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Hyperemesis gravidarum and vitamin K deficiency: a systematic review

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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 aimed to summarise 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 12 November 2020. We identified 1564 articles, of which we included fifteen in this study: fourteen case reports (*n* 21 women) and one retrospective cohort study (*n* 109 women). Nine out of twenty-one 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.

Key words: **Hyperemesis gravidarum: Morning sickness: Vitamin K deficiency: Haemorrhage: Embryopathy: Systematic review**

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 synthesised 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

Abbreviations: HG, hyperemesis gravidarum; PT, prothrombin time.

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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 aimed to summarise 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 17 August 2020 (CRD42020199501). This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 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 12 November 2020. Our search included the following terms: 'hyperemesis gravidarum', 'pregnancy sickness', 'vitamin K deficiency', 'embryopathy', 'haemorrhage' and their synonyms, as shown in online Supplementary Appendix A. De-duplication of database search results was 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 (e.g. 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 and (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 PT, 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 for included cohort studies[21,22]. The Newcastle-Ottawa Scale 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). 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 and standard deviations if they were normally distributed. Not normally distributed continuous data were presented as medians with interquartile ranges. 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 Fig. 1. After removing duplicates, 1564 articles remained for title and abstract screening, of which thirty-six were deemed possibly eligible. Upon further eligibility screening after full texts for possibly eligible papers had been retrieved, we included fifteen 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].

British Journal of Nutrition

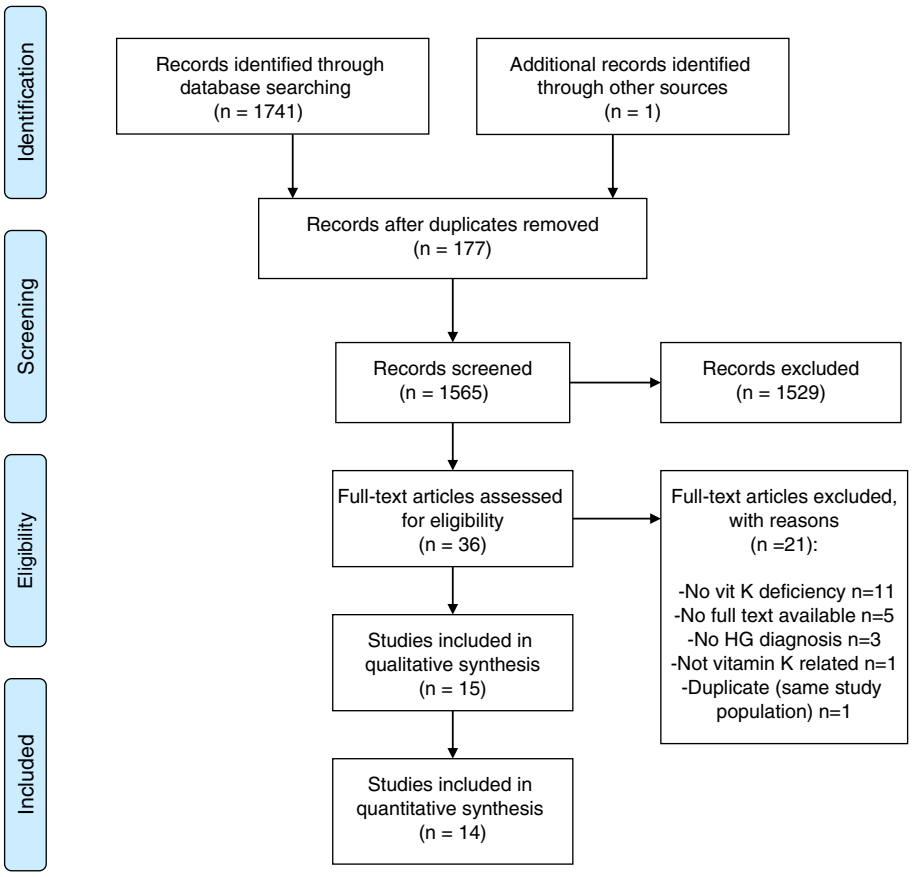

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram: selection process of articles.

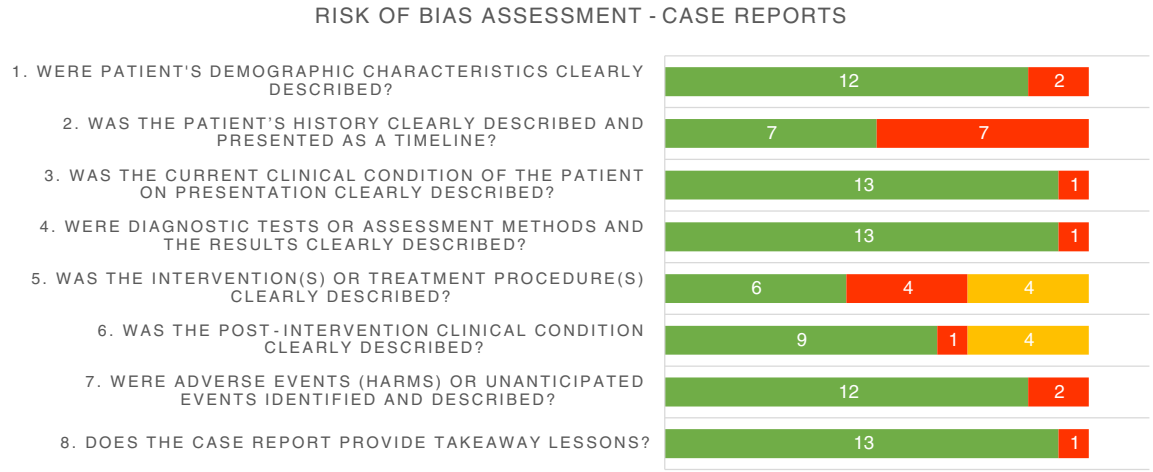

Fig. 2. Risk of bias assessment of included case reports. ■, low; ■, high; ■, not applicable.

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 shown in Fig. 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

British Journal of Nutrition

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.*	2		3	5	Fair quality

The NOS risk consisted of eight 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.

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.

Baseline characteristics

Baseline characteristics of all included studies are shown in Table 2 and data of the included women from case reports were combined and shown in Table 3. In seventeen 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 (SD 3·16) weeks) (Tables 2 and 3). Ten articles (*n* 14 women) reported whether weight loss during pregnancy due to HG had occurred: thirteen out of fourteen women had some degree of weight loss, ranging from 5 to 28 kg with an average weight loss of 13·64 (SD 8·03) kg compared with 5·6 (SD 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 seventeen 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 twenty-one women included from case reports, eleven 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 nine out of twenty-one women included in case reports: 8/21 women (38·1 %) had a prolonged PT (Tables 4 and 5)[23–25,29,31,34,36,37]. In four out of nine women, PT was measured secondary to maternal signs of haemorrhage[24,25,29,34]. In the other five 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[24,29,34]. Two of them found a prolonged activated partial thromboplastin time, but also found a decreased factors 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 0·05 ng/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 factors II, VII, IX and X was found[30].

In the cohort study from Chraïbi *et al.*[28], PT was measured in thirty-nine out of 109 women (35·8 %) admitted for HG: ten out of these thirty-nine women (25·6 %) had a prolonged PT with a level below 70 % and two out of these ten 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 ten out of twenty-one (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 normalised after vitamin K supplementation[23–25,29–31,34,36,37].

In the cohort study of Chraïbi *et al.*[28] three out of ten 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 seven out of twenty-one women included in case reports of whom four women (19·0 %) had elevated liver transaminases (Tables 4 and 5)[23,29,31,36]. Three out of these four women also had elevated total bilirubin levels and two women had elevated gamma glutamyl transferase levels.

As shown in Table 4, Chraïbi *et al.*[28] reported elevated alanine transaminase and aspartate aminotransferase in respectively 20·7 and 25·7 %. PT levels were significantly lower in women with an increased alanine transaminase than in women with normal alanine transaminase levels (68 (SD 14) % *v.* 78 (SD 9) %).

Maternal complications due to hyperemesis gravidarum-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

Table 2. Baseline characteristics of included studies
(Means and standard deviations)

	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 weeks)	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 weeks)	No	Yes	No	No	–	–	–	Large myoma with intestinal obstruction
Bailey	1964	UK	Case report	21	–	G1P1	–	–	12 weeks	–	Yes (5 weeks)	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*	2015	France	Cohort (*n* 109)		46·5 % French	56·4 % Nulli-para					109 100 %	12·8 %	100 %	98·1 %	–		57 % Girl		–
Mean				28			64·3	23·9	46	5·6						274		3283	
SD				5·7			13·7	4·5	15 (d)	3·1						16 (d)		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 weeks)	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	"	"	"	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Robinson†	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	–				–

Table 2. (*Continued*)

	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
Shigemi	2015	Japan	Case report	39	Asian	G1P0	64·1	25·0	8 weeks	–	Yes (1 week)	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(12 weeks)	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	–	–

GP, gravidity parity; IV, intravenous; TPN, total parenteral nutrition; UK, United Kingdom; USA, United States of America.
* Cohort study: characteristics presented as means and standard deviations, median (IQR) or frequency (%).
† Case of Robinson *et al.* is the same case as case 1 of Toriello *et al.*, so available data are combined.

Table 3. Combined baseline characteristics of included case reports in this systematic review (Numbers and percentages; median and interquartile ranges)

	n 21		
	n	%	% missing
Demographic characteristics			
Age (years)			
Median	26·00		42·9
IQR	21·25–35·25		
Pre-pregnancy weight (kg)			
Median	63·05		61·9
IQR	50·00–68·63		
Pre-pregnancy BMI (kg/m^2)			
Median	25·00		76·2
IQR	19·75–26·25		
Ethnic origin			33·3
Western	7	33·3	
Asian	4	19·0	
African American	3	14·3	
Primigravida	6	28·6	38·1
HG severity and course			
Gestational age at onset of symptoms of HG (weeks)			
Mean	8·47		19·0
SD	3·16		
Total weight loss (kg)			
Mean	−13·64		33·3
SD	8·03		
HG-related hospital admission	11	52·4	47·6
Length of initial hospitalisation (weeks)			
Median	5·00		71·4
IQR	3·25–7·50		
Readmission	3	14·3	52·4
HG treatment			
Received treatment for HG	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	37·00		38·1
IQR	32·50–39·00		
Sex of neonate			33·3
Female	10	47·6	
Male	4	19	
Birth weight of neonate (grams)			
Median	2640·00		47·6
IQR	2200·00–3000·00		

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

haemorrhage (Tables 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 activated partial thromboplastin time and international normalised ratio. Coagulopathy was strongly suspected to be secondary to vitamin K deficiency, since PT normalised 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 hyperemesis gravidarum-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 fourteen neonates, reported neonatal embryopathy as shown in Tables 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

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 phenol type	Chrondro dysplasia punctata	Brachy tele-phalangy	Grey matter hetero-topia	Anomaly first detected	Additional information
Alessandri	Yes (42 %; 11 weeks 25 %; 12 weeks)		Yes (ALAT 186 UI/l)	Iv at 12 weeks	–	–	Yes	Yes	Yes	–	US: 24 weeks	–
Baba	Yes (14·2 s; 16 weeks)	Normal aPTT	–	Iv 10 mg/d at 16 weeks	Intraperitoneal haemorrhage	–	–	–	–	–	–	–
Bailey	Yes (63 s)	–	–	im	Haematuria, vaginal bleeding	–	–	–	–	–	–	–
Bhoj	–	–	–	–	–	–	Yes	Yes	Yes	–	Postpartum	Epileptic seizures, Chiari type II malformation
Brunetti-Pierri	–	–	–	–	–	–	Yes	Yes	Yes	Yes	US: 20 weeks	Epileptic seizures, ventilatory support, long-term disability
Chraïbi*	Yes (10 out of 39 women (25·6 %))†	–	Yes (in 20·7 to 25·7 %)	3 out of 10 (30 %)	–	–	–	–	–	–	–	–
Devignes	Yes (11 %; 18 weeks)	aPTT↑, factor II, VII, X, proteïn C,S↓	Yes (ALAT 353 UI/l)	10 mg iv once at 18 weeks	Haematuria, rectal bleeding	–	–	–	–	–	–	–
Eventov-Friedman	Normal		–	–	–	Intracranial haemorrhage	–	–	–	–	Postpartum	Neonatal lab: PT↑, Factors II, VII, IX , X↓. Treatment: 1 mg iv
Kawamura	Yes (28 %; 14 weeks)		Yes	10 mg iv & 2 mg/d at 14 weeks	–	Intracranial haemorrhage	–	–	–	–	US: 17 weeks	Induced abortion due to US anomalies, hydrocephalus
Lane	–	–	Normal	In TPN at 15 weeks	–	–	yes	–	–	–	US: 14 weeks	–
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	–
Robinson	Yes (36·5 s; 15 weeks)	aPTT↑, Factors II, VII, IX, X↓	Normal	10 mg sc/d for 3 d at 15 weeks	Epistaxis with 1 liter blood loss	–	Yes	–	–	–	US: 17 weeks	Calcaneal asymmetry
Selvarajah	–	Deranged clotting profile at 13 weeks	Normal	Iv at 13 weeks	–	–	–	–	–	–	–	–
Shigemi	Yes (15·2 s; 9 weeks. 19·7 s; 11 weeks)	Vit K↓ (< 0·05 ng/ml) & factor VII↓	Yes (ALAT 72 UI/l)	15 mg oral/d for 5 weeks at 11 weeks	–	–	–	–	–	–	–	–

British Journal of Nutrition

Table 4. *(Continued)*

Study	Maternal				Maternal complications	Neonatal	Vitamin K embryopathy					Additional information
	PT prolonged (seconds or %; gestation)	Vitamin K and/or other coagulation factors measured	Elevated Liver-enzymes	Vitamin K supplementation (dosage; gestation)		Neonatal Haemorrhage	Binder phenol type	Chrondro dysplasia punctata	Brachy tele-pha-langy	Grey matter hetero-topia	Anomaly first detected	
Toriello												
Case 2	–	–	–	–	–	–	Yes	–	Yes	–	Postpartum	–
Case 3	Yes (22 %; 8 weeks)	–	–	Iv at 8 weeks	–	–	Yes	–	Yes	–	US: 30 weeks	–
Case 4	–	–	–	–	–	–	Yes	Yes	Yes	–	Postpartum	Spastic quadriplegia and severe intellectual disability
Case 5	–	–	–	–	–	–	Yes	–	Yes	Yes	Postpartum	Normal development (1/2 years)
Case 6	–	–	–	–	–	–	Yes	Yes	Yes	–	Postpartum	Normal development (3 years)
Case 7	–	–	–	–	–	–	Yes	Yes	–	–	US	Tracheostomy and gastrostomy

PT, prothrombin time; US, ultrasound (perinatal); aPTT, activated partial thromboplastin time; TPN, total parenteral nutrition.
* Cohort study: data presented as frequencies/percentages.
† PT measured in 39/109 women.

Table 5. Combined outcomes of included case reports in this systematic review
(Numbers and percentages; median and interquartile ranges)

	n 21	
	n	%
Maternal		
PT Prolonged	8	38·1
Vitamin K measured	1	4·8
Elevated liver transaminases	4	19·0
Vitamin K supplementation	10	47·6
Oral*	2	20·0
Subcutaneous*	1	10·0
Intramuscular*	1	10·0
Intravenous*	6	60·0
Gestational age when women received vitamin K supplementation (weeks)		
Median	14·00	
IQR	11·50–15·50	
Maternal haemorrhage occurred	4	19·0
Neonatal		
Neonatal haemorrhage occurred	2	9·5
Vitamin K embryopathy	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	7	33·3
Gestational age when anomalies were first detected		
Median	18·50	
IQR	16·25–25·50	
Anomalies detected postpartum	6	28·6

PT, prothrombin time. Skewed variables are presented as medians with interquartile ranges (IQR) and dichotomous or categorical variables as frequencies with percentages (%).
* Percentage shown is percentage of women who received vitamin K supplementation.

accompanied by hydrocephalus was detected during the mid-trimester ultrasound at 17 weeks gestation. Due to these fetal anomalies, the woman decided to terminate her pregnancy. Autopsy showed a subarachnoid haemorrhage with haemosiderin 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 min. 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 fourteen neonates diagnosed with vitamin K-related embryopathy in the studies included in our review, all neonates had Binder phenotype, nine 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 eleven out of fourteen neonates with vitamin K-related embryopathy[23,26,27,33,37]. Genetic testing was performed in nine out of fourteen 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 ten women who received vitamin K supplementation, five 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 (interquartile range 12–16) compared with the median gestational age of 19 weeks (interquartile range 16–26) when fetal anomalies were detected on perinatal ultrasound (Table 5).

Neonatal prognosis. Eleven out of twenty-one 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 fifteen 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 summarises 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, ten out of thirty-nine 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 thirty-nine 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 thirty-nine 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

British Journal of Nutrition

found mostly studies reporting on neonatal complications (nine studies) instead of maternal complications (four studies), could be explained by the given that only very little vitamin K crosses the placenta from mother to fetus, which can decrease even more when there is maternal vitamin K deficiency. This would suggest that the fetus is more at risk to develop a more severe vitamin K deficiency and corresponding complications 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 18 kg[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 (SD 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 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 the 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 caregivers 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 four 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 to prevent maternal or neonatal complications.

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Supplementary material

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British Journal of Nutrition

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