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.

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, hypotension, 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
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 Ca²⁺), 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 hypomagnesemia 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 bigemism 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.

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.
| 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                                                                      |
| 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     | 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            | 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              | 2002   | Case report    | 25                       | Japan   | 15 weeks               | Pneumomediastinum following esophageal rupture    | Disturbance of consciousness                       | Conservative                                                              |
| Yamamoto et al           | 2001   | Case report    | 29                       | Japan   | 6 weeks                | Pneumomediastinum                                | Face swelling, severe toothache                    | Conservative                                                              |
| Germes-Piña et al        | 2016   | Case report    | 21                       | Mexico  | 15 weeks               | Pneumomediastinum                                | Neck swelling and pain, odynophagia, dysphonia      | Conservative                                                              |
| Chen et al               | 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            | 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 1,156,650 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 hypertending 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 'thythic 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 cytology 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 aminiotics, 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    | 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    | 1999 | Case report   | 29                       | Japan   | 12 weeks               | Rhabdomyolysis                       | Severe muscle weakness of extremities | Conservative                                                              |
| Shenhav et al   | 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     | 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     | 2018 | Case report   | 39                       | Australia | 15+5 weeks         | Cardiac arrest                       | Cardiac arrest | Conservative                                                              |
| Daskalakis et al| 2009 | Case report   | 20                       | Greece  | 10 weeks               | Gitelman syndrome-associated severe hypokalemia and hypomagnesemia | Tiredness and muscle weakness | Conservative                                                              |
| Lane et al      | 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   | 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  | 2008 | Case report   | 33                       | Japan   | 9 weeks                | Vitamin K deficiency-induced fetal intracranial hemorrhage and hydrocephalus | Persisting vomiting | Conservative                                                              |
| 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\(^{17}\) 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 contributions 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

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Competing interests

The authors declare that they have no competing interests.
References

1. McPartlin C, O’Donnell A, Robson SC, Beyer F, Moloney E, Bryant A, Bradley J, Muirhead CR, Nelson-Piercy C, Newbury-Birch D, et al: Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: A systematic review. BMJ 2014; 349:1392-1401, 2016.

2. Grooten JJ, Vink ME, Roseboom TJ and Painter RC: A systematic review and meta-analysis of the utility of corticosteroids in the treatment of hyperemesis gravidarum. Nutr Metab Insights 8 (Suppl 1): S23-S32, 2016.

3. Matthews A, Haas DM, O’Mathúna DP and Dowswell T: Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev 9: CD007575, 2015.

4. Mullin PM, Ching C, Schoenberg F, MacGibbon K, Romero R, Goodwin TM and Fejoz MS: Risk factors, treatments, and outcomes among women with prolonged hyperemesis gravidarum. J Matern Fetal Neonatal Med 25: 632-636, 2012.

5. Fell DB, Dodds L, Joseph KS, Allen VM and Butler B: Risk factors for hyperemesis gravidarum requiring hospital admission during pregnancy. Obstet Gynecol 107: 277-284, 2006.

6. Summers A: Emergency management of hyperemesis gravidarum. Emerg Nurse 20: 24-28, 2012.

7. Ahmed KT, Almahashri AA, Rahman RN, Hammoud GM and Ibdlah JA: Liver diseases in pregnancy; Diseases unique to pregnancy. World J Gastroenterol 19: 7639-7646, 2013.

8. Erick M, Cox JT and Mogensen KM: ACOG practice bulletin 189: Nausea and vomiting of pregnancy. Obstet Gynecol 131: 935, 2015.

9. Koudijis HM, Savitri AI, Browne JL, Amelia D, Baharudin M, Grobbe DE and Uiterwaal CS: Hyperemesis gravidarum and placental dysfunction disorders. BMC Pregnancy Childbirth 16: 1, 2016.

10. Lanska DJ and Kryscio RJ: Risk factors for peripartum and postpartum stroke and intracranial venous thrombosis. Stroke 31: 1274-1282, 2000.

11. Seki M, Shibata M, Itoh Y and Suzuki N: Intracerebral hemorrhage due to venous thrombosis of developmental venous anomaly during pregnancy. J Stroke Cerebrovasc Dis 24: e185-e187, 2015.

12. Kennedy MM, Baker MR, Birchall D, Hanley JP, Turnbull DM and Loughney AD: Hyperemesis gravidarum: First trimester sagittal sinus thrombosis. J Obstet Gynaecol 28: 453-454, 2008.

13. Kanayama N, Khatun S, Belayet HM, Yamashita M, Yonezawa M, Kobayashi T and Terao T: Vasospasms of cerebral arteries in hyperemesis gravidarum. Gynecol Obstet Invest 46: 139-141, 1998.

14. Mitchell SJ and Cox P: ECG changes in hyperemesis gravidarum. J Emerg Nurse 20: 24-28, 2012.

15. O’Brien MD and Gilmour-White SK: Management of epilepsy in pregnancy. BMJ 339: 189: Nausea and vomiting of pregnancy. Obstet Gynecol 131: 935, 2015.

16. Grobbee DE and Uiterwaal CS: Hyperemesis gravidarum and placental dysfunction disorders. BMC Pregnancy Childbirth 16: 1, 2016.

17. Kinney CA, Scholl TO, Hyslop TH, Moise KJ, Pena A, Mowry JB, Woolley J, De Cubas C and Moore RV: Adverse maternal and birth outcomes in women admitted to hospital for hyperemesis gravidarum: A population-based cohort study. Paediatr Perinat Epidemiol 32: 40-51, 2018.

18. Fox R, Kett J, Leeson P, Aye CYL and Leducq ST: Preeclampsia: Risk factors, diagnosis, management, and the cardiovascular impact on the offspring. J Clin Med 10: 1625, 2019.

19. Karson EM, Saltzman D and Davis MR: Pneumomediastinum in pregnancy: Two case reports and a review of the literature, pathophysiology, and management. Obstet Gynecol 64 (3 Suppl): 395-438, 1984.

20. Schwartz M and Rosloff L: Pneumomediastinum and bilateral pneumothoraces in a patient with hyperemesis gravidarum. Chest 106: 1904-1906, 1994.

21. Gorbach JS, Counselman FL and Mendelson MH: Spontaneous pneumomediastinum secondary to hyperemesis gravidarum. J Emerg Med 15: 639-643, 1997.

22. Liang SG, Ooka F, Santo A and Kaibara M: Pneumomediastinum following esophageal rupture associated with hyperemesis gravidarum. J Obstet Gynaecol Res 28: 172-175, 2002.

23. Yamamoto T, Suzuki Y, Kojima K, Sato T, Tanemura M, Kaji M, Yamakawa Y, Yokoi M and Suzuki K: Pneumomediastinum secondary to hyperemesis gravidarum during early pregnancy. Acta Obstet Gynecol Scand 80: 1143-1145, 2001.

24. Gernes-Piña F, Acosta-Orozco DM, Flores-Franco RA and Verdugo-Castro PN: Pneumomediastinum associated with hyperemesis gravidarum: A case report. Ginecol Obstet Mex 84: 398-402, 2016 (In Spanish).

25. Chen X, Yang X and Cheng W: Diaphragmatic tear in pregnancy induced by intractable vomiting: A case report and review of the literature. J Matern Fetal Neonatal Med 25: 1822-1824, 2012.

26. Ibdah JA: Liver diseases in pregnancy: Diseases unique to pregnancy. World J Gastroenterol 19: 7639-7646, 2013.

27. Karson EM, Saltzman D and Davis MR: Pneumomediastinum in pregnancy: Two case reports and a review of the literature, pathophysiology, and management. Obstet Gynecol 64 (3 Suppl): 395-438, 1984.

28. Schwartz M and Rosloff L: Pneumomediastinum and bilateral pneumothoraces in a patient with hyperemesis gravidarum. Chest 106: 1904-1906, 1994.

29. Chen X, Yang X and Cheng W: Diaphragmatic tear in pregnancy induced by intractable vomiting: A case report and review of the literature. J Matern Fetal Neonatal Med 25: 1822-1824, 2012.

30. Ibdah JA: Liver diseases in pregnancy: Diseases unique to pregnancy. World J Gastroenterol 19: 7639-7646, 2013.
48. Shigemi D, Nakanishi K, Miyazaki M, Shibata Y and Suzuki S: A case of maternal vitamin K deficiency associated with hyperemesis gravidarum: Its potential impact on fetal blood coagulability. J Nippon Med Sch 82: 54-58, 2015.

49. Kawamura Y, Kawamata K, Shinya M, Higashi M, Niiro M and Douchi T: Vitamin K deficiency in hyperemesis gravidarum as a potential cause of fetal intracranial hemorrhage and hydrocephalus. Prenat Diagn 28: 59-61, 2008.

50. Brunetti-Pierri N, Hunter JV and Boerkoel CF: Gray matter heterotopias and brachytelephalangic chondrodysplasia punctata: A complication of hyperemesis gravidarum induced vitamin K deficiency? Am J Med Genet A 143: 200-204, 2007.

51. Toriello HV, Erick M, Alessandri JL, Bailey D, Brunetti-Pierri N, Cox H, Fryer A, Marty D, McCurdy C, Mulliken JB, et al: Maternal vitamin K deficient embryopathy: Association with hyperemesis gravidarum and Crohn disease. Am J Med Genet A 161: 417-429, 2013.

52. Eventov-Friedman S, Klinger G and Shinwell ES: Third trimester fetal intracranial hemorrhage owing to vitamin K deficiency associated with hyperemesis gravidarum. J Pediatr Hematol Oncol 31: 985-988, 2009.

53. Robinson JN, Banerjee R and Thiet MP: Coagulopathy secondary to vitamin K deficiency in hyperemesis gravidarum. Obstet Gynecol 92: 673-675, 1998.

54. Yilmaz BA, Altay M, Değertekin CK, Çimen AR, Iyidir ÖT, Biri A, Yüksel O, Türünfer FB and Arslan M: Hyperparathyroid crisis presenting with hyperemesis gravidarum. Arch Gynecol Obstet 290: 811-814, 2014.

55. Sun S, Qu X and Zhou J: Clinical analysis of 65 cases of hyperemesis gravidarum with gestational transient thyrotoxicosis. J Obstet Gynaecol Res 40: 1567-1572, 2014.

56. Katz VL, Farmer R, York J and Wilson JD: Mycobacterium chelonae sepsis associated with long-term use of an intravenous catheter for treatment of hyperemesis gravidarum. A case report. J Reprod Med 45: 581-584, 2000.

57. Paranyuk Y, Levine G and Figueroa R: Candida septicemia in a pregnant woman with hyperemesis receiving parenteral nutrition. Obstet Gynecol 107: 535-537, 2006.

58. Fejzo MS, MacGibbon K and Mullin PM: Why are women still dying from nausea and vomiting of pregnancy? Gynecol Obstet Case Rep: Jul 4, 2016 (Epub ahead of print).