Hyperemesis gravidarum

Maternal and neonatal future health

Nijsten, K.

Publication date
2022

CHAPTER 6

Hyperemesis gravidarum and vitamin K deficiency: a systematic review

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British Journal of Nutrition, 2021; 1-13.

ABSTRACT

Hyperemesis gravidarum (HG), severe nausea and vomiting in pregnancy, can lead to vitamin deficiencies. Little is known about HG-related vitamin K deficiency. We aim to summarize available evidence on the occurrence of HG-related vitamin K deficiency and corresponding maternal and neonatal complications.

A systematic review was conducted, searching Medline and EMBASE from inception to November 12th, 2020.

We identified 1564 articles, of which we included 15 in this study: 14 case reports (n=21 women) and one retrospective cohort study (n=109 women). Nine out of 21 women reported in case reports had a prolonged prothrombin time (PT). The cohort study measured PT in 39/109 women with HG, of whom 10/39 women (26%) had prolonged PT. In total, 30-50% women received vitamin K supplementation after vitamin K deficiency had been diagnosed. Four case reports (n=4 women) reported corresponding maternal complications, all consisting of coagulopathy-related haemorrhage. Nine case reports (n= 16 neonates) reported corresponding neonatal complications including intracranial haemorrhage (n=2 neonates) and embryopathy (n=14 neonates), which consisted of Binder phenotype (n=14 neonates), chondrodysplasia punctata (n=9 neonates) and grey matter heterotopia (n=3 neonates).

In conclusion, vitamin K deficiency and related complications occur among women with HG. In our systematic review, we were unable to assess the incidence rate.

INTRODUCTION

Hyperemesis gravidarum (HG) is severe nausea and vomiting in pregnancy. HG can be complicated by dehydration, electrolyte disturbances, poor nutritional intake and weight loss.[1] Vitamin deficiencies, including vitamin B1 deficiency, can further complicate HG, although little is known about the incidence and consequences of such deficiencies.[2]

The fact that vitamin K deficiency has been frequently described in chronic malnutrition makes it of possible interest in the context of HG.[3, 4] Vitamin K is primarily obtained through dietary intake, but is also synthesized by bacteria in the large intestine.[5] Although vitamin K is a fat soluble vitamin, the body's stores of vitamin K are limited, and vitamin K can be depleted after metabolic surgery and in fat malabsorption syndromes.[3, 4, 6] Vitamin K is important for coagulation, serving as a cofactor in the synthesis of multiple vitamin K-dependent proteins (Factors II, VII, IX, X and protein C and S) in the intrinsic pathway.[7] Besides its effects on coagulation, vitamin K deficiency can also lead to abnormal calcium depositions and growth of cartilage.[6]

Vitamin K deficiency can cause a range of maternal and fetal complications. Maternal and neonatal coagulopathy-related haemorrhage has been described[8, 9] as well as neonatal vitamin K deficiency embryopathy and grey matter heterotopia, most commonly described in the context of maternal vitamin K antagonist medication use.[10, 11] Vitamin K deficiency embryopathy includes Binder phenotype and chondrodysplasia punctata. Binder phenotype is the result of maxillonasal hypoplasia and causes a flat facial profile with a short nose and flat nasal bridge.[12] Chondrodysplasia punctata is a skeletal abnormality classified by stippled calcifications of certain bones, most commonly toes, ankles or fingers.[13] Short or misshapen bones can also be present, for example short distal phalanges, also known as brachytelephalangy.[11] Vitamin K deficiency-related chondrodysplasia punctata should not be mistaken for the genetic form of chondrodysplasia punctata, which is caused by mutations in the X-linked arylsulfatase E (ARSE) gene and can be ruled out by genetic testing.[13] Grey matter heterotopia is a neurological disorder classified by common malformations of cortical development, possibly caused by depletions in the vitamin K dependent growth arrest specific 6 protein which is widely expressed in the nervous system.[14-16]

The fact that HG has a profound impact on nutritional intake, sometimes necessitating enteral or parenteral nutrition, has raised concerns about the possibility that vitamin K deficiency can also occur in pregnancies complicated by HG.[1, 17, 18] Recently, the identification of the immediate

and long term effects of HG for pregnant women and their offspring were selected as urgent research questions by patients and health care professionals, which triggered the current work.[19] In this systematic review, we aim to summarize the available literature on HG-related maternal and neonatal vitamin K deficiency and determine the relevance of measuring vitamin K-related coagulopathy factors or prothrombin time (PT) in routine work-up for women with HG.

METHODS

The study protocol was registered at the website of Prospero, an international prospective register of systematic reviews, on August 17th, 2020 (CRD42020199501). This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search strategy

We performed a search to identify all available studies reporting on vitamin K deficiency in women suffering from HG and their offspring. We searched Medline and Embase from inception to November 12th, 2020. Our search included the following terms: 'hyperemesis gravidarum', 'pregnancy sickness', 'vitamin K deficiency', 'embryopathy', 'haemorrhage' and their synonyms, as shown in Appendix A. De-duplication of database search results were conducted using Endnote software.[20] We also searched citation lists of eligible primary studies and reviews.

Study selection

Two reviewers (KN and LM) independently screened titles and abstracts. Conflicts were resolved by discussion until consensus was reached, or by consultation of a third reviewer (RP). All potentially relevant articles were retrieved as full text and assessed on the following inclusion and exclusion criteria. Inclusion criteria were: 1. women diagnosed with or admitted for HG with either 2. Maternal vitamin K deficiency or signs/symptoms of vitamin K deficiency (for example: prolonged PT or signs of any type of haemorrhage) and/or 3. Offspring of women with HG with vitamin K deficiency embryopathy or any type of vitamin K deficiency-related haemorrhage. Exclusion criteria were: 1. Non-human subjects, 2. Women with vitamin K deficiency due to any other cause than HG. We included observational studies, case reports, case series and research letters. Conference abstracts were included, if they provided sufficient information. We did not apply any language restrictions.

Data extraction

Data extraction was performed independently by two reviewers (KN and LM). We extracted data on study characteristics, demographics, details about pregnancy and specifically about the severity and clinical course of HG (if available), laboratory results (including prothrombin time, coagulation factors and vitamin K measurements) and both maternal and neonatal outcomes (vitamin K deficiency-related haemorrhage or embryopathy).

Quality assessment

We assessed the risk of bias of included case reports using the Joanna Briggs Institute checklist for case reports and the Newcastle-Ottawa Scale (NOS) for included cohort studies.[21, 22] The NOS assigns up to a total maximum score of 9 based on eight items: a score ≥7 was considered as good quality, a score ≥5 as fair quality and a score ≤4 as poor quality.[22] All included articles were critically appraised and were included, despite of their quality assessment.

Statistical analysis

Data of included case reports were combined by entering available information on baseline characteristics and outcome measures of each reported case of women with HG or their offspring into a SPSS database (SPSS Statistics, version 26.0 for Windows, IBM Corp., Armonk, NY, USA). If a case report included multiple HG patients or multiple HG-exposed offspring, all of the cases were entered separately. Continuous data were presented as means with standard deviations (SD) if they were normally distributed. Not normally distributed continuous data were presented as medians with interquartile ranges (IQR). Dichotomous and categorical data were displayed as frequencies with percentages.

RESULTS

Search results

We identified 1741 articles and one additional article through searching citation lists as shown in **Figure 1.** After removing duplicates, 1564 articles remained for title and abstract screening, of which 36 were deemed possibly eligible. Upon further eligibility screening after full-texts for possibly eligible papers had been retrieved, we included 15 articles reporting on HG and vitamin K deficiency.[23-37] Fourteen of the included studies were case reports[23-27, 29-37] and we included one retrospective cohort study.[28] Two of the included studies were conference abstracts [33, 35] and two additional included studies were written in French.[28, 29]

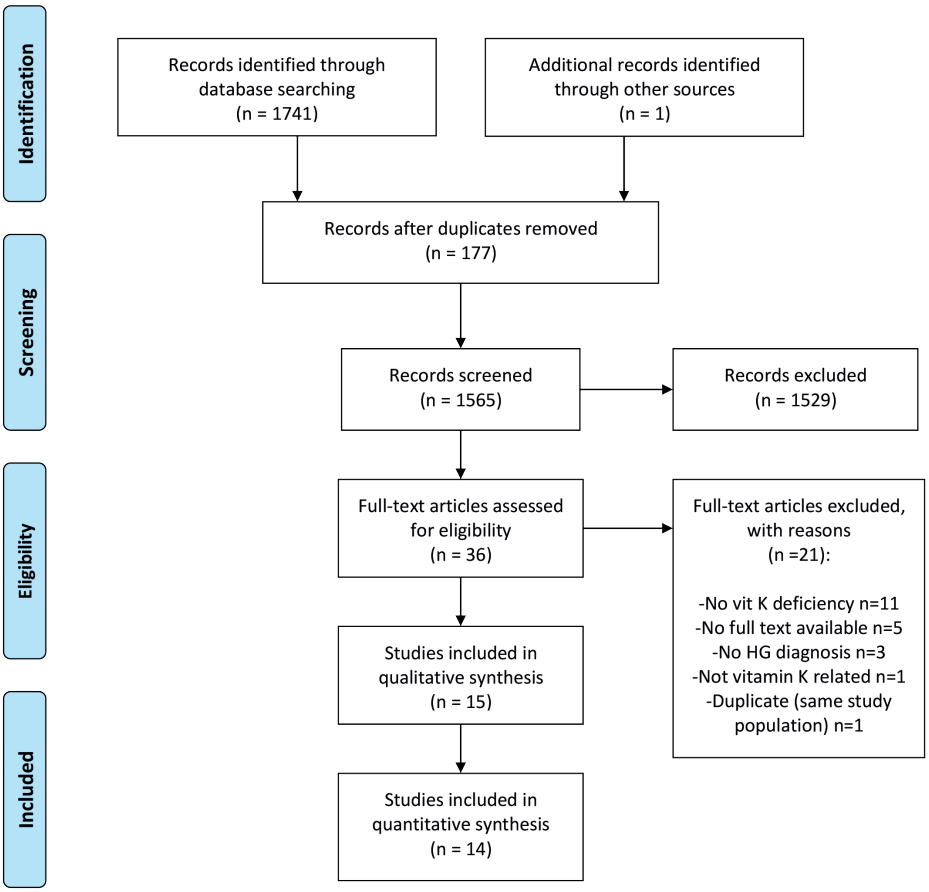

Figure 1. PRISMA diagram selection process of articles

Two case reports included multiple cases: Miller *et al.*[33] included three cases and Toriello *et al.*[37] included eight cases. From the eight cases of Toriello *et al.*[37], case 8 was excluded for this review since vitamin K deficiency was caused by Crohn's disease instead of HG. Case 1 of Toriello *et al.*[37] was identical to the included case report of Robinson *et al.*[34], but contained follow-up information of the neonate, so we combined data of these two case reports.

Risk of bias assessment

The risk of bias assessment of case reports is showed in **Figure 2.** For most domains, case reports were assessed as low risk of bias. However, in half of the studies a patient's medical history was not or poorly described. In addition, in almost half of the studies which reported

a treatment, the treatment was not clearly described in terms of dosage or frequency and therefore was rated as having a high risk of bias. The cohort study was rated to be of fair quality, as shown in **Table 1**.

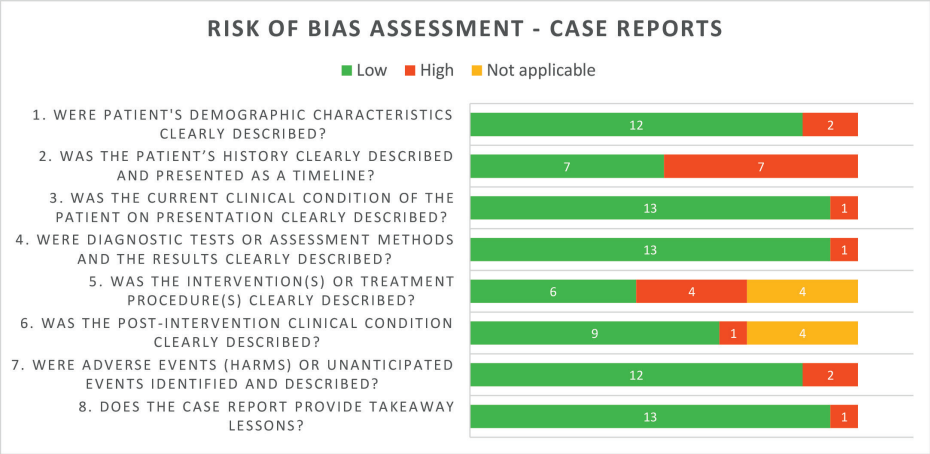

Figure 2. Risk of bias assessment of included case reports

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Table 1. Risk of bias assessment of the included cohort study using the Newcastle-Ottawa Quality Assessment Scale (NOS)

	Selection	Comparability	Outcome	Total score	Quality score
Chraïbi *et al*, 2014	**		***	5	Fair quality

The NOS risk consisted of 8 items with a total maximum score of 9. A score ≥7 was considered as good quality, a score ≥5 as fair quality and a score ≤4 as poor quality.

Baseline characteristics

Baseline characteristics of all included studies are shown in **Table 2** and data of the included women from case reports was combined and shown in **Table 3**. In 17 women the gestational age of onset of symptoms was reported; in the vast majority (16/17) symptoms of HG had started in the first trimester (mean 8.47±3.16 weeks) **(Table 2 and 3)**. Ten articles (n=14 women) reported whether weight loss during pregnancy due to HG had occurred: 13 out of 14 women had some degree of weight loss, ranging from 5 to 28 kg with an average weight loss of 13.64±8.03 kg compared to 5.6±3.1 kg weight loss reported in the cohort study.[23, 24, 27-32, 34, 35, 37] Nine out of twenty-one women of included case reports had more than 10 kg weight loss.[23, 27, 29, 32, 34, 37]

In all three cases of Miller *et al.*[33] and in case 4 of Toriello *et al.*[37] treatment for HG was not described **(Table 2)**. All other 17 included women of remaining case reports received some form of treatment for HG[23-27, 29-32, 34-37], varying from receiving anti-emetics (9/17) [23, 27, 29, 30, 32, 34, 35, 37], intravenous rehydration (13/17)[23, 24, 27, 29-32, 34, 36, 37] to receiving tube feeding (6/17)[23, 25-27, 32, 37]. Chraïbi *et al.*[28] described a cohort of women admitted for HG: all 109 included women (100%) received intravenous treatment and 106 women (98.1%) received at least one anti-emetic **(Table 2)**. From the 21 women included from case reports, 11 women had been admitted for HG **(Table 3)**.[23-26, 29, 31, 32, 34-37]

Vitamin K deficiency diagnosis

In half of the case reports, a vitamin K deficiency diagnosis was made retrospectively based on neonatal clinical signs of embryopathy.[26, 27, 32, 33, 37] The other half performed laboratory measurements to confirm vitamin K deficiency. PT was most commonly used and prolonged PT was reported as prolonged PT in seconds or as decreased prothrombin levels. PT was measured in 9 out of 21 women included in case reports: 8/21 women (38.1%) had a prolonged PT **(Table 4 and 5)**.[23-25, 29, 31, 34, 36, 37] In 4 out of 9 women PT was measured secondary to maternal signs of haemorrhage.[24, 25, 29, 34] In the other 5 cases PT was included in routine laboratory measurements, without the presence of clinical signs of maternal or fetal haemorrhage or embryopathy.[23, 30, 31, 36, 37]

Four case reports performed additional coagulopathy laboratory measurements. Three case reports measured activated Partial Thromboplastin Time (aPTT).[24, 29, 34] Two of them found a prolonged aPTT, but also found a decreased factor II, VII, IX, X and Protein C and S, which are vitamin K *dependent* coagulation factors.[29, 34] **(Table 4)** The fourth study was the only study that measured vitamin K concentrations in addition to PT and that found vitamin K deficiency (below 0.05ng/mL).[36] Selvarajah *et al.*[35] mentioned that the woman included had a deranged clotting profile, but did not further specify which laboratory measurements were performed **(Table 4)**.

In one neonate coagulation factors were measured postpartum because of low Apgar scores together with signs of haemorrhage: first a haematoma in the hand palm and later intracranial haemorrhage. A prolonged PT together with a decreased Factor II, VII, IX and X was found.[30]

In the cohort study from Chraïbi *et al.*[28], PT was measured in 39 out of 109 women (35.8%) admitted for HG: 10 out of these 39 women (25.6%) had a prolonged PT with a level below 70% and 2 out of these 10 women (5.1%) had a PT level below 50% **(Table 5)**. The cohort

study did not describe why PT was initially measured or whether other coagulation factors were measured.[28]

Vitamin K supplementation

Vitamin K was supplemented in all case reports reporting a prolonged PT (n=8 women and n=1 neonate) and in one women described to had a 'deranged clotting profile' **(Table 4)**.[23-25, 29-31, 34, 36, 37] One additional woman received vitamin K as part of parenteral nutrition, so in total 10 out of 21 (47.6%) women and one neonate received vitamin K supplementation as shown in **Table 5**.[23-25, 29-32, 34, 36, 37] Vitamin K was administered by different routes, but most women (60.0%) and the described neonate received intravenous vitamin K supplementation **(Table 5)**.[23, 24, 29-31, 35, 37] In all of them, PT normalized after vitamin K supplementation.[23-25, 29-31, 34, 36, 37]

In the cohort study of Chraïbi *et al.*[28] 3 out of 10 women with a prolonged PT (level below 70%) received vitamin K, which was not further specified in route of administration, dosage or frequency **(Table 4)**.

Liver function measurements

Liver transaminases tests were performed in 7 out of 21 women included in case reports of whom 4 women (19.0%) had elevated liver transaminases **(Table 4 and 5)**.[23, 29, 31, 36] Three out of these 4 women also had elevated total bilirubin levels and 2 women had elevated gamma glutamyl transferase (GGT) levels.

As shown in **Table 4**, Chraïbi *et al.*[28] reported elevated alanine transaminase (ALAT) and aspartate aminotransferase (ASAT) in respectively 20.7 and 25.7%. PT levels were significantly lower in women with an increased ALAT than in women with normal ALAT levels (68±14% versus 78±9%).

Table 2. Baseline characteristics of included studies

	General			*Demographic characteristics*					*HG severity and course*				*HG treatment*			*Other pregnancy characteristics*			
Study	***Year***	***Country***	***Study design***	***Age (year)***	***Ethnicity***	***G..P..***	***Pre-pregnancy weight (kg)***	***Pre-pregnancy BMI***	***Gestation at onset of HG symptoms***	***Total weight loss (kg)***	***Admitted for HG (duration)***	***Re-admitted for HG***	***IV***	***Anti-emetics***	***TPN***	***Gestation at delivery***	***Sex***	***Birth weight (gram)***	***Medical history or complications***
Alessandri	2010	France	Case report	20	Western	G1P0	70	26.7	7 weeks	15	Yes (4 wks)	No	Yes	Yes	Yes	37 weeks	Girl	2780	Gallbladder lithiasis
Baba	2016	Japan	Case report	36	Asian	G1P0	62	25.8	10 weeks	8	Yes (6 wks)	No	Yes	No	No	-	-	-	Large myoma with intestinal obstruction
Bailey	1964	UK	Case report	21	-	G1P1	-	-	12 weeks	-	Yes (5 wks)	No	-	-	Yes	-	Girl	3000	-
Bhoj	2013	USA	Case report	-	-	G2P2	-	-	6 weeks	-	-	-	-	-	Yes	37 weeks	Girl	2190	-
Brunetti-Pierri	2007	USA	Letter	-	Western	G3P1	-	-	8 weeks	18	-	-	Yes	Yes	Yes	34 weeks	Boy	2540	-
Chraibi [a]	2015	France	Cohort (n=109)	28±5.7	46.5% French	56.4% Nullipara	64.3±13.7	23.9±4.5	46±15 (days)	5.6±3.1	109 (100%)	12.8%	100%	98.1%	-	274±16 (days)	57% Girl	3283 ±527	-
Devignes	2009	France	Case report	23	-	G1	-	-	14 weeks	18	Yes (-)	No	Yes	Yes	No	-	-	-	-
Eventov-Friedman	2009	Israel	Case report	41	-	G8P4	50	19.5	16 weeks	0	-	-	Yes	Yes	No	32 weeks	Boy	2200	-
Kawamura	2007	Japan	Letter	33	Asian	G2P0	45	20.0	9 weeks	5	Yes (5 wks)	No	Yes	No	No	20 weeks	-	-	-
Lane	2015	USA	Case report	21	African-American	G1P0	94.4	-	10 weeks	17	Yes (-)	No	Yes	Yes	Yes	-	Boy	-	
Miller ***CASE 1***	2018	USA	Case report	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CASE 2	"	"	"	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CASE 3	"	"	"	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 2. *Continued*

	General			*Demographic characteristics*					*HG severity and course*				*HG treatment*			*Other pregnancy characteristics*			
Robinson [b]	1998	USA	Case report	22	African-American	G2P0	-	-	4 weeks	14	Yes (-)	Yes (1 time)	Yes	Yes	No	40 weeks	Girl	2800	Anaemia
Selvarajah	2014	UK	Case report	33	Western	G1P0	-	-	7 weeks	6	Yes (-)	-	-	Yes	-				-
Shigemi	2015	Japan	Case report	39	Asian	G1P0	64.1	25.0	8 weeks	-	Yes (1 wk)	Yes (5 times)	Yes	-	-	38 weeks	Girl	2640	Oesophageal hiatus hernia diagnosed at 32 weeks
Toriello *CASE 2*	2012	USA	Case report	-	Western	-	-	-	-	9	-	-	Yes	No	No	40 weeks	Girl	3600	Syncope
CASE 3	"	"	"	27	Asian	G5P3	50	-	8 weeks	13	-	-	-		Yes	38 weeks	Girl	2520	-
CASE 4	"	"	"	25	Western	-	64.5	-	6 weeks	28	Yes(12wks)	No	-	-	-	33 weeks	Boy	-	-
CASE 5	"	"	"	-	Western	-	-	-	5 weeks	-	-	-	Yes	-	-	40 weeks	Girl	3540	-
CASE 6	"	"	"	-	Western	-	-	-	6 weeks	28	Yes (-)	Yes (3 times)	Yes	Yes	No	32 weeks	Girl	1280	Pre-eclampsia
CASE 7	"	"	"	-	African-American	-	-	-	8 weeks	12	-	-	Yes	Yes	-	33 weeks	Girl	-	-

Abbreviations: G..P..: Gravidity..Parity.., BMI: Body Mass Index, IV: intravenous, TPN: total parenteral nutrition, UK: United Kingdom, USA: United States of America. [a] Cohort study: characteristics presented as mean+SD, median (IQR) or frequency (%). [b] Case of Robinson *et al.* is the same case as case 1 of Toriello *et al.*, so available data is combined.

Table 3. Combined baseline characteristics of included case reports in this systematic review

	N=21		% missing
Demographic characteristics			
Age (years) , median (IQR)	26.00	21.25-35.25	42.9%
Pre-pregnancy weight (kg), median (IQR)	63.05	50.00-68.63	61.9%
Pre-pregnancy BMI (kg/m^2), median (IQR)	25.00	19.75-26.25	76.2%
Ethnic origin, n (%)			33.3%
- Western	7	33.3%	
- Asian	4	19.0%	
- African American	3	14.3%	
Primigravida, n (%)	6	28.6%	38.1%
HG severity & course			
Gestational age at onset of symptoms of HG (weeks), mean±SD	8.47	3.16	19.0%
Total weight loss (kg), mean±SD	-13.64	8.03	33.3%
HG-related hospital admission, n (%)	11	52.4%	47.6%
Length of initial hospitalization (weeks), median (IQR)	5.00	3.25-7.50	71.4%
Readmission, n (%)	3	14.3%	52.4%
HG treatment			
Received treatment for HG, n (%)	17	81.0%	19.0%
Anti-emetics	9	42.9%	
IV Fluids	13	61.9%	
Parenteral nutrition	6	28.6%	
Other pregnancy characteristics			
Gestational age at delivery (weeks), median (IQR)	37.00	32.50-39.00	38.1%
Sex of neonate, n (%)			33.3%
- Female	10	47.6%	
- Male	4	19%	
Birth weight of neonate (grams), median (IQR)	2640.00	2200.00-3000.00	47.6%

Abbreviations: HG: hyperemesis gravidarum, IV: intravenous. Normally distributed continuous variables are presented as means with standard deviations (mean±SDs), skewed variables as medians with interquartile ranges (IQR) and dichotomous or categorical variables as frequencies with percentages (%).

Table 4. Maternal and neonatal outcomes of included studies

	Maternal:					**Neonatal:**	*Vitamin K embryopathy*					
Study	***PT prolonged*** (seconds or %; gestation)	***Vitamin K and/or other coagulation factors measured***	***Elevated Liver-enzymes***	***Vitamin K supplementation*** *(dosage; gestation)*	***Maternal complications***	***Neonatal Haemorrhage***	***Binder pheno type***	***Chrondro dysplasia punctata***	***Brachy tele-phalangy***	***Grey matter hetero topia***	***Anomaly first detected***	***Additional information***
Alessandri	Yes (42%; 11wks 25%; 12 wks)		Yes (ALAT 186 UI/l)	iv at 12 wks	-	-	Yes	Yes	Yes	-	US: 24 wks	-
Baba	Yes (14.2s; 16 wks)	Normal APTT	-	iv 10mg/day at 16 wks	Intraperitoneal haemorrhage	-	-	-	-	-	-	-
Bailey	Yes (63s)	-	-	im	Haematuria, vaginal bleeding	-	-	-	-	-	-	-
Bhoj	-	-	-	-	-	-	Yes	Yes	Yes	-	Postpartum	Epileptic seizures, chiari type II malformation
Brunetti-Pierri	-	-	-	-	-	-	Yes	Yes	Yes	Yes	US: 20 wks	Epileptic seizures, ventilary support, long term disability
Chraïbi [a]	Yes (10 out of 39 women (25.6%)) [b]	-	Yes (in 20.7 to 25.7%)	3 out of 10 (30%)	-	-	-	-	-	-	-	-
Devignes	Yes (11%; 18 wks)	aPTT↑, factor II, VII, X, proteïn C,S↓	Yes (ALAT 353 UI/l)	10 mg iv once at 18 wks	Haematuria, rectal bleeding	-	-	-	-	-	-	-
Eventov-Friedman	Normal		-	-	-	Intracranial haemorrhage	-	-	-	-	Postpartum	Neonatal lab: PT↑, Factor II, VII,IX,X↓. Treatment: 1mg iv
Kawamura	Yes (28%; 14 wks)		Yes	10mg iv & 2mg/ day at 14 wks	-	Intracranial haemorrhage	-	-	-	-	US: 17 wks	Induced abortion due to US anomalies, hydrocephalus
Lane	-	-	Normal	In TPN at 15 wks	-	-	yes	-	-	-	US: 14 wks	-
Miller CASE 1	-	-	-	-	-	-	Yes	Yes	Yes	-	Unclear	Neonate died at 3.5 months
CASE 2	-	-	-	-	-	-	Yes	Yes	Yes	Yes	Unclear	-
CASE 3	-	-	-	-	-	-	Yes	Yes	yes	-	Unclear	-

Table 4. *Continued*

	Maternal:					**Neonatal:**	*Vitamin K embryopathy*					
Robinson	Yes (36.5s; 15 wks)	aPTT↑, Factors II, VII, IX, X↓	Normal	10 mg sc/day for 3 days at 15 wks	Epistaxis with 1 liter blood loss	-	Yes	-	-	-	US: 17 wks	Calcaneal asymmetry
Selvarajah	-	Deranged clotting profile at 13 wks	Normal	Iv at 13 wks	-	-	-	-	-	-	-	-
Shigemi	Yes (15.2s; 9 wks 19.7s; 11 wks)	Vit K↓ (<0.05 ng/mL) & factor VII↓	Yes (ALAT 72 UI/l)	15 mg oral/day for 5 wks at 11 wks	-	-	-	-	-	-	-	-
Toriello CASE 2	-	-	-	-	-	-	Yes	-	Yes	-	Postpartum	-
CASE 3	Yes (22%; 8 wks)	-	-	Iv at 8 wks	-	-	Yes	-	Yes	-	US: 30 wks	-
CASE 4	-	-	-	-	-	-	Yes	Yes	Yes	-	Postpartum	Spastic quadriplegia and severe intellectual disability.
CASE 5	-	-	-	-	-	-	Yes	-	Yes	Yes	Postpartum	Normal development (1/2yr)
CASE 6	-	-	-	-	-	-	Yes	Yes	Yes	-	Postpartum	Normal development (3yr)
CASE 7	-	-	-	-	-	-	Yes	Yes	-	-	US	Trachystomy & gastrostomy

Abbreviations: PT: prothrombin time, US: ultrasound (perinatal), aPTT: activated Partial Thromboplastin Time, TPN: total parenteral nutrition. [a] Cohort study: data presented as frequencies/percentages. [b] PT measured in 39/109 women.

Table 5. Combined outcomes of included case reports in this systematic review

	N=21	
Maternal		
PT Prolonged, n (%)	8	38.1%
Vitamin K measured, n (%)	1	4.8%
Elevated liver transaminases, n (%)	4	19.0%
Vitamin K supplementation, n (%)	10	47.6%
- Oral [a]	2	20.0%
- Subcutaneous [a]	1	10.0%
- Intramuscular [a]	1	10.0%
- Intravenous [a]	6	60.0%
Gestational age when women received vitamin K supplementation (weeks), median (IQR)	14.00	11.50-15.50
Maternal haemorrhage occurred, n (%)	4	19.0%
Neonatal		
Neonatal haemorrhage occurred, n (%)	2	9.5%
Vitamin K embryopathy, n (%)	14	66.7%
- Binder phenotype	14	66.7%
- Chondrodysplasia punctata	9	42.9%
- Brachytelephalangy	11	52.4%
- Grey matter heterotopia	3	14.3%
Anomalies detected on foetal ultrasound, n (%)	7	33.3%
- Gestational age when anomalies were first detected, median (IQR)	18.50	16.25-25.50
Anomalies detected postpartum, n (%)	6	28.6%

Abbreviations: PT: Prothrombin time. Skewed variables are presented as medians with interquartile ranges (IQR) and dichotomous or categorical variables as frequencies with percentages (%). [a] Percentage shown is percentage of women who received vitamin K supplementation.

Maternal complications due to HG-related vitamin K deficiency

We identified four studies, including four women, that reported on maternal complications due to HG-related vitamin K deficiency. All four studies reported coagulopathy-related haemorrhage **(Table 4 and 5)**. Two women had mild haemorrhage symptoms, not in the context of their delivery, consisting of haematuria, bruising and/or vaginal or rectal bleeding.[25, 29] Two other studies reported more severe cases of haemorrhage. Robinson *et al.*[34] described a case of severe epistaxis with one litre blood loss, which was initially treated with topical silver nitrate and after the diagnosis of vitamin K deficiency was made vitamin K was supplemented. Baba *et al.*[24] described a case of a woman with HG who developed intraperitoneal haemorrhage due to a pedunculated myoma, which was operatively resected at 16 weeks gestation. In total,

perioperative blood loss contained 290 ml of which 110 ml intraperitoneal blood loss was noted at the start of the operation. Postoperative laboratory results revealed coagulopathy based on a prolonged PT with a normal aPTT and international normalized ratio (INR). Coagulopathy was strongly suspected to be secondary to vitamin K deficiency, since PT normalized after intravenous supplementation of vitamin K, and the amount of blood loss was thought to be insufficient to induce secondary coagulopathy.

Neonatal complications due to HG-related vitamin K deficiency

Nine studies reported neonatal complications due to HG-related vitamin K deficiency.[23, 26, 27, 30-34, 37] Two case reports, including two neonates, reported neonatal intracranial haemorrhage[30, 31] and seven case reports, including 14 neonates, reported neonatal embryopathy as shown in **Table 4 and 5**.[23, 26, 27, 32-34, 37]

Neonatal intracranial haemorrhage

Two studies reported neonatal intracranial haemorrhage **(Table 5)**. Kawamura *et al.*[31] described a case where fetal intracranial haemorrhage accompanied by hydrocephalus was detected during the midtrimester ultrasound at 17 weeks gestation. Due to these fetal anomalies the woman decided to terminate her pregnancy. Autopsy showed a subarachnoid haemorrhage with hemosiderin deposits to the choroid plexus near the foramen of Luschka and on the surface of the brainstem which blocked the pathway of cerebrospinal fluid absorption and subsequently lead to a non-obstructive hydrocephalus. No evidence of chromosomal abnormalities was found and a diagnosis of a Dandy-Walker syndrome was rejected because of the presence of a non-obstructive hydrocephalus.

Eventov-Friedman *et al.*[30] also reported a case of neonatal intracranial haemorrhage, which was diagnosed postpartum **(Table 4)**. An emergency caesarean was performed at 32 weeks gestation due to suspected fetal distress. The neonate had an Apgar score of 1, 1 and 3, after respectively 1, 5 and 10 minutes. A cranial ultrasound revealed extensive intracranial haemorrhage and neonatal coagulopathy laboratory results confirmed a vitamin K deficiency. A cranial computed tomography on day two postpartum showed no midline shift and therefore the infant was managed conservatively. The neonate developed recurrent seizures which was treated with phenobarbital. No further neonatal long term outcomes were described.

Neonatal vitamin K related-embryopathy

From the 14 neonates diagnosed with vitamin K related-embryopathy in the studies included in our review, all neonates had Binder phenotype, 9 neonates also had chondrodysplasia punctata

of whom three also suffered from grey matter heterotopia as shown in **Table 5**.[23, 26, 27, 32-34, 37] Also brachytelephalangy was noted in 11 out of 14 neonates with vitamin K-related embryopathy.[23, 26, 27, 33, 37] Genetic testing was performed in 9 out of 14 neonates, none of which found genetic abnormalities.[23, 26, 27, 32, 34, 37] Three studies specifically described that no mutations in the ARSE gene were found.[26, 27, 37]

Anomalies detected and timing of vitamin K supplementation

Of the 10 women who received vitamin K supplementation, 5 cases had neonatal complications.[23, 31, 32, 34, 37] Four cases had neonatal vitamin K deficiency-related embryopathy[23, 32, 34, 37] and one case had intracranial haemorrhage.[31] As shown in **Table 4**, in Alessandri *et al.*[23], Kawamura *et al.*[31], Robinson *et al.*[34] and case 3 of Toriello *et al.*[37] vitamin K supplementation was started *before* fetal anomalies were detected on perinatal ultrasound. Here, PT was measured on maternal indication or during routine maternal laboratory measurements and subsequently vitamin K was supplemented at respectively 12, 14, 15 and 8 weeks gestation. In Lane *et al.*[32] vitamin K was administered *after* fetal anomalies were detected on perinatal ultrasound. Vitamin K was included in parenteral nutrition which was started at 15 weeks gestation. The median gestational age when vitamin K supplementation was commenced was 14 weeks (IQR 12-16) compared to the median gestational age of 19 weeks (IQR 16-26) when fetal anomalies were detected on perinatal ultrasound **(Table 5)**.

Neonatal prognosis

Eleven out of 21 neonates had been given a good prognosis by the paediatrician during follow-up visits.[23, 24, 26, 29, 32, 36, 37] One neonate described in Miller *et al.*[33] died at 3.5 months: she had a severe nasal aperture stenosis, critical cervical spinal stenosis and myelomalacia of the upper cervical cord **(Table 4)**. Two neonates were described as having a poor prognosis.[27, 37] One of these neonates suffered from long term disability due to ventilatory support dependence and severe neurodevelopmental delay.[27] While the other neonate described in case 4 of Toriello *et al.*[37] suffered from severe intellectual disability and spastic quadriplegia following spinal surgery because of severe cervical spinal stenosis **(Table 4)**. [27] Two neonates described in Bhoj *et al.*[26] and case 6 of Toriello *et al.*[37] had a mild delay in neurodevelopment.

DISCUSSION

Principal findings

In this systematic review, which identified 15 articles, we found evidence that vitamin K deficiency secondary to HG can lead to severe adverse maternal and neonatal outcomes. Our review highlights the fact that HG, usually considered a benign and self-limiting condition of early pregnancy, can lead to irreversible morbidity and mortality, and therefore deserves the prompt attention of clinicians to avoid these sequelae. Although selective reporting likely has affected our findings, two thirds of the neonates included in the case reports suffered from vitamin K embryopathy, making it the most commonly reported vitamin K deficiency-related complication among women with HG, followed by maternal haemorrhage (19%) and neonatal haemorrhage (10%). A further 26-38% of cases showed evidence of disturbed maternal coagulation due to vitamin K deficiency, with 30-48% receiving vitamin K supplementation.

Strengths and limitations of the study

One of the main strengths of this study is that it presents an overview of a rare complication, and summarizes the evidence on vitamin K deficiency in women with HG and their offspring. Besides case reports, research letters and conference abstracts, we were also able to include one cohort study. We did not apply a date or language restriction, which avoided selective inclusion of English language literature. Lastly, all articles included were critically appraised and were rated as low to moderate bias.

Our study also has some limitations. Although we were able to include one cohort study, the remainder of the included studies were case reports. Case reports are subject to publication bias, and could result in a bias towards the increased reporting of more unfavourable outcomes. The fact that our review only recovered case reports and one cohort study hampers estimation of the incidence of vitamin K deficiency among women with HG. Furthermore, the case reports suffered from incomplete reporting of data essential to our review, which compromised our ability to link indicators of the severity or course of HG to maternal, fetal and neonatal outcomes in many studies; some articles focused primarily on the course of HG and maternal complications, while other case reports focused more on neonatal complications and did not report extensive details of HG. In addition, direct measures of vitamin K deficiency, for example PT, were only reported in 43% of included women, which hampered our ability to determine timing of maternal vitamin K depletion and its relation to fetal and neonatal outcomes in many cases.

Interpretation

Due to the fact that our review included mostly case reports, we are not able to estimate the incidence of vitamin K deficiency among women with HG. In the included cohort study however, 10 out of 39 women (26%) had a prolonged PT, suggesting that the presence of vitamin K deficiency may be more common among women suffering from HG than currently recognised.[28] However, the fact that PT was only measured in 39 out of the 109 women in the cohort, raises the possibility of this percentage only being representative of a selected group of more severely affected patients. Unfortunately, we are uninformed about the severity of HG in these specific 39 cases. Unlike the included case reports, the cohort study reported no further vitamin K deficiency complications, suggesting that only a small proportion of cases of vitamin K deficiency lead to complications including haemorrhage and embryopathy. A larger prospective cohort study measuring vitamin K deficiency in women with HG could determine the true incidence of both phenomena. The fact that this systematic review found mostly neonatal complications (9 studies) instead of maternal complications (4 studies) could largely be explained by the given that only very little vitamin K crosses the placenta from mother to fetus. This would suggest that the fetus is more at risk to develop a more severe vitamin K deficiency than mother.[38, 39]

It is hypothesised that in women with HG vitamin K deficiency is caused by poor nutritional intake, as is evident from marked weight loss. Most women in the included case reports had severe weight loss, with a mean weight loss of 13.6 kg. In examining the association between the severity of weight loss and presence of vitamin K deficiency induced complications, we found that in three cases reporting maternal haemorrhage, the maternal weight loss varied from 8 to 18kg.[24, 29, 34] In two included cases where neonates had long term disabilities, the maternal weight loss due to HG was respectively 18 and 28 kg.[27, 37] The woman who lost 28 kg, was also admitted to the hospital for 12 weeks in total.[37] The mean weight loss of 5.6±3.1 kg in women with HG included in Chraïbi *et al.*[28], but also in other HG cohort studies[40, 41], was considerably lower and they did not report any vitamin K deficiency-related complications This may suggest that a more severe clinical course of HG causes more severe malnutrition which can in line lead to an increased risk of developing vitamin K deficiency and related complications.

Embryopathy is also described in neonates born to women using warfarin, a vitamin K antagonist, during pregnancy, better known as the fetal warfarin syndrome.[10] Studies assessing the fetal warfarin syndrome showed that mainly first trimester deficiency of vitamin K results in embryopathy[42, 43] and that warfarin use throughout every trimester of pregnancy can result

in neonatal central nervous system (CNS) abnormalities.[10, 44] This corresponds to the onset, duration and severity of HG and its relation to neonatal complications reported in included case reports. In all cases reporting embryopathy the onset of HG lay in the first trimester and the two neonates described to have long term disabilities were born to mothers with a severe HG with a prolonged disease course. [27, 37]

The optimal timing of measuring vitamin K deficiency though is difficult to define. When maternal haemorrhage complications occurred, laboratory tests were performed at the time and vitamin K deficiency was then diagnosed and subsequently supplemented.[24, 25, 29, 34] In case reports describing neonatal embryopathy however, in the majority of the cases fetal anomalies were found on antenatal ultrasonography, despite earlier treatment with vitamin K. Since the origin of neonatal embryopathy lays in the first trimester and vitamin K supplementation took place primarily in the *second* trimester, the most likely explanation for this would be that vitamin K was supplemented too late and that fetal anomalies were already present at time of vitamin K treatment. Bearing this in mind, a solution would be to prophylactically administer vitamin K in women with HG, which has been proposed in previous studies.[23, 24, 27, 30, 31, 33-36] Most of these studies suggested that prophylactic treatment should be given in women with severe HG, undernutrition or severe weight loss but do not further specify this.[23, 24, 35] On the contrary, the Royal College of Obstetricians and Gynaecologists advices that women admitted with HG should be offered thromboprophylaxis because of an increased risk of venous thromboembolism. This might make care givers reluctant to follow that advice, although it is important to clarify that vitamin K supplementation does not increase the risk of venous thromboembolic complications.[45]

HG is known to be associated with raised transaminases, and can lead to liver dysfunction. Nonetheless, we think it is unlikely that liver dysfunction due to HG led to increased PT described in a number of articles. This is illustrated by the fact that the 4 case reports to measure liver transaminases found universally raised PT, which promptly resolved after vitamin K supplementation.

Conclusion

In this systematic review, we have demonstrated that women with HG can develop vitamin K deficiency and the corresponding maternal and neonatal complications. We were not able to derive the incidence among women with HG from the studies we retrieved, but found evidence vitamin K deficiency could affect up to 26% of HG patients. Which aspects of HG severity or disease course increase the risk of vitamin K deficiency remains unclear; severe

weight loss and prolonged disease did appear to be common factors in affected HG patients, and may therefore present risk factors. Larger prospective cohort studies of women with HG are needed to assess the incidence of vitamin K deficiency. It remains to be established whether early prophylactic vitamin K supplementation is safe and effective in preventing complications including embryopathy. Meanwhile, in women with HG and severe malnutrition or weight loss, measuring and supplementing vitamin K should be considered in order to prevent maternal or neonatal complications.

Acknowledgements

None.

Funding

Drs. K. Nijsten is funded by the Amsterdam Reproduction & Development (AR&D), project number 23346, and the Dutch Heart Foundation, grant number 2013T085.

Contribution to authorship

KN and RCP conceived the study. KN and LvdM performed the search, screened for eligible studies and performed data extraction. KN and LvdM performed all statistical analyses, supervised by RCP. KN and LvdM drafted the manuscript. HMGW, SM, MHK, IJG, TJR and RCP contributed in interpreting the results and revising the manuscript. All authors approved the final draft of the manuscript.

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Appendices, Supplementary Tables and/or Figures

Appendix A is available through the QR code below.