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Short communication

Women with epilepsy and post partum bleeding – Is there a role for vitamin K supplementation?

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ABSTRACT

Purpose: Guidelines for women with epilepsy (WWE) are advising those on enzyme inducing drugs EIAEDs to take vitamin K the last month of pregnancy. The primary aim of this study was to investigate whether WWE have a higher frequency of large post partum hemorrhage. Secondary we wanted to see if this was more severe in women taking EIAEDs, and also to evaluate whether those receiving prenatal vitamin K supplementation have a less pronounced risk.

Methods: All patients ($n = 109$), with the diagnosis of epilepsy giving birth at OUS Rikshospitalet from 2006 to 2011 were selected to be in the epilepsy group. They were compared to controls with regard to the amount of post partum hemorrhage, gestational age for the mother, birth weight and APGAR score in the newborns.

Results: No significant difference between the groups regarding post partum hemorrhage, gestational age, birthweight or APGAR score in the newborn was found. Also, comparing the WWE using EIAED who received prenatal vitamin K with those who did not receive vitamin K, no significant difference in post partum hemorrhage could be demonstrated.

Conclusion: In this study, WWE was not found to have increased risk of post partum hemmorrhage including those using EIAED with/without vitamin K supplementation.

1. Introduction

Women with epilepsy (WWE) are faced with particular challenges related to pregnancy and delivery. EIAEDs have been thought to have a negative effect on the synthesis of vitamin K and vitamin K dependent coagulation factors in the liver, in particular in the fetus. Guidelines for women with epilepsy have subsequently advised those using EIAEDs to take vitamin K the last month of pregnancy In addition, it is customary to give the newborn an intramuscular injection of vitamin K.

The association between bleedings in the newborn and the use of EIAEDs was first mentioned in some case studies [1,2]. Crossing of the EIAED over the placenta causing increased degeneration of vitamin K in the fetus has been thought to be the cause [3]. However, no epidemiological studies were done until Kaaja et al. [4] prospectively followed 662 WWE who used EIAEDs. A bleeding complication was found in five (0.7%) of the newborn of mothers using EIAEDs and in five (0.4%) control subjects. Bleeding was associated with birth <32 weeks of gestation and alcohol abuse but not with EIAEDs. This was followed by a retrospective cohort study showing no increase of bleedings in infants of mothers on EIAEDs, even though no vitamin K supplementation was taken by all but 1 of the 169 mothers [5].

In 2009 The American Academy of Neurology updated their guidelines [6] after an evaluation of all evidence based literature 1985–2007. They concluded that there is inadequate evidence to determine if the newborns of WWE taking AEDs have a substantially increased risk of hemorrhagic complications.

The aim of this study was to study whether there was a difference in the occurrence of post-partum bleedings between WWE and healthy women. Further, whether a difference could be detected between those taking EIAEDs and the women either taking no AED or non-EIAED. Finally we also registered complications concerning the newborn, in particular bleedings related to birth and the neonatal period.

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2. Methods

The epilepsy group consisted of all patients (n = 109), with the diagnosis of epilepsy giving birth at OUS Rikshospitalet from 2006 to 2011. One control for each of the WWE was chosen based on age (±5 years for all but 4 controls), time of delivery and delivery method, resulting in a total of 218 subjects in the study. All information was gathered from delivery charts and patient charts at Oslo University Hospital. The groups were compared with regard to the amount of post partum hemorrhage, gestational age, complications related to pregnancy and birth, and also to the birth weight, APGAR score and complications in the newborns. Epilepsy medication was divided into two groups, EIAEDs and non-EIAEDs. Further, it was registered whether the mother had received vitamin K profylaxis the last 4 weeks before birth. Mean and standard deviations were calculated for all analyses. The student T test was used for comparisons of the groups. Statistical analyses were performed using SPSS.

3. Results

3.1. Postpartum bleedings

Mean amount of post partum bleeding for the whole study population was 432 ml. Only three patients had bleedings over 1000 ml (1000, 1700 and 2150 ml), 2 of the 3 was epilepsy patients. With this exception, the amount of bleeding was approximately normally distributed.

3.2. The epilepsy groups and the control group

Mean amount of bleeding in the epilepsy group was 438 ml (SD 232). This was not significantly different (p = 0.67) from the control group who had a mean amount of bleeding of 426 ml (SD 189) (Table 1).

By comparing the control group with those using EIAEDs whose amount of bleeding was 431 ml (SD 154), no differences were found (p = 0.54). The controls were also compared with the non-EIAED group (mean post partum bleeding 449 ml, SD 295) and no difference was found here either (p = 0.50). Finally, the control group was compared to those in the epilepsy group using vitamin K in the pregnancy. Mean amount of bleeding in this group was 418 ml (SD 148), again no difference was found (p = 0.85).

Table 1
Post partum bleeding in the control and the different epilepsy patient groups.

	N=	Bleeding volume, ml (mean)	*P*-value
Controls	109	426	
All epilepsy patients	109	438	0.67
With EIAED	66	431	0.54
With non-EIAED	43	449	0.496
All epilepsy patients taking vitamin K	20	418	0.85

3.3. The epilepsy groups

The epilepsy patients taking vitamin K during pregnancy (n = 20, mean amount of bleeding 418 ml) was further compared to those not taking vitamin K (n = 89, mean amount of bleeding 443 ml). No differences could be demonstrated (p = 0.66). The comparison between the EIAED group and the non-EIAED group also did not reveal any differences (p = 0.70) (Table 2).

Finally, the difference within the group of patients on EIAEDs either on or not on vitamin K supplementation was evaluated. Mean amount of bleeding in the vitamin K group was 408 ml (SD 146), which was not different from those not on vitamin K (441 ml, SD 161 ml) with a p value of 0.44.

3.4. Other outcomes

The birth weight of the children of the epilepsy patients was not significantly different from the mean birth weight of the study population; 3348 and 3404 g, respectively. The mean APGAR for the study population as a whole was 9.23. The children of the epilepsy patients had an APGAR of 9.21 whereas the newborns of the control groups had an APGAR of 9.24, thus no significant difference.

3.5. The child

The focus of this study was to evaluate complications related to post partum bleeding in the mother. We did, however also register complications in the child (Table 3). In the 218 newborn, 42 complications were registered, with a slight preponderance in the epilepsy group. Two deaths occurred, both in the epilepsy group. With regard to bleedings, 3 complications in the newborn were registered, 2 in the epilepsy group (1 little subependymal bleeding, 1 cerebral bleeding in a very premature child leading to death) and 1 in the control group (1 subgaeal hematoma). Five of the infants in the epilepsy group had major malformations (MM) (1 analatresia, 1 patent foramen ovale, 1 situs inversus/duodenal atresia, 1 hypoplastic left ventricle, 1 congenital cystic adenomatoid malformation), whereas MM was registered in 2 born to mothers in the control group (1 transposition of the large arteries, 1 tetralogy of Fallot) (Table 3).

4. Discussion

The relation between the use of EIAEDs in the mother and the amount of postpartum bleeding has not previously been investigated. None of the different comparisons between the epilepsy group and the control group could demonstrate any differences regarding postpartum bleedings. 3/218 of the patients had bleedings more than 1000 ml. With this exception, the amount of bleeding was approximately normally distributed in the study population as a whole, and also among the epilepsy patients and among the controls. When the different subgroups of epilepsy patients were compared no differences were also not found. Especially, no difference was observed between patients on EIAEDs

Table 2
Post partum bleeding in the different epilepsy patient groups according to the use of vitamin K.

	N	Bleeding volume, ml (mean)		*N*	Bleeding volume, ml (mean)	*P*-value
All epilepsy patients with Vit K supplementation	20	418	All epilepsy patients without Vit K supplementation	89	443	0,66
Epilepsy patients taking EIAED and Vit K supplementation	19	408	Epilepsy patients taking EIAED and no Vit K supplementation	47	441	0,44
All epilepsy patients taking EIAED	66	431	All epilepsy patients taking non-EIAED	43	449	0,70

Table 3
Complications in the newborn.

Type of complication	Epilepsy group	Control group
Respiratory problems	6	4
Major malformations	5	2
Bleeding	2	1
Sepsis, fever, infection	2	2
Low birth weight	1	4
Premature	4	1
Others	4	2
Death	2	0
Total	26	16

taking vitamin K supplementation and patients on EIAEDS not taking vitamin K supplementation.

This is a retrospective study collecting the hospital based data. Whether the patient has been taking vitamin K and not reported this is therefore not controllable. Another possible source of error is the methods for measuring the bleedings. Also, in this study 1000 ml was used as a limit for a large bleeding. In practical obstetrics, both 800 and 1000 ml are used. In further studies a limit of 800 ml may be more useful. In addition, one can discuss whether the patients in a university hospital are representative. However, the comparisons between the healthy controls and the patients indicate that this does not represent any bias.

As mentioned in the introduction there are now both prospective and cohort studies that cannot demonstrate any increase of bleedings in the neonates after the mothers use of EIAEDs. In this study three infants had bleedings; one of them born to a mother in the epilepsy group had a serious intracerebral bleeding resulting in death. This child however, was born after 192 days, and since prematurity in itself gives the highest risk for internal bleedings in the newborn, is it not possible to conclude that this was because of the mother's epilepsy or her use of EIAEDs.

In the study population 10 women experienced premature birth, 9 of them were epilepsy patients. Even though the number is too small to conclude in this study, an increased incidence in permature birth in women with epilepsy is also reported in other studies.

5. Conclusion

Enzyme inducing drugs have been related to increased amount of bleeding in the newborn and guidelines have recommended K vitamin in the last month of pregnancy. This has lately been questioned, but the relation between EIAEDs and postpartum bleedings has not been studied previously. This study could not demonstrate any differences between epilepsy patients and controls, nor between those using EIAEDs and non-EIAEDs. In addition no increased bleeding could be demonstrated in the women on EIAEDs and not using vitamin K and those on EIAEDs taking K vitamin. These findings along with further studies in this field, may contribute to an altering of the guidelines concerning WWE and prenatal vitamin K supplementation.

Conflict of interest

The authors declare that they have no conflict of interest.

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