value at delivery and the HPT value measured in a venous blood from the umbili cord. The members of the study group were Dr. MASAHIRO MAKI of Akita University, Dr. KOICHI SHIRAKAWA of Fukuoka University, Dr. TOSHIKO TERAO of Hamamatsu Medical College and Dr. SHIGETO SUZUKI. The results showed that in the 222 cases studied the average value of maternal venous HPT was 151.10 ± 34.65 percent (figure 3).

To study the possible relationship between higher and lowest umbilical venous HPT (> or ⩽ 30% of normal) and maternal HPT levels, the mothers were devided into three groups. Those with a value > 150% (the mean level of the whole group), those with a value of below 120% (-ISD below the mean) and those with a level between these extremes (120–150%).

In the group of mothers whose HPT was under 120 percent the HPT level was under 30% in 33.3% of umbilical samples. In the babies of mothers with HPT values between 120 to 150 percent 19.4% of umbilical samples were ⩽ 30% of normal, whereas in those with a level of > 150% in only 8.2% of the umbilical venous samples had low levels of HPT (figure 4).

4 The relationship between the volume of blood lost and the maternal HPT level at delivery

The relationship between the HPT at delivery and the volume of blood-loss is shown in figure 5. This blood-loss at delivery is dependent on a number of factors including uterine contractions, and it is therefore quite difficult to quantify the influence of coagulation factors including vitamin K. However, when two groups, one with maternal HPT more than 110 percent, and the other with levels of HPT less than or equal to 110 percent were compared for abnormal bloodless (more than 500 ml) at delivery, we noted that 38.5% of the group with low HPT values had abnormal blood-loss, whereas such abnormal loss occurred in only 13.5% of those with higher HPT value of > 110% (figure 6).

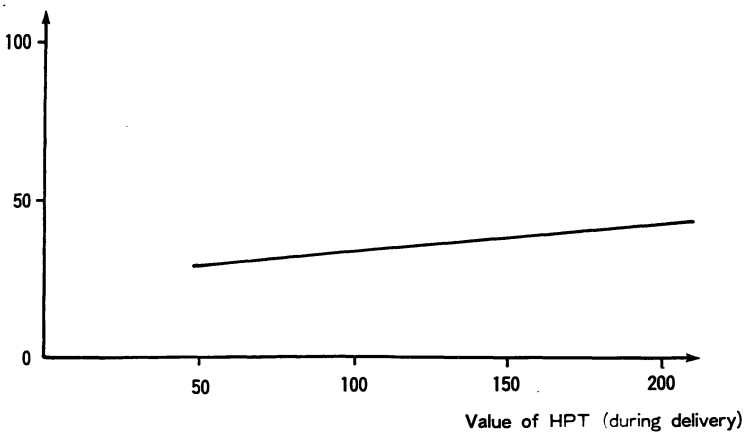


Figure 3. Correlation between the value of HPT during delivery and cord venous blood.

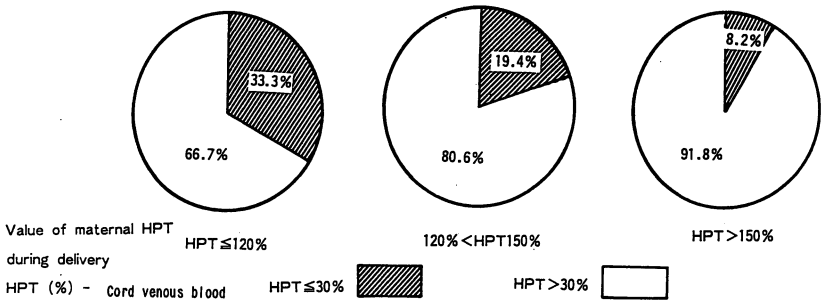


Figure 4. Incidence of hypoprothrombinemia of the newborn related to the value of maternal HPT during delivery.

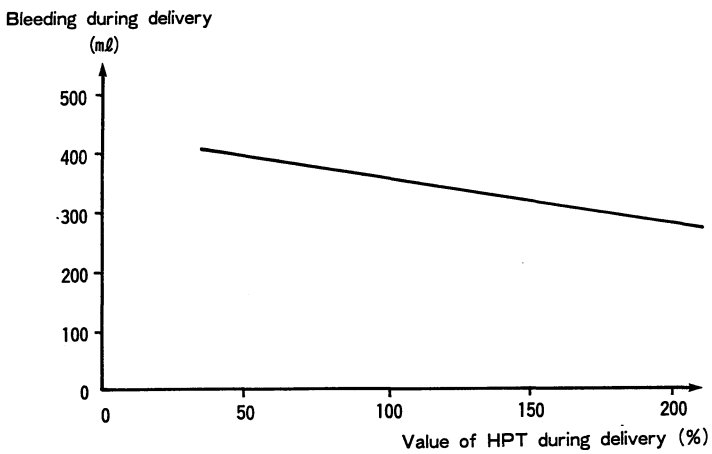


Figure 5.

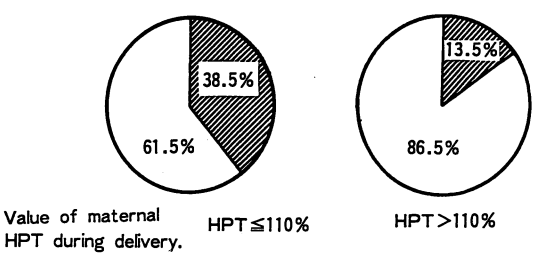


Figure 6. Incidence of abnormal maternal postpartum haemorrhage related to the value of maternal HPT during delivery.

MAKI and others, using oral vitamin K2 in a double-blind study, observed that when pregnant women were given 20 mg daily for seven days, the severity of blood-loss decreased markedly in comparision to that found in a control group given a placebe. We can therefore conclude that coagulation produced by administered vitamin K is clinically useful in pregnant women even when used in excess.

5 Passage of vitamin K through the placenta

VAN CREVELD and his group administered vitamin K, to more than 10,000 mothers and reported that the frequency of neonatal bleeding (neonatal malaena) did not change. This study concluded that vitamin K does not pass through the placenta. However, according to the report of SHEARER and others, vitamin K at the end of pregnancy is present in a very small concentration that amount can hardly be detected (table I). They also reported that a very small amount of vitamin K (an average of 0.12 ng/ml) was detected in umbilical venous blood after they had given an infusion of vitamin K to the mother about one hour before delivery (table II).

Table I. Concentration of Vk_1 in the maternal and cord venous blood (SHEARER). (Vk_1 = vitamin K_1)

Subject no.	Plasma vitamin K_1 (ng/ml)	
	Maternal	Cord
1	0.29	n.d.
2	0.14	n.d.
3	0.14	n.d.
4	0.17	n.d.
5	n.d.	n.d.
6	0.21	n.d.
7	0.13	n.d.
8	0.26	n.d.
9	0.27	n.d.
	Mean 0.20 (8 subjects)	

n.d. = not detected (< 0.10 ng/ml)

Table II. Concentration of Vk_1 of cord venous blood after administration of Vk_1 1 mg to the to the mothers. (SHEARER) (Vk_1 = vitamin K_1)

Subject no.	Time after vitamin K_1 (min)		Plasma vitamin K_1 (ng/ml)	
	Maternal	Cord	Maternal	Cord
1	21	11	72	0.13
2	26	23	78	0.11
3	35	39	80	0.10
4	30	20	85	0.14
5	52	47	45	n.d.
6	19	14	93	n.d.

n.d. = not detected (< 0.10 ng/ml)

However, in the present study, when an intravenous infusion of 60 mg of vitamin K2 was administered to two patients who had elective caesarean section deliveries for cephalo-pelvic disproportion it was found that transfer of vitamin K2 occurred:

Case 1: Patient A primigravid and 28 years old. The concentration of plasma vitamin K2 rose to a peak in one to three hours and declined in seven to eight hours. The pattern is almost similiar to that of normal adults and newborn babies, and 5.3 ng/ml VK2 was detected in the umbilical venous blood (figure 7).

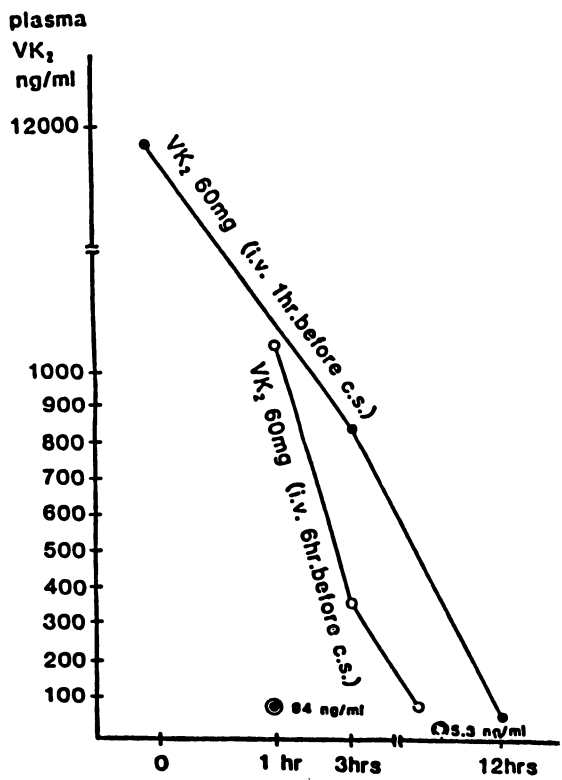


Figure 7. Concentration of Vk_2 in cord venous blood, after administrating to Vk_2 60 mg to the mother before Caesarean section.
(Vk_1 = vitamin K_1
Vk_2 = vitamin K_2)
o—o concentration of Vk_2 in the mother. (case. I)
◎ concentration of Vk_2 in cord venous blood. (case I)
●—● concentration of Vk_2 in the mother. (case II)
◉ concentration of Vk_2 in cord venous blood. (case II)

Case 2: Patient B primigravid and 40 years old. Pregnant for ten months.
The fetus was in a quiet state, and she was given a slow constant infusion of 60 mg of vitamin K2 together with 20 ml of glucose one hour before the performance of the caesarean section. The concentration of vitamin K2 in the plasma a level of 11900 ng/ml was found to be highest just after administration. The level of VK2 was 94 ng/ml in the umbilical venous blood.

The observations from these two case studies are of great importance in view of the fact that, after 69 mg of vitamin K2 was administered by intravenous infusion six hours prior to surgery, a concentration of 5.3 ng/ml of vitamin K2 was detected in the umbilical venous blood.

Comparing these results with those of SHEARER and others, there is a 60 fold difference between the dose of vitamin K1 (1 mg) and that of vitamin K2 (60 mg), and 5.3 ng/ml (equivalent to 44 times of the previously reported umbilical level 0.12 ng/ml) of vitamin K2 was detected.

In the second case, 60 mg of vitamin K2 together with glucose was administered via a slow intravenous injection. A significantly greater amount of vitamin K2 (94 ng/ml) was detected in the umbilical blood of this baby compared to that found in the first case. In the second case, the baby was delivered one hour after the administration of vitamin K2, and in the first case, the baby was delivered six hours after administration of vitamin K2.

The 94 ng/ml of vitamin K2 detected only one hour after administration is 17 times the concentration of vitamin K2 detected in the first case (5.3 ng/ml) after six hours. This suggests that vitamin K2 corsses the placenta immediately.

It is therefore evident that vitamin K2 crosses the placenta though not in any great amount. This might be due to a lower level of binding lipoprotein in the fetus which reduces fetal uptake.

We should mention that there are many problems associated with the dosage and timing of administration of vitamin K2 and estimation of the proportion likely to be transferred to the fetus. It would seem to be necessary to investigate decrease of uptake, as the lipoprotein level becomes lower as pregnancy advances.

Abstract

Little is known about the absorption, excretion and transplacental transport of vitamin K in the perinatal period.
From this point of view, the following studies were carried out.

1) Hepaplastin tests were performed on 65 women in the last stage of pregnancy and each coagulation factor was estimated as well.
2) Correlations were made between mothers' and babies' Hepaplastin test values.
3) Transplacental transport of vitamin K_2 was studied.

The general activity of vitamin K dependent factors in pregnant women was much higher than in non pregnant women.
As far as the correlation between mothers' venous blood during delivery and cord venous blood is concerned, in the group of mothers with Hepaplastin test value of less than 120% of the normal adult value, the value of the Hepaplastin test was less than 30% of normal adult value in the cord venous blood.
We also established that vitamin K passed through the placenta but only in small qualities.

Keywords: Hepaplastin test (HPT), hypothrombinemia, postpartum hemorrhage, vitamin K.

Zusammenfassung

Metabolismus Vitamin K-abhängiger Faktoren bei Müttern und ihren Neugeborenen

Über die Absorption, Exkretion und den transplazentaren Transport von Vitamin K in der Perinatalperiode ist wenig bekannt.
Unter diesem Aspekt wurden folgende Untersuchungen durchgeführt:

1) Bei 65 Frauen wurden am Ende der Schwangerschaft Hepaplastin-Tests durchgeführt und die verschiedenen Gerinnungsfaktoren bestimmt.
2) Wir korrelierten die Ergebnisse der Hepaplastin-Tests der Mütter mit denen der Neugeborenen.
3) Der transplazentare Transport von Vitamin K_2 wurde untersucht.

Generell war die Aktivität von Vitamin K-abhängigen Faktoren bei Schwangeren sehr viel höher als bei nichtschwangeren Frauen.
Betrachtet man die Korrelation der Werte zwischen mütterlichem Venenblut unter der Geburt und dem

Nabelvenenblut, gilt folgendes: in der Gruppe der Mütter mit Hepaplastin-Test-Werten von weniger als 120% als die von normalen Erwachsenen hatten deren Kinder im Nabelvenenblut Hepaplastin-Test-Werte von weniger als 30% gegenüber dem Normalwert bei Erwachsenen.
Wir konnten ebenfalls nachweisen, daß Vitamin K die Plazenta nur in geringem Umfang passiert.

Schlüsselwörter: Hepaplastin-Test (HPT), Hypothrombinaemie, Nachgeburtsblutung, Vitamin K.

Résumé

Métabolisme des facteurs dépendants de la vitamine K chez les mères et leurs nouveaux-nés
On connait peu de choses concernant l'absorption, l'excrétion et le transport transplacentaire de la vitamine K en période périnatale. Dans cette optique les études suivantes ont été réalisées.
1 – Les tests d'hépaplastine ont été effectués chez 65 femmes en fin de grossesse et chaque facteur de coagulation a été dosé.
2 – Des corrélations ont té cherchées entre les valeurs des tests d'hépaplastine des mères et de leurs enfants.
3 – Le transport transplacentaire de vitamine K2 a été étudié.
L'activité générale des facteurs dépendants de la vitamine K est beaucoup plus élevée chez les femmes enceintes que chez les femmes en dehors de la grossesse. Il y a une corrélation entre le sang veineux des mères au cours de l'accouchement et le sang veineux du cordon, en effet, dans le groupe des mères ayant des valeurs du test d'hépaplastine de moins de 120% des valeurs de l'adulte normal, les valeurs des tests d'hépaplastine au sang veineux du cordon sont inférieures à 30% des valeurs de l'adulte normal.
Nous avons également établi que la vitamine K traverse le placenta mais seulement en petites quantités.

Mots-clés: Hypoprothrombinémie, hemorrhagie du post partum, test d'hépaplastine, vitamine K.

References

[1] SHEARER et al: Plasma vitamin K_1 in mothers and their newborn babies. Lancet II (1982)
[2] VAN CREVELD et al: Prothrombin and accelerator globulin in the plasma of newborn under normal and pathological conditions. Neonatal Studies 1 (1952) 1
[3] SUZUKI S, K KANAGAWA, M MAKI, K SHIRAKAWA, T TERAO: Die Wirkung von Vitamin K_2-Sirup bei neonatal Hypoprothrombinaemie. Monatsschr Kinderheilkd, Vol 132/5 (1984) 290

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