Life-threatening complications of hyperemesis gravidarum

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Abstract. Hyperemesis gravidarum (HG) refers to severe nausea and emesis noted during pregnancy. However, no consensus exists on the specific diagnostic criteria that can be used for this condition. The aim of the present systematic review was to summarize the available evidence regarding the severe complications observed during HG with a heightened risk of fatality. A systematic search was conducted on PubMed, Cochrane Library, EMBASE and WILEY databases for the relevant publications regarding the severe and life-threatening complications of HG. The search terms were as follows: '(Hyperemesis gravidarum)' AND ('complications' OR 'severe' OR 'adverse pregnancy outcomes' OR 'stroke' OR 'seizures' OR 'Wernicke's encephalopathy' OR 'arrhythmias' OR 'pneumomediastinum' OR 'coagulopathy' OR 'electrolytic imbalance'). Abstracts, conference presentations, letters to the editor, studies written in languages other than English and editorials were all excluded. This search identified 43 studies analyzing life-threatening complications of HG, of which 11, seven, eight and 17 articles analyzed neurological, cardiovascular, thoracic and systemic complications, respectively. Reports on life-threatening complications were exceptionally rare in HG. The most frequent severe complications noted were Wernicke's encephalopathy, electrolyte imbalance and vitamin K deficiency. The low mortality rate for patients with HG over the last decade could be explained by the high efficiency of modern therapy, and the precise management of every complication according to current guidelines.

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Abbreviations: CPM, central pontine myelinolysis; DVA, developmental venous anomaly; ECG, electrocardiogram; HG, hyperemesis gravidarum; WE, Wernicke's encephalopathy

Key words: hyperemesis gravidarum complications, adverse pregnancy outcomes, electrolyte disturbances, death, life threatening, management

Introduction

Hyperemesis gravidarum (HG) is defined as intractable vomiting and nausea during pregnancy. Ptyalism, fatigue, weakness and dizziness are frequent symptoms, whilst rare symptoms also include hyperolfaction, dysgeusia, decreased gustatory discernment, sleep disturbance, depression, anxiety, irritability and mood changes (1-4). Although >75% of pregnant women suffer from nausea or vomiting during pregnancy, only 0.3-2% pregnant women are diagnosed with HG. The most frequent reasons for hospital admission in women diagnosed with HG include weight loss (>5% pre-pregnancy weight), ketonuria, dehydration, electrolyte imbalance, acid-base imbalances and arrhythmias (1-4).

Although the pathogenesis of HG remains widely unknown, pregnancy in the first trimester, first pregnancy, multiple pregnancies, obesity, family history of HG, trophoblastic disorder, hyperthyroid disorders, psychiatric illness, previous molar pregnancy, preexisting diabetes, gastrointestinal disorders, allergies prior to pregnancy and a history of eating disorders are known risk factors (2-5). The list of complications noted in HG are classified as complications associated with pregnancy [malnutrition, anemia, hyponatremia, Wernicke's encephalopathy (WE), kidney failure, central pontine myelinolysis (CPM), stroke, vasospasms of cerebral arteries, seizures, coagulopathy, hypoglycemia, esophageal rupture or perforation, hepatic disease, jaundice, pancreatitis, deep vein thrombosis, pulmonary embolism, pneumothorax, pneumomediastinum, rhabdomyolysis, vitamin K deficiency and coagulopathy, splenic avulsion, depression and post-traumatic stress disorder], complications associated with central nutrition (sepsis, fungemia, tamponade, local infection, venous thrombosis, fatty infiltration of the placenta and transaminitis) and infant

complications (lower weight at birth, small for gestational age and birth before 37 weeks of gestation) (6-9).

The aim of the present systematic review was to summarize the available evidence regarding severe complications in HG with a heightened risk of fatality.

Materials and methods

PubMed (https://pubmed.ncbi.nlm.nih.gov/), Cochrane Library (https://www.cochranelibrary.com/), EMBASE (https://www.elsevier.com/solutions/embase-biomedical-research) and WILEY (https://onlinelibrary.wiley.com/) databases were screened for relevant publications regarding severe and life-threatening complications of HG. The search terms used were as follows: '(Hyperemesis gravidarum)' AND ('complications' OR 'severe' OR 'adverse pregnancy outcomes' OR 'stroke' OR 'seizures' OR 'Wernicke's encephalopathy' OR 'arrhythmias' OR 'pneumomediastinum' OR 'coagulopathy' OR 'electrolytic imbalance'). The exclusion criteria were abstracts, conference presentations, letters to the editor, studies written in languages other than English and editorials (Fig. 1). Two independent authors (SLP and CA) reviewed the studies for eligibility titles, abstracts and full text of eligible articles. Disagreements between the two authors were resolved by discussion. The search strategy using the PRISMA flow diagram is shown in Fig. 1.

Results

Neurological complications. The search identified 11 articles regarding severe HG neurological complications, of which four articles examined stroke (10-13), two articles focused on seizures (14,15), three focused on CPM (16-18), of which two case reports with associated WE (17,18), and two articles focused only on WE (19,20) (Table I). A study performed by Lanska and Kryscio (10) analyzed the incidence of peripartum stroke and cerebral venous thrombosis (CVT) in the United States from 1993 to 1994. The aim of their study was to identify potential risk factors for peripartum or postpartum stroke and IVT (10). The results reported that 183 cases of peripartum stroke and 170 cases of peripartum intracranial venous thrombosis (IVT) were identified out of 1,408,015 sampled deliveries (10). Furthermore, 975 cases of stroke and 864 cases of IVT during pregnancy, where puerperium was observed among 7,463,712 deliveries. Statistical analysis demonstrated that the following conditions exerted a significant association with peripartum and postpartum stroke: Cesarean delivery, fluid, electrolyte and acid-base disorders and hypertension (10). The risk of stroke and CVT in patients with HG was statistically significant (P=0.009). Similar findings were noted for fluid, electrolyte and acid-base disorders (P<0.001) (10). The authors concluded that the risk of severe, life-threatening neurological complications was low in patients with HG (10).

A total of three articles were case reports. In the first case report (11), a 26-year-old woman with intracerebral hemorrhage due to the venous thrombosis of a developmental venous anomaly (DVA) was described. Although DVA is the most common cerebral vascular malformation, diagnosis is frequently made incidentally on routine brain imaging due to the lack of symptoms (11). The patient was diagnosed with hemorrhagic stroke and epilepsy secondary to thrombosis of the DVA during week 8 of pregnancy. The authors concluded that HG and the resulting intravascular dehydration increased the risk of thrombosis in this patient with previously undiagnosed DVA (11). The second case report analyzed the severe effects of sinus thrombosis in patients with HG whereas the third case report was regarding transient ischemic attack (12,13). Although the majority of pregnant women with seizures exhibited epilepsy prior to pregnancy, HG was a risk factor for pregnant women without prior diagnosis of epilepsy to develop seizures (14,15). It is important to note that limited evidence is present regarding the risk of seizures in patients with HG. In addition, although brain damage is responsible for their onset, other factors may also be involved, including variations in blood pressure, metabolic disorders and infections (14,15).

CPM is one of the rarest but potentially fatal complications of HG (4). HG may be a risk factor when CPM is mainly caused by the following conditions: Rapid correction of hyponatremia, alcoholism, malnutrition, severe burns, hypokalemia, psychogenic polydipsia (patients with schizophrenia), liver cirrhosis and severe electrolyte and acid-base disorders (4). However, limited evidence has been found to support this notion. A number of case reports were published (16-19), each of these illustrating patients that were diagnosed with CPM in an HG context.

WE is an important type of encephalopathy that is caused by a single vitamin B1 deficiency (21). This disease is clinically characterized by the classic triad of ocular findings, cerebellar dysfunction and confusion (20,21). Epidemiological studies are rare and unreliable, since >80% patients with WE are either not diagnosed or misdiagnosed, making it impossible to calculate the morbidity and mortality rates (20,21). WE is the most frequent neurological complication of HG, with over 70 papers reporting this over the past 6 decades. Those papers were not included in the current review, because they all were case reports. At present, WE can be readily diagnosed, treated, prevented and reversed even in severe cases due to new pharmacological agents and tailored therapies (20,21).

Cardiovascular complications. Existing literature regarding cardiovascular complications of HG is scarce and the majority of the articles published are case reports. The search strategy revealed the following seven articles related to cardiovascular complications of HG: Three case reports (22-24) related to ventricular arrhythmias, all discussing consequences of serum electrolyte imbalance, mainly hypokalemia, among which one case report described a case of QT prolongation (22) and two case reports involved ventricular tachycardia (23,24); one population-based cohort study evaluating, among other placental disorders, the risk of developing pre-eclampsia (25); one nationwide cohort study evaluating the subsequent long-term risk of maternal cardiovascular morbidity (26); one case report on right atrial thrombus with a central venous catheter placement complication (27) and one case report regarding important arterial blood pressure variations (28) (Table II).

QT interval prolongation, with or without subsequent malignant ventricular arrhythmias (generally torsade de pointes), is a condition caused by serum electrolyte imbalance (mainly hypokalemia, but also hypomagnesemia and

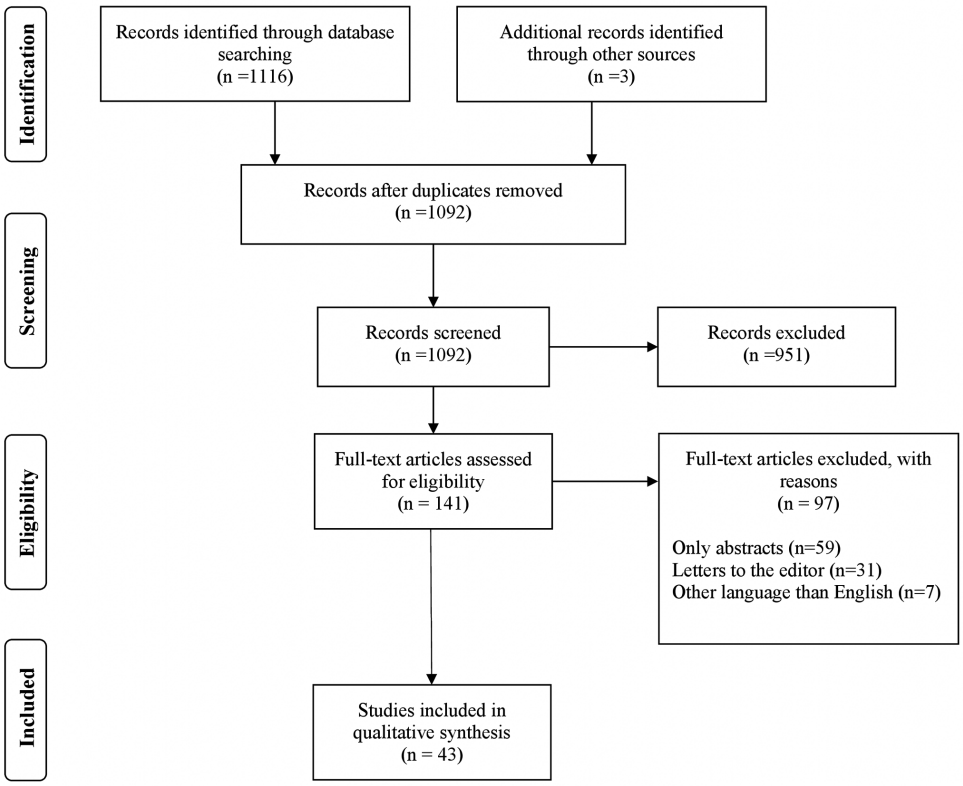

Figure 1. PRISMA flow diagram for study selection. In total, 1,119 were identified using the search terms, 1,092 records were screened, 141 full-text articles were evaluated for eligibility, before 43 studies were finally included in the qualitative synthesis.

hypocalcemia) that can be treated by the administration of antiemetics, including metoclopramide, ondansetron and domperidone (29). Severe episodes of nausea and vomiting in patients with HG can easily lead to dehydration, hypokalemia, hypomagnesemia and hypocalcemia (4). Nausea is treated with antiemetics, which can prolong the QT interval further on the 12-lead electrocardiogram (ECG) and favor the appearance of malignant ventricular arrhythmias (22). Mitchel and Cox 22) described a case of QT prolongation in a patient at 24-week primiparous pregnancy presenting due to hyperemesis, severe vomiting and loss of appetite for 1 week prior to hospital admission. These events led to hypokalemia, hypomagnesemia and hypocalcemia, with subsequent QT prolongation on the ECG with a QTc interval of 510 msec. This increase in the QTc interval was most likely aggravated by antiemetic drug administration (metoclopramide and ondansetron). Patient management consisted of intravenous fluid resuscitation, electrolyte administration (K^+, Mg^+, phosphates and Ca^{2+}), antalgics, thromboembolism prophylaxis, gastric protection with intravenous proton pump inhibitors, nasojejunal tube nutrition and vitamin (B and C) supplements. The patient's condition was improved and she was discharged from the hospital following a reduction in the QTc interval to normal values with corrected electrolyte levels. Prompt treatment of prolonged QTc is essential, since a QTc interval >500 msec increases the risk of malignant ventricular arrhythmias, notably torsades de pointes (30), which can result in adverse events, including syncope and sudden cardiac arrest. Kochhar and Ghosh (23) described a case of ventricular arrhythmia due to hypokalemia and hypomagnesaemia in a patient with HG and structurally normal heart. The patient was 7 weeks pregnant and developed ventricular bigeminy in a context of hypokalemia (2.3 mEq/l; normal 3.5 to 5.5 mEq/l) and hypomagnesemia (107 mEq/l; normal- 130-145 mEq/l) due to frequent episodes of vomiting, who was treated with antiemetics (metoclopramide and ondansetron). The arrhythmia was treated with an intravenous administration of lidocaine, magnesium sulfate, potassium supplements and oral metoprolol in combination with supportive treatment (23). Her condition improved and she was discharged 5 days later. Although the authors state that the patient developed short-term ventricular tachycardia and episodes of polymorphic ventricular tachycardia, the ECG data obtained in this previous study demonstrated that only isolated premature ventricular complexes and monomorphic ventricular bigeminism were present with an outflow tract origin, which is frequently presented in individuals with a normal heart (23). Therefore, their conclusions should be interpreted with caution. Jadhav *et al* (24) presented a case of a 25-year-old female patient, who was 13 weeks pregnant and developed ventricular tachycardia due to severe hypokalemia (2.4 mmol/l; normal 3.5 to 5.5 mEq/l) as a consequence of repeated episodes of nausea and vomiting and lack of appetite, with severely reduced intake of both solids and fluids. Her nausea was also treated with metoclopramide. On day 4 of admission, she developed torsade de pointes and was treated with electrical cardioversion, lidocaine and magnesium sulfate. During hospitalization, she experienced recurrent episodes of polymorphic ventricular tachycardia and was treated successfully with electrical cardioversion. She aborted spontaneously on day 5 of admission. The authors focused on this potential severe cardiovascular complication of HG. The mechanism of torsade de pointes was not discussed further

Table I. Neurologic complications of hyperemesis gravidarum.

Author	Year	Evidence type	Age of patient (s), years	Country	Gestational period on presentation, weeks	Complication	Symptoms	Treatment
Lanska and Kryscio (10)	2000	Cohort study	15-44	USA	Not specified	Peripartum and postpartum stroke and intracranial venous thrombosis	Not specified	Conservative
Seki *et al* (11)	2015	Case report	26	Japan	8 weeks	Intracerebral hemorrhage due to venous thrombosis	Sudden generalized seizures	Conservative
Kennelly *et al* (12)	2008	Case report	26	UK	11 weeks	Sagittal sinus thrombosis	A history of vomiting, headaches and tonic clonic seizures. Drowsy with a left homonymous hemianopia and brisk tendon reflexes in the left upper and lower limbs.	Conservative intravenous unfractionated heparin and dexamethasone direct catheter thrombolysis with tissue plasminogen activator
Kanayama *et al* (13)	1998	Case report	29, 26	Japan	10 and 8 weeks	Vasospasms of cerebral arteries	Frequent vomiting, general fatigue and weight loss	Conservative
Beach and Kaplan (14)	2008	Review	Not specified	Not specified	Not specified	Seizures	Not specified	Conservative
O'Brien *et al* (15)	2004	Review	Not specified	Not specified	Not specified	Epilepsy	Not specified	Conservative
Sinn *et al* (16)	2013	Case report	16	USA	20 weeks	Simultaneous optic neuropathy and osmotic demyelinating syndrome	Blurry vision	Conservative
Bergin and Harvey (17)	1992	Case report	25	India	9 weeks	Wernicke encephalopathy and central pontine myelinolysis	Confusion and ataxia	Concentrated intravenous injections of the vitamin B complex and ascorbic acid and parenteral feeding.
Sutamnartpong *et al* (18)	2013	Case report	21	Thailand	16 weeks	Wernicke encephalopathy and central pontine myelinolysis	Progressive difficulty in walking	Conservative
Zara *et al* (19)	2012	Case report	29	Italy	20 weeks	Wernicke encephalopathy	Weight loss (14 kg), hematemesis and episodes of bilious vomiting, diarrhea, weakness, drowsiness and increased body temperature (39˚C)	Thiamine was administered (100 mg/day intravenously for 10 days, then 300 mg/day orally)
Oudman *et al* (20)	2019	Systematic review	26.9±5.5	Not specified	15-25 weeks	Wernicke encephalopathy	Mental status change	Thiamine supplementation

Table II. Cardiovascular and thoracic complications of hyperemesis gravidarum.

Author	Year	Evidence type	Age of patient (s), years	Country	Gestational age, weeks	Complication	Symptoms	Treatment
Mitchell and Cox (22)	2016	Case report	30	UK	24 weeks	Long QTc	Severe epigastric pain, long QTc on ECG.	Conservative
Kochhar and Ghosh (23)	2018	Case report	26	India	7 weeks	Ventricular tachycardia	Shortness of breath, palpitations and atypical chest tightness	Intravenous lidocaine, isotonic saline and parenteral potassium and magnesium supplementation, metoprolol at 25 mg twice daily
Jadhav *et al* (24)	2010	Case report	25	India	13 weeks	Ventricular tachycardia and seizure	Recurrent generalized clonic tonic convulsions and sustained ventricular tachycardia with hypotension and evidence of Torsade de pointes on cardiac monitor	Conservative
Bolin *et al* (25)	2013	Population-based cohort study	<25 (172,336 subjects), 25-29.9 (358,454 subjects), 30-34.9 (400,752 subjects), >35 (221,216 subjects),	Sweden	First or second trimester	Placental dysfunction disorders (preeclampsia, placental abruption, stillbirth and small for gestational age)	Not specified	Not specified
Fossum *et al* (26)	2019	Nationwide cohort study	24 (with HG), 25 (without HG)	Norway	Not specified	Long-term cardiovascular morbidity (nonfatal stroke, myocardial infarction, or angina pectoris, or cardiovascular death)	Not specified	Not specified
Turrentine *et al* (27)	1994	Case report	23	USA	26 weeks	Right atrial thrombus	Left-side chest pain	Removal of central catheter, i.v. heparinization at 33,000 U/day
Salmon (28)	2009	Case report	25	Australia	18 weeks	Postural hypotension and autonomic neuropathy	Labile blood pressure	Fludrocortisone 0.1 mg daily

Table II. Continued.

Author	Year	Evidence type	Age of patient (s), years	Country	Gestational age, weeks	Complication	Symptoms	Treatment
Schwartz and Rossoff (34)	1994	Case report	26	USA	10 weeks	Pneumomediastinum and bilateral pneumothorax	Hematemesis followed by severe nonpleuritic chest pain without dyspnea. Swelling of the head, neck, and anterior chest	Total parenteral nutrition and systemic antibiotic therapy
Gorbach *et al* (35)	1997	Case report	21	USA	9.5 weeks	Spontaneous pneumomediastinum	Sore throat, sharp pain in the middle of the chest at deep inspiration and a 'squishy' sensation when the patient rubbed the outside of her throat	Conservative
Liang *et al* (36)	2002	Case report	25	Japan	15 weeks	Pneumomediastinum following esophageal rupture	Disturbance of consciousness	Conservative
Yamamoto *et al* (37)	2001	Case report	29	Japan	6 weeks	Pneumo-mediastinum	Face swelling, severe toothache	Conservative
Germes-Piña *et al* (38)	2016	Case report	21	Mexico	15 weeks	Pneumo-mediastinum	Neck swelling and pain, odynophagia, dysphonia	Conservative
Chen *et al* (39)	2012	Case report	18	China	13 weeks	Diaphragmatic tear	Upper abdomen discomfort	Glucose and saline, antiemetic therapy, and parenteral nutrition with 3-4 l input volume per day
Fiaschi *et al* (40)	2017	Population-based cohort study	All ages	England	Not specified	Subjects grouped in patients experiencing no HG; only one or at least one hospital admission due to HG and complications grouped in antenatal, perinatal and postnatal complications, delivery and birth factors	Not specified	Not specified

in the case report (24). This ventricular tachyarrhythmia, usually referred to as torsade de pointes, was associated with an increased QT interval and in the majority of the cases, aggravated by hypokalemia and drug administration, such as metoclopramide (31). In addition, Jadhav *et al* (24) did not present ECG data in patients with or without torsade de pointes in their article, which was an important limitation of the study, since this type of ventricular arrhythmia was the key object of discussion of this case report.

The association between HG and pre-eclampsia was discussed by a study by Bolin *et al* (25), who assessed the possible association between HG during the first or second trimester of pregnancy and placental dysfunction disorders, including pre-eclampsia, placental abruption, stillbirth and small for gestational age births. During a period of 13 years 1,156,050 pregnancies were included and the data indicated that individuals with HG in the first trimester of pregnancy exhibited a slightly higher risk of pre-eclampsia compared with that noted in individuals with HG in the second trimester of pregnancy, who exhibited increased risk of preterm (<37 weeks) pre-eclampsia by >2-fold (25), with an odds ratio of 2.09 and 95% confidence interval (CI) of 1.38-3.16. Pre-eclampsia may have a negative impact on the fetus (fetal hypoxia, premature birth, placental abruption, fetal death *in utero*, hypertension, abnormal endothelial dilation, arterial thickening, reduced microvascular density, increased LV wall thickness and reduced left ventricular end-diastolic volume), the offspring (8% increase in mortality risk from ischemic heart disease and 12% increase in the risk of stroke) and on the mother (eclampsia, hypertension, ischemic heart disease, thromboembolic events, kidney or liver failure, stroke and an increased risk of mortality) (32). The impact of HG on the long-term risk of maternal cardiovascular morbidity was assessed by Fossum *et al* (26), which is the largest study that assessed more concrete cardiovascular endpoints in women with HG. This Norwegian cohort study included births from 1967 to 2002 from individuals with and without HG. These cases were followed-up from 1994 to 2009, where the following cardiovascular outcomes were recorded: Non-fatal stroke, myocardial infarction or angina pectoris and cardiovascular death. The authors highlighted that the prevalence of HG in a cohort of 989,473 women was 1.3%. At least one adverse cardiovascular event was experienced by 4.4% individuals. However, no association was found between HG and the risk of fatal or non-fatal cardiovascular events [adjusted hazards ratio (HR), 1.08; 95% CI, 0.99-1.18]. Only the risk of hospitalization for angina pectoris was found to be higher in patients with HG (adjusted HR, 1.28; 95% CI, 1.15-1.44). The risk of mortality due to a cardiovascular event was not significantly different in patients with and without HG (HR, 0.73; 95% CI, 0.59-0.91) following adjustment for age, whilst the association was not significant following adjustment for other possible confounders data pertaining the mother: age at first pregnancy, year of birth, highest education obtained, country of birth, hypertensive disorders during pregnancy, placental abruption, pre-gestational hypertension and diabetes) (26).

In terms of vascular complications of HG, Turrentine *et al* (27) described a case of right atrial thrombus as a complication of central venous catheter placement in a patient with HG that required parenteral nutrition. The thrombus was successfully treated with heparin, which led to its resolution and therefore did not exhibit a negative outcome on pregnancy. Venous thrombosis with or without subsequent pulmonary embolism is a known complication of central catheter placement (27). Pregnancy is associated with a hypercoagulable state and an increased risk of venous thrombosis (27). Should a central venous catheter be deemed necessary for a patient who is also pregnant, measures should be taken to minimize the risk of thromboembolic complications, including limiting the duration of placement and anticoagulant treatment. In this aforementioned case, the right atrial thrombus most likely developed as a complication of the central catheter *per se* and not the direct presence of HG (27).

Salmon (28) described a case of a 25-year-old woman with arterial blood pressure variations and HG, with a personal history of pre-eclampsia. These values varied between 60/30 mmHg and 180/118 throughout the pregnancy. A high value of 220/130 mmHg was recorded immediately after spontaneous vaginal delivery, where postpartum vomiting was also observed. She was treated with chlorpromazine and her blood pressure stabilized. The author attributed the marked blood pressure variations to autonomic nervous system dysfunction, causing subsequent postural hypotension. In this particular patient, HG caused repeated episodes of vomiting, resulting in significant hypovolemia and aggravated postural hypotension due to autonomic dysfunction, which may explain the cause of the low blood pressure values (28). The high blood pressure values could be explained by her personal history of pre-eclampsia. Given the unique nature of this case report, firm conclusions could be drawn regarding the association between HG and arterial blood pressure.

Thoracic complications. This search strategy yielded eight articles (33-40) related to thoracic complications of HG, most of which were case reports. Among the selected articles, evidence regarding pneumothorax, pneumomediastinum, diaphragmatic tears and thromboembolic events was presented (Table II). Spontaneous pneumomediastinum and pneumothorax occur most frequently during the second stage of labor (33). Although pneumomediastinum during pregnancy is rare, it can be lethal (35). The case reports presented in the literature regarding this complication are exceptionally rare. Therefore, at present a thorough study is not possible. The etiology for pneumomediastinum is characterized by esophageal tear and spontaneous alveolar ruptures (33-38). Esophageal tear can be determined by increased intraluminal esophageal pressure due to the vomiting hyperextending the tensile strength of its wall (34). In addition, abdominal muscles contracting against a closed glottis may rupture the alveoli and bronchovascular sheaths (34). It is important to differentiate between these two causes since the treatment option must be selected based on the precise cause of pneumomediastinum. Risk factors include nulliparity, pregnancy at a young age, increased estrogen levels, excessive emotional response to stress, excessive coughing, drug use via inhalation and alcohol abuse (34-36). The studies included in the present review demonstrated that all patients with pneumothorax and pneumomediastinum were <30 years of age, multiparous and presented with an extended history of emesis (33-39). The majority of patients were admitted for hematemesis, chest pain and subcutaneous

emphysema (Mackler's triad). Yamamoto *et al* (37) presented a case with unusual symptomatology (toothache, face swelling), which rendered appropriate diagnosis and treatment difficult. Abnormal results in esophageal barium examination, fever and leukocytosis can aid the diagnosis of an esophageal tear (35). However, establishing the appropriate selection of treatment, whether it is conservative, or surgical, remains difficult. Although esophageal rupture is a surgical emergency, in all cited cases, any esophageal lacerations reported were limited without extensive signs of sepsis (36,39) (Table II). All patients received only supportive care, antibiotics and *nihil per os* for ≥7 days. High flow oxygen was also administered, since it was thought to result in the increased rapid reabsorption of mediastinal air (35). The association between pneumomediastinum and pneumothorax was presented in case reports (33,34). However, Schwartz and Rossoff (34) demonstrated that the bilateral pneumothorax described in the radiological findings may in fact represent 'extrapleural air', as air may outline the tissue planes of the neck, pectoral muscles and axilla. Lateral decubitus exposure may be helpful in differential diagnosis. Elevation of the thymus by underlying air or 'thymic sail sign' may assist the diagnosis of pneumomediastinum (34). If correctly diagnosed and treated, the prognosis for spontaneous pneumomediastinum during pregnancy is favorable (33).

The diaphragm is vulnerable during pregnancy due to increased intra-abdominal pressure (mass effect of the gravid uterus, vomiting) and high progesterone levels, which can lead to muscle relaxation and diaphragmatic hernia (DH). Chen *et al* (39) described a rare case of diaphragmatic tear secondary to an enlargement of a preexisting DH at a young (18-year-old) nulliparous patient. In the majority of the cases of DH, gastric decompression surgery was recommended in the second trimester (39). In terms of delivery following DH repair, the vaginal alternative remained preferable to the cesarean (39).

Another possible cardiovascular complication, venous thromboembolism (VTE) can appear during pregnancy, at delivery and during the first 12 weeks postpartum. The distinction between deep vein thrombosis and pulmonary thromboembolism is possible. A higher risk was described for women with > one admission for HG (40).

Systemic complications. The search strategy yielded 17 articles related to systemic complications of HG, of which two articles were on rhabdomyolysis (41,42), one on porphyria (43), three on electrolyte imbalance (44-46), seven on vitamin K deficiency (47-53), two on endocrine complications (54,55) and two on infectious complications (56,57) (Table III). Rhabdomyolysis is the destruction of a significant amount of strained muscle, leading to disruptions in fluid balance, electrolytes and renal function (41). Diagnosis is made through serum creatine kinase determination and main symptoms include fatigue, weakness, myalgia and swelling, although it is possible that this condition remains completely asymptomatic (41,42).

Severe hyperemesis can result in hypovolemia and electrolyte abnormalities, in turn causing rhabdomyolysis (41). A total of two case reports described this complication in the first trimester of pregnancy (41,42). One case described acute intermittent porphyria (43). All patients received aggressive fluid resuscitation and repletion. Administration of oxygen was used as prophylaxis against extreme hypokalemia and renal failure (41,42). HG is frequently associated with weight loss, acetonuria and electrolytic imbalance with dehydration (40). Hyponatremia, hypokalemia, hypochloremia, hypophosphatemia and dehydration caused by HG can influence other parameters, including QRS prolongation, hematocrit increase, liver cholestasis and cytolysis with increased transaminases, liver steatosis and hypoalbuminemia (4,23). Hypokalemia is usually caused by nutritional deficiencies as a result of electrolyte wasting, extracellular fluid volume reduction and activation of the renin-angiotensin-aldosterone axis (44). In addition, physiological changes that promote potassium wasting during pregnancy, such as volume expansion, increased renal blood flow, increased glomerular filtration rate and increased cortisol levels can all contribute to reduced total body potassium levels (44). Kondo *et al* (44) reported a case of nephrogenic diabetes insipidus (characterized by polyuria with impaired urine concentration) and rhabdomyolysis (with increases in creatine kinase increase) as a consequence of electrolytic imbalance, with hypokalemia noted during prolonged HG (44). In addition, profound hypokalemia was reported by Walch *et al* (45), which caused cardiac arrest and spontaneous miscarriage. Cardiopulmonary resuscitation, stabilization and electrolyte repletion was performed. The patient suffered after 4 h a reversible episode of ventricular fibrillation (venous blood potassium levels were decreased compared with the time of hospital admission). The final outcome was favorable, and the patient was released. Gitelman syndrome is a genetic disorder caused by a defect in the *solute carrier family 12 member 3* gene, which leads to the impaired function of thiazide-sensitive sodium-chloride co-transporter (46). This is a condition that predisposes the patient to electrolytic imbalance, notably in the context of HG (46). However, appropriate treatment with antiemetics, fluid and electrolyte supplementation with restorations in nutritional balance may lead to full recovery of the majority of patients in a few days (44-46).

Vitamin K deficiency has been rarely associated with HG but can present with possible severe complications. Lane *et al* (47) reported that embryopathy with nasal hypoplasia was causally associated with HG. In addition, Shigemi *et al* (48) reported a case of HG associated with fetal intracranial hemorrhage due to severe HG. Vitamin K deficiency is a complication of malnutrition and liver dysfunction associated with prolonged HG (48). In exceedingly rare cases, vitamin K deficiency can cause coagulopathy and fetal intracranial hemorrhage resulting in hydrocephalus and miscarriage (49). Several reports have concluded a possible association between HG and severe fetal complications, including gray matter heterotopias associated with seizures and various types of bone dysplasias, such as brachytelephalangic chondrodysplasia punctata, consistent with the Binder phenotype (50,51). Vitamin K deficiency can cause fetal intracranial hemorrhage associated with seizures even in the absence of fetal morphological complications (52). Complications of HG associated-vitamin K deficiency can also affect the progression of pregnancy in women. Robinson *et al* (53) reported a severe case of epistaxis in a patient at 15 weeks of gestation. When detected early and treated with vitamin K replacement, complete correction of all clotting factors was achieved (53). Endocrine complications

Table III. Systemic complications of hyperemesis gravidarum.

Author	Year	Evidence type	Age of patient (s), years	Country	Gestational age, weeks	Complication	Symptoms	Treatment
Lassey *et al* (41)	2016	Case report	20	USA	19 weeks	Rhabdomyolysis	Fatigue, with general muscle weakness in upper and lower extremities. Frequent falls.	Aggressive rehydration and a phosphorous binder.
Fukada *et al* (42)	1999	Case report	29	Japan	12 weeks	Rhabdomyolysis	Severe muscle weakness of extremities	Conservative
Shenhav *et al* (43)	1997	Case report	29	Israel	13 weeks	Acute intermittent porphyria	Abdominal pain, constipation, and weakness of the lower extremities. Neuro-psychiatric syndrome: irritability, memory loss, concentration difficulties, hallucinations and depression.	Metoclopramide was stopped, and concentrated glucose was commenced i.v., at the rate of 20 ml/kg per day (600 ml 50% glucose). Supplemented with a high carbohydrate diet.
Kondo *et al* (44)	2018	Case report	34	Japan	17 weeks	Electrolytic imbalance inducing rhabdomyolysis and diabetes insipidus	General fatigue, myalgia, muscle weakness and appetite loss, polyuria	Conservative
Walch *et al* (45)	2018	Case report	39	Australia	15+5 weeks	Cardiac arrest	Cardiac arrest	Conservative
Daskalakis *et al* (46)	2009	Case report	20	Greece	10 weeks	Gitelman syndrome-associated severe hypokalemia and hypomagnesemia	Tiredness and muscle weakness	Conservative
Lane *et al* (47)	2015	Case report	21	USA	21 weeks	Vitamin K deficiency embryopathy	Nasal hypoplasia, flat facial profile, and prominent forehead	Conservative with vitamin K supplementation
Shigemi *et al* (48)	2015	Case report	39	Japan	8 weeks	Vitamin K deficiency	Recurrent vomiting, no food or drink for 1 week	Conservative with vitamin K supplementation
Kawamura *et al* (49)	2008	Case report	33	Japan	9 weeks	Vitamin K deficiency-induced fetal intracranial hemorrhage and hydrocephalus	Persisting vomiting	Conservative

Table III. Continued.

Author	Year	Evidence type	Age of patient (s), years	Country	Gestational age, weeks	Complication	Symptoms	Treatment
Brunetti-Pierri *et al* (50)	2007	Case report	Not specified	USA	20 weeks	Brachytelephalangic chondro-dysplasia punctata and gray matter heterotopias	Loss of appetite	Conservative
Toriello *et al* (51)	2012	Clinical reports	Case 1: 22 years, Case 2: Not specified, Case 3: 27 years, Case 4: 25 years, Case 5: Not specified, Case 6: Not specified	USA	Case 1: $10^{3/7}$ weeks, Case 2: Not specified, Case 3: 18 weeks, Case 4: 11 weeks, Case 5: 8 weeks, Case 6: 6 weeks	Vitamin K deficiency embryopathy	Midfacial hypoplasia, absence of nasal spine, wide and flat nasal bridge	Conservative
Eventov-Friedman *et al* (52)	2009	Case report	41	Israel	16 weeks	Fetal intracranial hemorrhage associated with vitamin K deficiency	Infant at birth was pale, not breathing, bradycardic, and hypotonic	Conservative
Robinson *et al* (53)	1998	Case report	22	USA	15 weeks	Coagulopathy secondary to vitamin K deficiency	Sudden onset of severe right-sided epistaxis	Cauterization with topical silver nitrate and surgical packing. Vitamin K supplementation.
Yilmaz *et al* (54)	2014	Case report	22	Turkey	11 weeks	Hyper-parathyroid crisis	Lethargy, responding to noise and somatosensory stimulations with vocalization, eye opening and limb movement	Parathyroidectomy
Sun *et al* (55)	2014	Clinical analysis	25.8	Japan		Transient thyrotoxicosis		Conservative
Katz *et al* (56)	2000	Case report	38	USA	30 weeks	*Mycobacterium chelonae* sepsis associated with long-term use of an intravenous catheter	Development of tender, erythematous nodules on legs and arms	Clarithromycin
Paranyuk *et al* (57)	2006	Case report	33	USA	Not specified	Candida septicemia	Fever	Intravenous fluconazole

caused by HG are also relatively rare. However, at least one report of primary hyperparathyroidism has been published in pregnant women diagnosed with HG (54). Yilmaz *et al* (54) reported a case of severe hypercalcemia associated with a parathyroid crisis, which was resolved following urgent parathyroidectomy, without evidence of neonatal hypocalcemia or tetany. Gestational transient thyrotoxicosis in HG is highly prevalent, with an incidence of ~48% and its severity correlating with serum hCG values (55). By the second trimester, thyroid function was normalized without antithyroid treatment for all patients with clinical gestational transient thyrotoxicosis (55). Prolonged parenteral therapy is required for pregnant women who develop HG and is associated with an increased risk of infection development. Katz *et al* (56) reported a case of *Mycobacterium chelonae*-induced sepsis associated with the long-term use of an intravenous catheter for HG treatment, which was resolved slowly following treatment with clarithromycin without any adverse effects on the fetus. In addition, Candida septicemia was reported in a pregnant woman who underwent catheterization for parenteral nutrition (57). The patient recovered fully and gave birth to a healthy infant.

Discussion

The aim of the present systematic review was to summarize the available evidence regarding severe, life-threatening complications in HG. Observations from the majority of the studies included in the present review demonstrated that certain complications of HG could occur in cases of inadequate therapy or even lack of medical support (58). Nevertheless, some complications occurred even after the patient received the appropriate therapy. The most frequent life-threatening complication of HG was WE, which was demonstrated by >70 studies over the last six decades. However, these papers were not included in the present review since they were case reports and to avoid redundancy of information. The main limitations of the present study were the insufficient number of studies assessing each complication and the fact that the majority of the articles included were case reports. Another limitation was the fact that the pathogenesis of endocrine complications was insufficiently analyzed and inadequately clarified. Overall, the current available data regarding the cardiovascular complications of HG are limited, with most case reports being of low quality. Based on the present evidence, it can be concluded that cardiac complications in women with HG are rare but can be severe. These mostly refer to ventricular arrhythmias, which are caused by QTc prolongation due to electrolyte imbalance (hypokalemia, hypomagnesemia, hypocalcemia) and are provoked by repeated episodes of vomiting. Pre-eclampsia is another potential complication of HG, which usually occurs during the second trimester of pregnancy which if present, should be promptly managed. Data regarding vascular complications are also limited. Although complications, including thromboembolic episodes and marked arterial blood pressure variations have been described, no conclusion can be drawn. In addition, a high-quality study included in the present review, which assessed the impact on HG on the long-term risk of maternal cardiovascular morbidity (26) demonstrated no evidence suggesting an increased risk of mortality among women with HG and those without this condition.

The present systematic review exhibits several important strengths. The topic of this systematic review is of important clinical relevance due to the rapid increase in the prevalence of teenage pregnancy in addition to pregnant women with a history of long-term substance abuse (5). Both parameters are considered risk factors for HG. An innovation of this review is that the data provided by the present study, which analyses life-threatening complications in HG, have not been previously published in this form and can assist clinicians for developing an efficient tailored therapy.

In conclusion, life-threatening complications are exceedingly rare in HG. The most frequent severe complications are WE, electrolyte imbalance and vitamin K deficiency. The low mortality rate for patients with HG over the last decade is explained by the high efficiency of modern therapy, where and the precise management of every complication can be addressed by current guidelines.

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Authors' contributions

SLP suggested the selection of the methodology, searched the literature and made substantial contributions to the writing of the manuscript by confirming the authenticity of the studies used. MB analyzed the results, revised the manuscript and made contribution to the preparation of the manuscript, confirming the authenticity of the studies. AC made contributions to the preparation of the thoracic complications chapter. CP made contributions to the writing of the systemic complications chapter and revised the manuscript. LM made contributions to the preparation of the cardiovascular complications chapter and revised the manuscript. LCP made contributions to the writing of the neurological complications chapter. LPD made contribution to the writing of the neurological complications chapter and revised the manuscript. Data sharing is not applicable. All authors read and approved the final version of the manuscript.

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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