Ref: Ro Med J. 2021;68(4)
DOI: 10.37897/RMJ.2021.4.7

The role of vitamin K during pregnancy – a literature review

Maria Cemortan, Olga Cernetchi

Departament of Obstetrics and Gynecology, "Nicolae Testemitanu" State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

ABSTRACT

Micronutrients are indispensable substances for ensuring proper metabolism, which, in the case of pregnant women, has an indirect influence on perinatal outcomes. Hypovitaminosis K is a rare condition in adults. However, vitamin K deficiency can pose a significant risk to the health of both mother and fetus, which can cause bleeding, especially in newborns. Newborns have a low natural level of vitamin K because they do not receive the necessary amounts in the antenatal period, which is caused by the slower transfer of this vitamin through the placenta. The use of drugs that affect the metabolism of vitamin K by pregnant women can increase the rate of various complications in newborns, related to hypovitaminosis K. Micronutrients, especially vitamin K, are essential for the body of pregnant women, being crucial in fetal development.

Keywords: vitamin K, pregnancy, intrahepatic cholestasis of pregnancy, hemorrhages in newborns

INTRODUCTION

Micronutrients are crucial for maintaining pregnancy and ensuring adequate maternal metabolism, which enables fetal growth and development with an indirect influence on perinatal outcomes. Nutrient deficiencies, which can manifest during pregnancy in a wide range, have a negative impact on maternal and fetal health. Vitamins occupy a special place among physiologically active substances. The role of vitamins lies not only in the fact that they are indispensable components of living organisms, but also in the fact that they can be used as medication for the treatment of various pathological conditions.

Vitamin K is a family of fat-soluble vitamins, two forms of vitamin K are found in foods: K1 and K2, with other subtypes being synthetic forms [1]. Menaquinones have unsaturated isoprenyl side chains and are classified according to side chain length, from MK-4 to MK-13 [2]. Vitamin K1 is the main form found in the human body and is absorbed from food sources such as green vegetables. Vitamin K2 is mainly found in egg yolks, meat, vegetables, and fermented products. In addition, vitamin K2 is synthesised by the gut flora through receptors (B-class receptor type I and Niemann-Pick C1-Like 1), which have recently been reported to regulate intestinal absorption of vitamin K [3,4].

Vitamin K is emulsified by bile salts in the small intestine, then it is absorbed by enterocytes, where it is combined with triacylglycerol-rich lipoproteins (containing apolipoproteins A and B-48) and released into the lymphatic and circulatory systems. Then, vitamin K reaches the liver and, by endocytosis, chylomicrons, which are made up of lipoproteins and the vitamin K complex, enter hepatocytes where they form a complex with apolipoprotein B-100 and return to the circulation. These molecules are transformed by the addition and removal of apolipoprotein particles. Then, after being transported through the blood circulation, vitamin K molecules are absorbed by target tissues (such as

Corresponding author:
Maria Cemortan
E-mail: mariacemortan@yahoo.com

Article History:
Received: 30 November 2021
Accepted: 7 December 2021

the brain, heart, arteries, cartilage, and bone) via LDL receptors (figure 1) [5,6].

Following digestion, bile salts emulsify dietary vitamin K and the byproducts of triglyceride (TG) hydrolysis, generating mixed mycelia, which are then taken up by enterocytes in the intestinal epithelium and transformed into chylomicrons (CM), which contain apolipoproteins A (A) and B48 (B-48). The thoracic duct allows CM to exit the intestinal lymphatic capillaries and enter the circulation. After entering the bloodstream, CMs bind to the HDL proteins, apolipoproteins C and E. In order to remove TGs from CMs, lipoprotein lipase (LPL) is needed, and the process is done in the capillaries of muscle, adipose tissue, and other tissues.

Apolipoprotein A and apolipoprotein C particles are presented by the residual chylomicrons (CR), preserving vitamin K inside. Following receptor-mediated endocytosis, CRs bind to LDLR and LRP receptors and enter hepatocytes. VLDL molecules (containing apolipoprotein B-100) are used to repackage CR complexes before releasing them into the bloodstream, where they pick up apolipoproteins C and E. These complexes undergo modification in the capillaries via LPL, resulting in VLDL-remains known as IDL. Smaller LDL particles, which contain apolipoprotein B-100, are produced as a result of the metabolization and subsequent loss of apolipoproteins C and E from IDL. It is assumed that vitamin K is still concentrated in the lipophilic core. Osteoblasts can receive lipids from circulating lipoproteins like CR and LDL, which are found on the surface of the bone matrix. Osteoblasts contain lipoprotein receptors such as LDLR and LRP1, which can interact with CR and LDL to endocytose particles containing vitamin K. According to published data, LDL and CR particles are the primary sources of MK-7 and K1, respectively, for osteoblasts [7].

Vitamin K serves as a coenzyme for the vitamin K-dependent ɣ-glutamyl carboxylase, which is involved in hemostasis, bone metabolism, and other physiological processes [1]. ɣ-glutamyl carboxylase is synthesised in the central nervous system (CNS) during embryogenesis. The importance of vitamin K in preserving proper myelin production in the CNS has been documented in the literature. Vitamin K antagonists can also cause fetal CNS abnormalities and mental retardation when they are used during pregnancy. These findings point to a potential role for vitamin K in prenatal brain development [8]. Additionally, vitamin K acts through the blood clotting factors such as prothrombin (factor II), proconvertin (factor VII), factor Christmas (factor IX), and Stuart-Prower factor (X) to influence the coagulation process. Therefore, this vitamin partic-

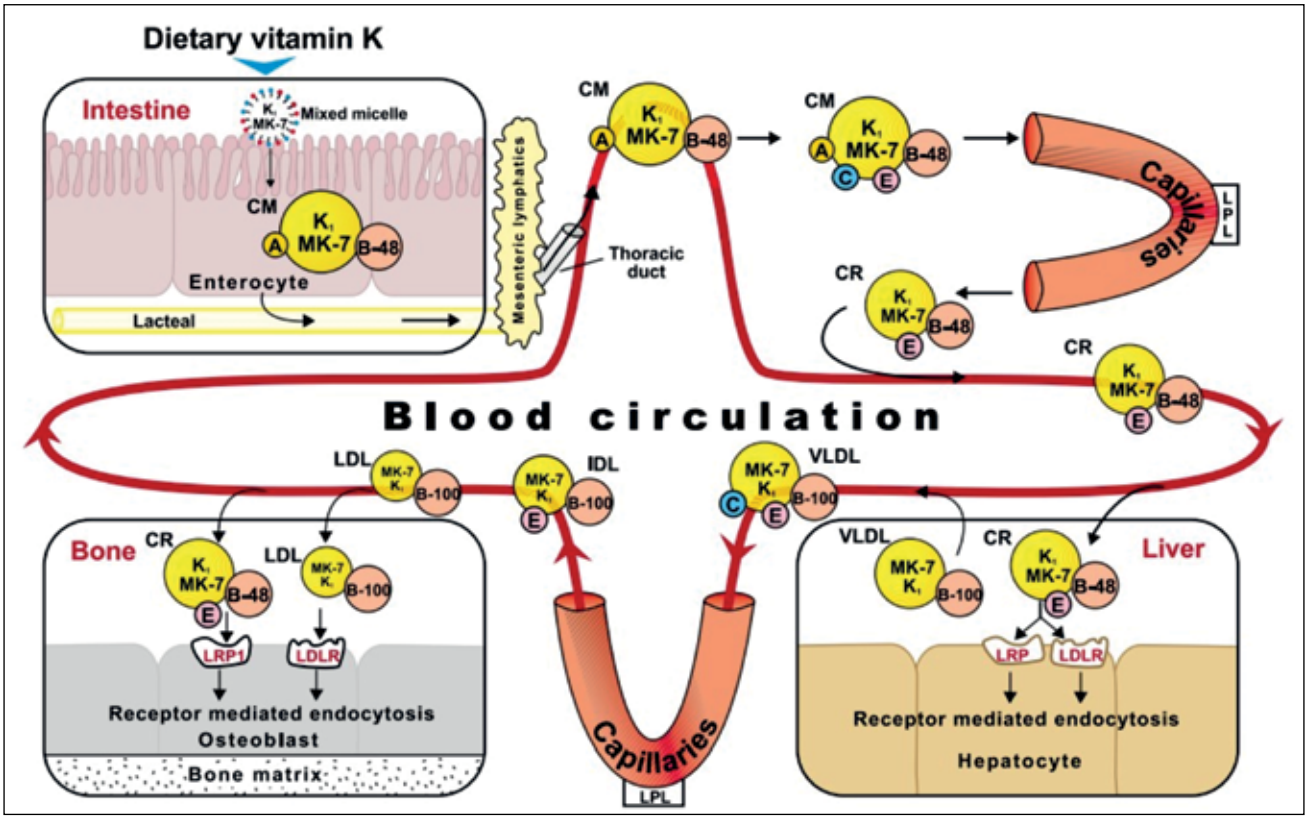

FIGURE 1. Schematic representation of the metabolism of dietary K1 and MK-7 [7]

ipates indirectly in the clotting mechanism through both extrinsic and intrinsic pathways [9]. Prothrombin time, for example, is a marker commonly used to estimate vitamin K levels indirectly. However, prothrombin time is more likely to assess vitamin K activity than its actual level. This method might underestimate the true prevalence of vitamin K deficiency since a prolonged prothrombin time is a late sign of hypovitaminosis K [10].

Hypovitaminosis K can severely impair the health of the mother and fetus by increasing the risk of coagulopathic hemorrhages, especially in neonates. In these cases, hemorrhage is due to low levels of prothrombin, a vitamin K-dependent factor. When prothrombin time increases noticeably due to decreased prothrombin activity, vitamin K insufficiency is thought to be clinically significant [1]. Although vitamin malabsorption due to related pathology may result in deficiency, however it is relatively uncommon in the general adult population. Whereas the function of vitamin K during pregnancy is largely unknown, the impact of clinically severe nutritional deficiencies also increases with the development of pregnancy, especially in women with poor nutrition [11]. In turn, maternal malnutrition not only has immediate impacts but also leads to a number of fetal conditions that can become evident over time, impairing the fetus's metabolic, immunological, cognitive, and neurological development [12].

THE ROLE OF VITAMIN K IN PREGNANT WOMEN

The effects of vitamin K on pregnant women are not well documented in the literature. The effects of this vitamin have been studied in relation to a number of clinical disorders in the general population, including osteodystrophy, osteoporosis, coronary heart disease, and chronic kidney disease [1,5]. There is information in the literature on the potential contribution of hypovitaminosis K to the etiology of Alzheimer's disease, however more studies are needed [13]. Vitamin K has also been used as a safe treatment for cases of pregnancy-related osteoporosis since it is crucial for bone metabolism [14,15]. Currently regarded as a promising agent in cancer prevention, vitamin K2 has been proven to inhibit some cancer cells without causing any negative side effects [16]. Clinical studies have demonstrated the potential role of vitamin K2 in improving the prognosis of cancer patients [17].

Vitamin K deficiency in pregnancy is frequently associated with maternal malabsorption of the vitamin, related not only to various conditions but also to the use of drugs that inhibit vitamin K activity, such as antiepileptics (carbamazepine, phenytoin, barbiturates), antituberculosis drugs (isoniazid, rifampicin), certain antibiotics (cephalosporins) and vitamin K antagonists (warfarin) [18].

Gastrointestinal diseases can compromise pancreatic and/or biliary functions, which can trigger lipid malabsorption mechanisms, such as in celiac disease, cystic fibrosis, ulcerative colitis, cholestasis, including intrahepatic cholestasis of pregnancy. Hypovitaminosis K may develop as a result of these conditions' poor vitamin absorption [16]. The authors have proposed that vitamin K insufficiency in pregnant women may increase the risk of coagulopathic hemorrhages given the effects of this vitamin that are already documented. As a result, Kenyon et al. found that the rate of postpartum hemorrhages was higher in the group of women who did not take vitamin K (45% versus 12%) [19]. An important detail in the given context is the steatorrhea, which occurs in intrahepatic cholestasis of pregnancy. Steatorrhea, being a direct but rare complication of cholestasis gravidarum, can induce malabsorption of vitamin K. At present, however, studies focusing on the assessment of risk and bleeding rates in intrahepatic cholestasis of pregnancy largely do not recommend direct assessment of maternal vitamin K levels. A study by Furrer et al. did not detect a difference in the volume of postpartum blood lost in women with cholestasis gravidarum compared to the control group, thus the authors had to assume that the role of vitamin K in postpartum hemorrhage in patients with intrahepatic cholestasis of pregnancy could be questionable [20]. It should be noted that this study did not include direct assessment of serum vitamin K levels in the women included in the study. However, Maldonado et al. described severe vitamin K deficiency and coagulopathy related to intrahepatic cholestasis of pregnancy, suggesting a direct relationship between them [21]. In this case report, the authors noted that there was no firm evidence as to the cause of hypovitaminosis K: intestinal malabsorption or insufficient dietary intake. But the low body mass index of the patient led the authors to suspect specific nutritional factors as the cause of vitamin K deficiency in this case. Although Lees et al. observed no cases of coagulopathy in women with cholestasis gravidarum in their research, the authors remark that prospective studies on a larger representative cohort are required to assess the actual incidence of coagulopathy in obstetric cholestasis [22]. As a result, the authors conclude that there is not enough data available in the literature to evaluate the direct relationship between vitamin K levels and the risk of maternal hemorrhage [11,14,23].

Antibiotics interfere with vitamin K levels because they generally cause a decrease in the level of bacteria in the gut, especially vitamin K-producing bacteria. Many bacteria colonising the human gut

(especially Bacteroides) synthesize vitamin K2, which plays a role in electron transport and oxidative phosphorylation. However, it remains controversial whether bacterial synthesis of vitamin K in the gut provides a significant supply of vitamin K to the human body [24]. Vitamin K deficiency is currently observed in patients with prolonged peroral antibacterial therapy, especially with broad-spectrum antibiotics. Antibiotics such as cephalosporins, which include the N-methylthiotetrazole side chain, are considered inhibitors of hepatic vitamin K epoxide reductase [25]. A case-control study of a cohort of 6,191 participants concluded that patients using cephalosporins and other antibiotics for more than 48 hours have a high risk of bleeding events [26].

Some drugs are also reported to influence vitamin K absorption. For example, drugs prescribed to reduce cholesterol levels in dyslipidaemia or those that interfere with intestinal lipases, used for the treatment of obesity, such as orlistat, or bile acid sequestrants such as cholestyramine [15]. However, these drugs are not widely used during pregnancy.

Epilepsy is one of the most common neurological disorders and affects more than 70 million people worldwide [27]. Recent studies have found an increased risk of various pregnancy complications in women with epilepsy compared to the control group, namely: premature detachment of the normally inserted placenta (aRR = 1.68), postpartum hemorrhage (aRR = 1.11), etc. [28]. At the same time, there is little data in the literature regarding the role of vitamin K in pregnant women with epilepsy. Some rodent studies have shown the anticonvulsant effect of vitamin K in minimal clonic seizures [8]. There is data in the literature suggesting that antiepileptic drugs may affect the metabolism of this vitamin, thus inducing hypovitaminosis K [18].

Women of reproductive age undergoing bariatric surgery for the treatment of morbid obesity may also experience adverse perinatal outcomes in subsequent pregnancies associated with various nutritional deficiencies [29]. Deficiencies of vitamin K, vitamin B12, and some minerals have been reported in pregnant women who have previously undergone this type of surgery [11]. There is data in the literature suggesting an increased rate of miscarriage in women in the first year after bariatric surgery, but the studies conducted include a small number of cases [30]. However, there is insufficient evidence to demonstrate a clear link between vitamin K deficiency and miscarriage.

THE ROLE OF VITAMIN K IN NEWBORNS

As mentioned above, vitamin K deficiency is a rare condition in adults. However, the situation is different among newborns, who have naturally low levels of vitamin K due to the fact that they do not receive adequate amounts during the antenatal period, caused by the slower transfer of this vitamin through the placenta. Umbilical cord blood vitamin K levels in healthy newborns are often below the detection limit of 0.02 ng/ml [31]. One study showed an extremely low level of vitamin K in cord blood, regardless of gestational age, in 5 neonates who died within the first 24 hours of life and who did not receive vitamin K supplementation [4]. Though breastfeeding is preferable for newborns, vitamin K levels in breast milk are significantly lower than those in formula feeding (on average 2.5 mg/l versus 24-175 mg/l) [32]. In addition to what has been reported, the authors suggest that the gut flora of newborns is immature and the amount of vitamin K synthesized by it is insufficient. Thus, studies comparing vitamin K levels in fecal masses have been conducted, reporting considerably lower levels of this vitamin in infant samples than in adult samples. These studies support the theory of the involvement of the immature intestinal flora of infants in the pathogenesis of vitamin K deficiency [4].

Vitamin K Deficiency Bleeding (VKDB) is a condition more commonly seen in infants with inadequate vitamin K levels, which can also lead to intracranial bleeding. VKDB was first described by Townsend in 1894, who reported 50 cases of hemorrhages in newborns occurring in the first 2-3 days of life [1].

Pregnant women taking medication that affect vitamin K metabolism may increase the rate of early-onset VKDB (within the first 24 hours of life) among newborns. Therefore, disorders of the coagulation system in newborns require immediate treatment with vitamin K given before diagnosis [11]. At the same time, there is data in the literature on late-onset VKDB, first described in Thailand in 1966. Over 10 years later, Bhanchet et al. summarized the cases of 93 breastfed infants in Thailand who experienced bleeding episodes between the 1st and 2nd month of life [4,33]. Thus, in this country, the incidence of late-onset VKDB was 72 per 100,000 births, with an intracranial hemorrhage rate of 82% in these infants. These data can be compared with those obtained from studies in Japan, where the incidence of late-onset VKDB was 8.8 per 100,000 births. Therefore, there is a significant discrepancy in the incidence of late VKDB even in the same geographical region [4]. In Western European countries, the incidence of late VKDB in infants not given vitamin K was found to be 5/105 births compared to 11 and 72/105 births in Japan and Thailand, respectively [11]. Immediately after birth, the proportion

of infants with VKDB who did not receive vitamin K was estimated to be between 0.01% and 0.44%. The mortality rate in infants with severe hemorrhage was 20%, of which 50% was due to intracranial hemorrhage and ongoing neurological damage [11].

Early onset of VKDH is frequently associated with maternal malabsorption of vitamin K and administration of drugs that inhibit the activity of this vitamin [18]. Moreover, recent studies have revealed impaired placental function in cases of pre-eclampsia and intrauterine fetal growth restriction, which could lead to impaired placental transfer of vitamin K [34,35].

At the same time, exposure of women to vitamin K antagonist anticoagulants during pregnancy may affect the fetus in utero, resulting in coumarin embryopathy. Approximately 6% of newborns exposed to coumarin consumed by their mothers during pregnancy develop coumarin embryopathy with the presence of skeletal abnormalities (e.g. medial hypoplasia and epiphyseal calcifications), which in turn are seen in 80% of these babies. Central nervous system malformations (e.g. midline structural defects) were detected in 45% of infants diagnosed with coumarin embryopathy; signs of intracranial hemorrhage were observed in 10% of infants. Moreover, since coumarin drugs pass transplacentally, they subsequently affect the fetal coagulation system, which increases the risk of antenatal intracranial hemorrhage [11].

VITAMIN K ADMINISTRATION RECOMMENDATIONS IN PREGNANCY AND NEWBORNS

The recommended daily dietary intake of vitamin K for adults is set at 70 mg/day in the European Union and 90 mg/day in the United States [14,36,37]. The authors suggest that vitamin K supplementation is not necessary in physiological pregnancy [11]. However, it may be indispensable in the case of associated pathologies that have caused the studied vitamin deficiency. It should be noted that the toxic dose for vitamin K2 is unknown at this time, and maximum daily doses for vitamins K1 and K2 in pregnancy have not been established because there have been no studies on reproductive or teratogenic risks in this area [14,38].

The South Australian Perinatal Practice Guidelines, in intrahepatic cholestasis of pregnancy, recommend vitamin K supplementation (10 mg per os daily) in cases where prothrombin time is prolonged [39]. The Royal College of Obstetrics and Gynaecology UK Guideline No. 43 supports this practice, suggesting the need to administer the water-soluble form of vitamin K in a dose of 5-10 mg in intrahepatic cholestasis of pregnancy [23]. The same guideline cautions that if prothrombin time is normal, administration of low-dose water-soluble vitamin K may be recommended after weighing the possible benefits and risks. At the same time, as mentioned above, the authors suggest that prothrombin time is a late marker of hypovitaminosis K and its assessment does not denote the real vitamin K level, underestimating the real incidence of hypovitaminosis K [10]. Some researchers emphasize the need for injectable vitamin K administration 3 days before birth and in the early lactation period [40].

To prevent the early onset of VKDB, pregnant women receiving medication that affects vitamin K metabolism (except warfarin) should be advised to administer vitamin K before delivery [4]. According to recommendations in Japan, pregnant women using this type of medication (except warfarin) should use 15-30 mg of vitamin K daily 2-4 weeks before delivery or newborns should be prescribed a single dose of vitamin K of 0.5-1.0 mg [41].

According to literature data, hypovitaminosis K can occur among women receiving antiepileptic treatment, especially enzyme-inducing drugs [42]. Enzyme-inducing drugs, such as phenobarbital, carbamazepine and phenytoin, cross the placenta, induce altered vitamin K metabolism and cause hypovitaminosis as well as hemorrhage in newborns of mothers undergoing such treatment [8]. Therefore, most authors suggest the need for vitamin K supplementation 2-4 weeks antepartum when antiepileptic treatment is applied, this recommendation being related to the risk of intracerebral hemorrhage in newborns [11,43]. However, a systematic review of the literature on the administration of antiepileptic drugs in pregnancy revealed that there is insufficient evidence that would conclusively establish that vitamin K supplementation in the last weeks of pregnancy reduces the risk of VKDB [4]. At the same time, studies among women with epilepsy have shown increased vitamin K levels in newborns of mothers who consumed vitamin K in pregnancy compared to those whose mothers did not receive the supplement [23, 44].

In the Republic of Moldova, the National Clinical Protocol for Newborn Care recommends routine administration of a single dose of phytomenadione (synthetic vitamin K1) of 1.0 mg i/m for term infants and 0.5 mg i/m for preterm infants for prophylaxis of hemorrhagic disease of the newborn, the dose being effective also in the late form of the disease [45].

CONCLUSIONS

Micronutrients, especially vitamin K, are indispensable for the pregnant woman's body and are crucial for the intrauterine development of the fe-

tus. Nutritional deficiencies, arising during pregnancy for a variety of reasons, have an impact on the health of the mother and the fetus, influencing perinatal outcomes.

Conflict of interest: none declared
Financial support: none declared

REFERENCES

1. U.S. Department of Health & Human Services, National Institutes of Health, Factsheet for Health Professionals: Vitamin K. Available at: https://ods.od.nih.gov/factsheets/VitaminK-HealthProfessional/.
2. Booth SL. Vitamin K: food composition and dietary intakes. Food Nutr Res. 2012;56.
3. Takada T, Yamanashi Y, Konishi K, Yamamoto T, Toyoda Y, Masuo Y, Yamamoto H, Suzuki H. NPC1L1 is a key regulator of intestinal vitamin K absorption and a modulator of warfarin therapy. *Sci Transl Med.* 2015 Feb 18;7(275):275ra23.
4. Araki S, Shirahata A. Vitamin K Deficiency Bleeding in Infancy. *Nutrients*. 2020 Mar 16;12(3):780.
5. de Oliveira RB, Stinghen AEM, Massy ZA. Vitamin K role in mineral and bone disorder of chronic kidney disease. *Clin Chim Acta.* 2020 Mar;502:66-72.
6. Ferland G. Vitamin K. In: Erdman JW, Macdonald IA, Zeisel SH, eds. Present Knowledge in Nutrition. 10th ed. Washington, DC: Wiley-Blackwell, 2012:230-247.
7. Shearer MJ, Newman P. Metabolism and cell biology of vitamin K. *Thromb Haemost.* 2008 Oct;100(4):530-47.
8. Zalkhani R, Moazedi AA. Basic and clinical role of vitamins in epilepsy. *Journal of Research in Applied and Basic Medical Sciences.* 2020; 6(2):104-114.
9. Țuțuianu B. Fiziologia coagulării – despre modelul celular (I). *Jurnalul de Chirurgie.* Iasi, 2007;3(2):102.
10. Card DJ, Gorska R, Harrington DJ. Laboratory assessment of vitamin K status. *Journal of Clinical Pathology.* 2020;73(2):70-75.
11. Shahrook S, Ota E, Hanada N, Sawada K, Mori R. Vitamin K supplementation during pregnancy for improving outcomes: a systematic review and meta-analysis. *Sci Rep.* 2018 Jul 30;8(1):11459.
12. Oh C, Keats EC, Bhutta ZA. Vitamin and Mineral Supplementation During Pregnancy on Maternal, Birth, Child Health and Development Outcomes in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis. *Nutrients.* 2020 Feb 14;12(2):491.
13. Allison AC. The possible role of vitamin K deficiency in the pathogenesis of Alzheimer's disease and in augmenting brain damage associated with cardiovascular disease. *Med Hypotheses.* 2001 Aug;57(2):151-5.
14. Brown B, Wright C. Safety and efficacy of supplements in pregnancy. *Nutr Rev.* 2020 Oct 1;78(10):813-826.
15. Tsuchie H, Miyakoshi N, Hongo M, Kasukawa Y, Ishikawa Y, Shimada Y. Amelioration of pregnancy-associated osteoporosis after treatment with vitamin K_2: a report of four patients. *Ups J Med Sci.* 2012 Aug; 117(3):336-41.
16. Simes DC, Viegas CSB, Araújo N, Marreiros C. Vitamin K as a Diet Supplement with Impact in Human Health: Current Evidence in Age-Related Diseases. *Nutrients.* 2020 Jan 3;12(1):138.
17. Dasari S, Ali SM, Zheng G, Chen A, Dontaraju VS, Bosland MC, Kajdacsy-Balla A, Munirathinam G. Vitamin K and its analogs: Potential avenues for prostate cancer management. *Oncotarget*. 2017 May 19; 8(34):57782-57799.
18. Merchant R, Doctor P, Kulkarni S, Choudhari A, Pandey AK. Early Vitamin K Deficiency – A Rare Presentation. *J Radiol Diagn Methods.* 2020;2:101.
19. Kenyon AP, Piercy CN, Girling J, Williamson C, Tribe RM, Shennan AH. Obstetric cholestasis, outcome with active management: a series of 70 cases. *BJOG.* 2002 Mar;109(3):282-8.
20. Furrer R, Winter K, Schäffer L, Zimmermann R, Burkhardt T, Haslinger C. Postpartum Blood Loss in Women Treated for Intrahepatic Cholestasis of Pregnancy. *Obstet Gynecol.* 2016 Nov;128(5):1048-1052.
21. Maldonado M, Alhousseini A, Awadalla M, Idler J, Welch R, Puder K, Patwardhan M, Gonik B. Intrahepatic Cholestasis of Pregnancy Leading to Severe Vitamin K Deficiency and Coagulopathy. *Case Rep Obstet Gynecol.* 2017;2017:5646247.
22. Lees J, Al-Rawi S, McPhee H; Southcoast Perioperative Audit and Research Collaboration. Coagulopathy in obstetric cholestasis in Wessex Deanery. *Int J Obstet Anesth.* 2019 Feb;37:130-131.
23. Royal College of Obstetricians and Gynaecologists. Obstetric cholestasis. Green-top Guideline no. 43. 2011. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_43.pdf
24. Lippi G, Franchini M. Vitamin K in neonates: facts and myths. *Blood Transfusion.* 2011;9(1):4.
25. Aziz F, Patil P. Role of prophylactic vitamin K in preventing antibiotic induced hypoprothrombinemia. *Indian J Pediatr.* 2015 Apr;82(4):363-7.
26. Chen LJ, Hsiao FY, Shen LJ, Wu FL, Tsay W, Hung CC, Lin SW. Use of Hypoprothrombinemia-Inducing Cephalosporins and the Risk of Hemorrhagic Events: A Nationwide Nested Case-Control Study. *PLoS One.* 2016 Jul 27;11(7):e0158407.
27. Li X, Himes RA, Prosser LC, Christie CF, Watt E, Edwards SF, et al. Discovery of the First Vitamin K Analogue as a Potential Treatment of Pharmacoresistant Seizures. *J Med Chem.* 2020 Jun 11; 63(11):5865-5878.
28. Kashif T, Fathima N, Usman N, Qaseem A, Jayaraj JS. Women with Epilepsy: Anti-epileptic Drugs and Perinatal Outcomes. *Cureus.* 2019 Sep 13;11(9):e5642.
29. American College of Obstetricians and Gynecologists. ACOG Committee opinion no. 549: obesity in pregnancy. *Obstet Gynecol.* 2013 Jan; 121(1):213-7.
30. Yau PO, Parikh M, Saunders JK, Chui P, Zablocki T, Welcome AU. Pregnancy after bariatric surgery: the effect of time-to-conception on pregnancy outcomes. *Surg Obes Relat Dis.* 2017 Nov;13(11):1899-1905.
31. Ardell S, Offringa M, Ovelman C, Soll R. Prophylactic vitamin K for the prevention of vitamin K deficiency bleeding in preterm neonates. *Cochrane Database Syst Rev.* 2018 Feb 5;2(2):CD008342.
32. Clarke P, Mitchell SJ, Shearer MJ. Total and Differential Phylloquinone (Vitamin K1) Intakes of Preterm Infants from All Sources during the Neonatal Period. *Nutrients.* 2015 Sep 25;7(10):8308-20.
33. Bhanchet P, Tuchinda S, Hathirat P, Visudhiphan P, Bhamaraphavati N, Bukkavesa S. A bleeding syndrome in infants due to acquired prothrombin complex deficiency: a survey of 93 affected infants. *Clinical Pediatrics.* 1977;16(11):992-998.
34. Chiofalo B, Laganà AS, Vaiarelli A, La Rosa VL, Rossetti D, et al. Do miRNAs Play a Role in Fetal Growth Restriction? A Fresh Look to a Busy Corner. *Biomed Res Int.* 2017;2017:6073167.
35. Laganà AS, Vitale SG, Sapia F, Valenti G, Corrado F, Padula F, Rapisarda AMC, D'Anna R. miRNA expression for early diagnosis of preeclampsia onset: hope or hype? *J Matern Fetal Neonatal Med.* 2018 Mar; 31(6):817-821.
36. Institute of Medicine (US) Panel on Micronutrients. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington (DC): National Academies Press (US); 2001.
37. European Food Safety Authority (EFSA). Dietary Reference Values for Nutrients: Summary Report. EFSA Supporting Publication. 2017:e15121.
38. European Food Safety Authority (EFSA). Scientific Committee on Food Scientific Panel on Dietetic Products, Nutrition and Allergies. Tolerable Upper Intake Levels for Vitamins and Minerals. 2016.

39. South Australia Maternal & Neonatal Community of Practice. *Obstetric Cholestasis.* April 2016.
40. Eremina EY, Masharova AA. Intrahepatic cholestasis in pregnant women. Experimental and Clinical Gastroenterology. 2011;6:87-91.
41. Shirahata A., Itou S., Takahashi Y., Nishiguchi T., Mastuda Y. Modified guideline of vitamin K administration for vitamin K deficiency in infancy. *J Jpn Pediatric Soc.* 2011;115:705-712.
42. Ali A. Global health: epilepsy. *Seminars in Neurology.* 2018;38(2):191-199.
43. Khuda I, Aljaafari D. Epilepsy in pregnancy. A comprehensive literature review and suggestions for saudi practitioners. *Neurosciences* (Riyadh). 2018 Jul;23(3):185-193.
44. Cornelissen M, Steegers-Theunissen R, Kollée L, Eskes T, Motohara K, Monnens L. Supplementation of vitamin K in pregnant women receiving anticonvulsant therapy prevents neonatal vitamin K deficiency. *Am J Obstet Gynecol.* 1993 Mar;168(3 Pt 1):884-8.
45. Ministerul Sănătății, Muncii și Protecției Sociale al Republicii Moldova. Protocolul clinic național PCN-217 Îngrijirea nou-născutului sănatos. Chișinău, 2019. Available at: https://msmps.gov.md/wp-content/uploads/2021/03/PCN-217-Ingrijirea-nou-nascutului-sanatos.pdf.