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Treatments for Hyperemesis Gravidarum and Nausea and Vomiting in Pregnancy
A Systematic Review

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IMPORTANCE Nausea and vomiting affects approximately 85% of pregnant women. The most severe form, hyperemesis gravidarum, affects up to 3% of women and can have significant adverse physical and psychological sequelae.

OBJECTIVE To summarize current evidence on effective treatments for nausea and vomiting in pregnancy and hyperemesis gravidarum.

EVIDENCE REVIEW Databases were searched to June 8, 2016. Relevant websites and bibliographies were also searched. Titles and abstracts were assessed independently by 2 reviewers. Results were narratively synthesized; planned meta-analysis was not possible because of heterogeneity and incomplete reporting of findings.

FINDINGS Seventy-eight studies (n = 8930 participants) were included: 67 randomized clinical trials (RCTs) and 11 nonrandomized studies. Evidence from 35 RCTs at low risk of bias indicated that ginger, vitamin B_6, antihistamines, metoclopramide (for mild symptoms), pyridoxine-doxylamine, and ondansetron (for moderate symptoms) were associated with improved symptoms compared with placebo. One RCT (n = 86) reported greater improvements in moderate symptoms following psychotherapy (change in Rhodes score [range, 0 {no symptoms} to 40 {worst possible symptoms}], 18.76 [SD, 5.48] to 7.06 [SD, 5.79] for intervention vs 19.18 [SD, 5.63] to 12.81 [SD, 6.88] for comparator [$P < .001$]). For moderate-severe symptoms, 1 RCT (n = 60) suggested that pyridoxine-doxylamine combination taken preemptively reduced risk of recurrence of moderate-severe symptoms compared with treatment once symptoms begin (15.4% vs 39.1% [$P < .04$]). One RCT (n = 83) found that ondansetron was associated with lower nausea scores on day 4 than metoclopramide (mean visual analog scale [VAS] score, 4.1 [SD, 2.9] for ondansetron vs 5.7 [SD, 2.3] for metoclopramide [$P = .023$]) but not episodes of emesis (5.0 [SD, 3.1] vs 3.3 [SD, 3], respectively [$P = .013$]). Although there was no difference in trend in nausea scores over the 14-day study period, trend in vomiting scores was better in the ondansetron group ($P = .042$). One RCT (n = 159) found no difference between metoclopramide and promethazine after 24 hours (episodes of vomiting, 1 [IQR, 0-5] for metoclopramide vs 2 [IQR, 0-3] for promethazine [$P = .81$], VAS [0-10 scale] for nausea, 2 [IQR, 1-5] vs 2 [IQR, 1-4], respectively [$P = .99$]). Three RCTs compared corticosteroids with placebo or promethazine or metoclopramide in women with severe symptoms. Improvements were seen in all corticosteroid groups, but only a significant difference between corticosteroids vs metoclopramide was reported (emesis reduction, 40.9% vs 16.5% at day 2; 71.6% vs 51.2% at day 3; 95.8% vs 76.6% at day 7 [n = 40, $P < .001$]). For other interventions, evidence was limited.

CONCLUSIONS AND RELEVANCE For mild symptoms of nausea and emesis of pregnancy, ginger, pyridoxine, antihistamines, and metoclopramide were associated with greater benefit than placebo. For moderate symptoms, pyridoxine-doxylamine, promethazine, and metoclopramide were associated with greater benefit than placebo. Ondansetron was associated with improvement for a range of symptom severity. Corticosteroids may be associated with benefit in severe cases. Overall the quality of evidence was low.

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Nausea and vomiting in pregnancy is a common but debilitating condition affecting up to 85% of women.[1] The most severe form, hyperemesis gravidarum, affects 0.3% to 3% of pregnant women and is characterized by intractable vomiting, dehydration, electrolyte imbalance, ketosis, nutritional deficiencies, and weight loss.[2] Symptoms usually start by 6 to 8 weeks' gestation and subside before 20 weeks.[1] In severe cases, women may require prolonged hospitalization and support from enteral or parenteral nutrition.

Symptoms can affect day-to-day functioning,[3] ability to work,[4] and interactions with offspring, family, and friends.[5] A recent systematic review and meta-analysis reported an association between hyperemesis gravidarum and preterm delivery and small-for-gestational age infants, although there was no association with congenital anomalies or perinatal death.[6]

This article reviews evidence regarding treatments for varying severity of symptoms of nausea and vomiting in pregnancy or hyperemesis gravidarum.

Key Points

Question Which interventions are associated with improved symptoms of nausea and vomiting in pregnancy or hyperemesis gravidarum?

Findings In this systematic review, ginger, vitamin B_6, antihistamines, metoclopramide (mild symptoms), and pyridoxine-doxylamine (moderate symptoms) were associated with improved nausea and vomiting in pregnancy as compared with placebo. Ondansetron was associated with symptom improvement for all severity of nausea and vomiting in pregnancy and hyperemesis gravidarum, and corticosteroids were associated with beneficial effects in severe cases.

Meaning Both over-the-counter and prescription therapies are associated with improved symptoms of nausea and vomiting in pregnancy and hyperemesis gravidarum, although the evidence supporting these therapies is generally of low quality.

Methods

We searched electronic databases (MEDLINE, EMBASE, CENTRAL, CDSR, DARE, CINAHL, British Nursing Index, PsycINFO, CAB Abstracts, LILACS, AMED, Science Citation Index, Social Science Citation Index, Scopus, Conference Proceedings Index-Science, ClinicalTrials.gov, NHS-EED, HEED, China National Knowledge Infrastructure) and key websites for randomized clinical trials (RCTs) and nonrandomized comparative studies of pharmacological or nonpharmacological interventions for nausea and vomiting in pregnancy or hyperemesis gravidarum, without language restriction, from inception to June 8, 2016, using terms describing (1) nausea, vomiting, or hyperemesis gravidarum; (2) pregnancy (see eBox 1 in the Supplement). We also searched for population-based case series, for estimates of rare adverse events and fetal outcomes, and for treatments reserved for the most severe cases of hyperemesis gravidarum.

Titles and abstracts were assessed independently by 2 reviewers (A.O., C.M.). The full text of each relevant article was reviewed to further determine eligibility. Major exclusion criteria were studies with participants recruited after 20 weeks' gestation and those with no relevant outcomes reported (either via a validated scale or author-defined scale; see **Table 1**). Discrepancies were resolved by consultation with another reviewer (A.B.). Full-text articles published in languages other than English were assessed by research-trained native speakers working alongside the reviewers to ensure consistency.

An electronic data form was used to compile abstracted information. Methodological quality was assessed using the Cochrane Collaboration's Risk of Bias tool[15] for RCTs and the Effective Public Health Practice Project (EPHPP) tool[16] for nonrandomized studies. An evidence grade (A-C) and recommendation (I-III) was assigned using the American Heart Association (AHA) scale for each treatment (see eBox 2 in the Supplement).[17]

Both fixed- or random- effects model meta-analysis and a Bayesian mixed treatment comparison were planned as stipulated in the protocol (PROSPERO CRD42013006642) but were not performed because of heterogeneity in interventions, trial populations, reporting, and definitions of outcome measures and methods. Data were therefore summarized narratively and prioritized to emphasize the highest quality of evidence, defined as randomized clinical trials with a low risk of bias.

Results

The search identified 13 075 titles, of which 222 underwent full review. Seventy-eight studies (n = 8930 participants) met our inclusion criteria (see eFigure in the Supplement). Of these, 11 RCTs were classified as having high within-study risk of bias, mainly attributable to allocation concealment bias, lack of blinding, incomplete outcome data, or selective outcome reporting. Twenty-one were classified as being at unclear risk of bias, mainly because of poor reporting and lack of methodological detail. The quality of case series and nonrandomized studies was weak (n = 9) or moderate (n = 2). The remaining 35 RCTs[18-52] were at low risk of bias and are presented below and summarized in eTables 1-3 in the Supplement (details for all other included studies are summarized in eTables 4-6 in the Supplement). Evidence grades and recommendations are reported in **Table 2**.

Treatment

Treatment focuses on relieving symptoms and preventing serious morbidity such as Wernicke encephalopathy, renal impairment, and extreme weight loss.[53-55] Treatments can be categorized into 3 broad yet overlapping groups. First-line treatments, including simple lifestyle changes (such as eating small amounts often, avoiding dietary triggers and strong odors, eating high-carbohydrate, low-fat foods) and over-the-counter remedies, such as vitamin B_6 (pyridoxine), ginger, and sea bands (an acupressure towelling wrist band that stimulates the Pericardium P6 acupressure point), are usually initiated by women when first experiencing symptoms. Second-line treatments are typically prescribed when a woman first presents to medical care, usually by her obstetric care provider, and include a range of antiemetic drugs as well as provision of intravenous fluid and electrolyte replacement for women who are dehydrated and ketotic. Third-line treatments are reserved for women

Table 1. Tools Used to Measure the Severity of Nausea and Vomiting in Pregnancy

Tool	Description	Scoring	Maximum Score	Cut Point for Severe Symptoms
Pregnancy-Unique Quantification of Emesis and Nausea (PUQE and PUQE 24 score)[7-9]	Three questions regarding nausea, vomiting, and retching during previous 12 h (original version) or 24 h (most commonly used version)	For each question, 0 = no symptoms; 5 = worst possible symptoms	15	Scores ≥13 indicate severe symptoms
The Rhodes Index of Nausea, Vomiting and Retching[10-12]	Eight questions about duration/amount, frequency, and distress caused by symptoms of nausea, vomiting, and retching	For each question, 0 = no symptoms; 5 = worst possible symptoms	40	Scores ≥33 indicate severe symptoms
Nausea and vomiting of pregnancy instrument[13,14]	Three questions relating to nausea, retching, and vomiting over the past 7 d	For each component, 0 = no symptoms; 5 = worst possible symptoms	15	Score ≥8 indicates severe symptoms
Visual analog scale	Patients rate their symptoms on a scale of 0-10	0 = no symptoms; 10 = extreme symptoms	10	Not applicable

with severe, persistent symptoms and are initiated in a hospital setting. These include corticosteroids and supportive therapy, such as enteral feeding. Depending on symptom severity, women may progress from one category to another or may bypass first-line treatments. When second- or third-line treatments fail, some women opt for termination of pregnancy.[56,57] An international online survey carried out by the Hyperemesis Education and Research Foundation reported that of 808 respondents, 15.2% stated that they had undergone at least 1 pregnancy termination for hyperemesis gravidarum.[56]

First-Line Treatments for Mild to Moderate Symptoms

Ginger | Ginger *(Zingiber officinale)* is available in several preparations: powdered fresh root, tablets, capsules, and syrup. Its antinausea properties were first described in traditional Chinese medicine.[58] Four RCTs compared ginger with placebo, and all reported an improvement in symptoms from baseline compared with placebo, regardless of the ginger dose and preparation.[18-21] Basirat et al[18] (n = 70) reported greater improvement in symptoms on a visual analog scale (VAS) (participants specify their level of symptom severity by indicating a position along a continuous line between 0 [no symptoms] and 10 [worst possible symptoms]; see Table 1). The ginger group changed from a mean of 5.88 (SD, 1.83) at baseline to 3.03 (SD, 2.19) on day 4 compared with 4.67 (SD, 1.97) to 3.03 (SD, 2.47) for the placebo group ($P = .01$), but there was no difference in episodes of vomiting. Fischer-Rasmussen et al[19] (n = 30) reported that mean nausea and vomiting relief score (a complex score designed by the authors that takes into account intensity of nausea, vomiting, weight loss, ketonuria, and hematocrit; range not provided), improved more for ginger compared with placebo over two 5-day treatment periods (4.1 vs −0.1 and 3.7 vs 0.9 [$P = .035$]). Vutyavanich et al[20] (n = 70) reported a greater improvement in VAS scores for nausea (2.1 v 0.9, $P = .014$) and vomiting episodes (1.4 v 0, $P < .001$) in the ginger group compared with placebo. Similarly, Keating and Chez[21] (n = 26) reported greater improvements in VAS scores for nausea (10 women in the ginger group had greater than a 4-point improvement compared with 2 women in the placebo group by day 9), and a greater proportion stopped vomiting in the ginger group (8 women in the ginger group compared with 2 in the placebo group by day 6, *P* value not reported).

Four RCTs compared ginger capsules and vitamin B_6.[22-25] Chittumma et al (n = 126)[22] and Ensiyeh and Sakineh[23] (n = 70) reported greater improvements in nausea scores in women taking ginger capsules compared with vitamin B_6 (Chittumma et al: improvement in Rhodes score 3.3 vs 2.5, $P < .05$; Ensiyeh et al: change in VAS scores, 2.2 v 0.9, $P = .024$). Smith et al[24] (n = 291) and Sripramote and Lekhyananda[25] (n = 138) found no differences between the efficacy of ginger and vitamin B_6. Sripramote and Lekhyananda reported improvements in symptoms within each group via VAS for nausea and episodes of vomiting but no difference between groups.[24,25] Similarly, Biswas et al[26] (n = 78) compared ginger with a doxylamine-pyridoxine combination and reported symptom improvement within each group via VAS but no difference between groups. Saberi et al[27] (n = 159), reported that ginger capsules compared with sea bands were associated with a greater improvement in symptoms (Rhodes score improvement, 8.61 for ginger and 4.17 for sea bands; $P < .001$).

In summary, treatment with ginger was associated with improvement in mild symptoms (level A, class IIa).

Acupressure, Acupuncture, and Nerve Stimulation | Acupressure involves the application of physical pressure to specific acupuncture points (eg, the Pericardium 6 [P6] point lies one-sixth of the distance up the arm from the inner aspect of the wrist between the 2 tendons; pressure at this point is believed to reduce symptoms of nausea and vomiting). Three RCTs compared acupressure with placebo in women with mild symptoms.[28-30] Bayreuther et al[28] (n = 23) and Belluomini et al[29] (n = 60) reported improved symptoms from baseline following acupressure at P6 compared with pressure at an alternative location. Bayreuther et al reported improvement in the VAS score for nausea (3.23 in the treatment group, 4.92 in the placebo group [$P = .019$]). Belluomini et al reported improvement in symptoms in both groups but only a significant improvement for vomiting in the acupressure group (change in Rhodes score from 2.09 [SD, 2.5] to 1.28 [SD, 1.9] [$P = .03$] vs 1.83 [SD, 2.7] to 1.63 [SD, 2.3] [*P* not reported in the placebo group]). Naemi-Rad et al[30] (n = 80) reported reduced symptoms of nausea and vomiting after 2 days when comparing acupressure at acupoint Kidney 21 (KID21, a traditional Chinese point on the upper abdomen, 6 cm above the umbilicus, 5 cm lateral to the anterior midline) with nonstimulation (median VAS scores for nausea intensity, 4 [interquartile range {IQR}, 2-5] for the acupoint group and 7 [IQR, 5-8] for the comparator group [$P < .001$]; mean scores for vomiting, 0 [IQR, 0-0.75] and 1 [IQR, 0-2], respectively [$P < .001$]).

Rosen et al[31] (n = 230) compared nerve stimulation with placebo and reported a greater improvement in the Rhodes score in the

Table 2. Grade of Evidence and Recommendation

Treatment[a]	No. of Studies[b]	Risk of Bias/Quality	AHA Rating
First-Line Treatments for Mild-Moderate Nausea and Vomiting in Pregnancy			
Ginger	17 Randomized clinical trials	10 = low[19-27] 3 = unclear[64-66] 4 = high[67-70]	Level A, class IIa
Acupressure	10 Randomized clinical trials	5 = low[27-30,32] 4 = unclear[71-74] 1 = high[75]	Level A, class IIa
	1 Case series	1 = weak[76]	
Nerve stimulation	3 Randomized clinical trials	1 = low[31] 2 = unclear[77,78]	Level B, class IIb
Acupuncture	6 Randomized clinical trials	3 = low[33-35]; 3 = high[79-81]	Level A, class IIb
Aromatherapy	2 Randomized clinical trials	2 = unclear[82,83]	Level B, class IIb
Vitamin B_6 (pyridoxine)	14 Randomized clinical trials	7 = low[22-25,32,36,37] 4 = unclear[65,84-86] 3 = high[68,69,87]	Level A, class IIa
Second-Line Treatments for Moderate-Severe Nausea and Vomiting in Pregnancy or Hyperemesis Gravidarum			
Psychotherapy	1 Randomized clinical trial	1 = low[42]	Level B, class IIa
Vitamin B_6 (pyridoxine)/doxylamine combination	5 Randomized clinical trials	4 = low[26,38-40] 1 = unclear[88]	Level A, class IIa
	1 Case-control study 1 Cohort-analytic	1 = weak[89] 1 = moderate[90]	
Antihistamines	7 Randomized clinical trials	1 = low[41] 4 = unclear[66,86,91,92] 2 = high[87,93]	Level B, class IIa
Dopamine antagonists	10 Randomized clinical trials	5 = low[43-45,50,51] 3 = unclear[94-96] 2 = high[70,79]	Level A, class IIa
	1 Case-control study 1 Cohort study	1 = weak[89] 1 = weak[97]	
Serotonin antagonists	7 Randomized clinical trials	3 = low[39,44,45] 4 = unclear[88,91,92,94]	Level A, class IIa
	1 Cohort analytic study	1 = weak[98]	
Intravenous fluids	1 Randomized clinical trial	1 = low[46]	Level B, class IIa
Intravenous fluids with or without diazepam	1 Randomized clinical trial	1 = unclear[99]	Level B, class III
Outpatient/day-case management	2 Randomized clinical trials 1 case series study	2 = low[47,48] 1 = weak[100]	Level A, class IIa
Third-Line Treatments for Moderate-Severe Nausea and Vomiting in Pregnancy or Hyperemesis Gravidarum			
Corticosteroids	6 Randomized clinical trials	3 = low[49-51] 2 = unclear[95,96] 1 = high[101]	Level A, class IIb
	1 Case series	1 = weak[102]	
Nasogastric/assisted feeding	2 Case series 1 Cohort analytic	2 = weak[103,104] 1 = moderate[105]	Level C, class IIb
Gabapentin	1 Case series	1 = weak[106]	Level C, class III
Transdermal clonidine	1 Randomized clinical trial	1 = low[52]	Level B, class IIb

Abbreviation: AHA, American Heart Association.

[a] Includes treatments excluded from the narrative summary due to the particularly low quality of available evidence (aromatherapy, intravenous fluids with or without diazepam, gabapentin, and nasogastric/assisted feeding.

[b] Number of studies includes all those with an appropriate treatment group (either intervention or comparator).

treatment group (mean change from baseline, 6.48 [95% CI, 5.31-7.66] vs 4.65 [95% CI, 3.67-5.63] [*P* = .02]).

Jamigorn and Phupong[32] (n = 66) compared 5 days of treatment with acupressure using sea bands plus placebo tablet vs treatment with bands at nonstimulating position plus vitamin B_6 (50 mg twice daily). Both were allowed to take dimenhydrinate (50 mg every 6 hours as needed). Symptoms improved in each group, with no difference in improvement between groups. Use of dimenhydrinate was not different between the groups.

Three RCTs compared acupuncture with other treatments.[33-35] A 4-group RCT conducted by Smith et al[33] (n = 593) compared traditional acupuncture, P6 acupuncture, sham treatment, and an information brochure. Women receiving traditional and P6 acupuncture had less nausea by the third week compared with women in the sham treatment and information-only group (Rhodes Index nausea component score [range, 0-12; 0 = best], 3.8 in the traditional acupuncture group; 4.3 in the P6 acupuncture group; 4.4 in the sham treatment group; and 5.8 in the control group [*P* = .001]). No differences in vomiting scores were found between the groups over the 3-week study period. A crossover trial by Carlsson et al[34] (n = 33) reported a reduction in symptoms over time but no difference between P6 and sham acupuncture in nausea symptoms

after a 6-day treatment period.[3] A similar outcome was found by Knight et al[35] (n = 56) (median final VAS score [range, 0 {no symptoms} to 100 {worst possible symptoms}] for nausea 3 days after session 4, 47.5 [IQR, 29.25-69.5] for P6 acupuncture vs 48.0 [IQR, 14.0-80.0] for sham treatment).

In summary for acupressure: treatment with acupressure was associated with symptom improvement for mild cases (level A, class IIa).

For nerve stimulation: evidence indicates treatment may be considered, but the benefit was unclear (level B, class IIb).

For acupuncture: the benefit was unclear (level A, class IIb).

Vitamin B_6 (Pyridoxine) | Two RCTs examined the association of vitamin B_6 with improvement in people with mild to moderate symptoms. Vutyavanich et al[36] (n = 342) compared vitamin B_6 (1 mg 3 times daily) with placebo. Vitamin B_6 was associated with a greater reduction in mean nausea VAS score from baseline compared with a placebo tablet (2.9 [SD, 2.2] vs 2.0 [SD, 2.7] [$P < .001$]). There was no difference in reported vomiting.[36] When high- and low-dose vitamin B_6 (10 mg vs 1.28 mg daily) were compared in 60 women, a greater change in Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score (3-question scale, scoring from 0 [no symptoms] to 15 [worst possible symptoms]; see Table 1) was reported in the high-dose group (mean change, 3.86 [SD, 2.12] in the high-dose group, 2.80 [SD, 1.78] in the low-dose group [$P < .05$]).[37]

In summary, treatment with vitamin B_6 was associated with symptom improvement for mild cases (level A, class IIa).

Second-Line Treatments for Moderate-Severe Symptoms

Vitamin B_6 (Pyridoxine)/Doxylamine Combination | Three RCTs compared pyridoxine-doxylamine combinations with either placebo or ondansetron. Koren et al[38] (n = 280) compared pyridoxine (10 mg) plus doxylamine (10 mg, slow-release preparation) with placebo over 14 days. Symptoms improved in both groups, but the improvement in the pyridoxine-doxylamine group was greater (mean change in PUQE score, 4.8 v 3.9; $P = .006$).

Oliveira et al[39] (n = 36) compared pyridoxine-doxylamine with ondansetron. Symptom improvement occurred in both groups but was greater in the ondansetron group (median change using a 0-100 VAS for nausea: 51 [IQR, 37-64] for ondansetron, 20 [IQR, 8-51] for pyridoxine-doxylamine [$P = .019$]; vomiting: 41 [IQR, 17-57] for ondansetron, 17 [IQR, 4-38] for pyridoxine-doxylamine [$P = .049$]). Maltepe and Koren[40] (n = 60) compared preemptive treatment with pyridoxine-doxylamine vs treatment once symptoms started. Moderate-severe symptoms were reduced in the preemptive group (15.4%) compared with the post-symptom group (39.1%) ($P < .04$).

In summary, treatment with vitamin B_6 (pyridoxine)–doxylamine was associated with symptom improvement for women with mild-moderate symptoms (level A, class IIa).

Erez et al[41] (n = 150) compared hydroxyzine hydrochloride (25 mg twice daily for 3 weeks) with placebo. Symptom improvement occurred in the treatment group with partial or complete relief of symptoms in 82% of women, compared with only 22% in the placebo group ($P < .01$).

In summary, limited-quality evidence indicated that treatment with antihistamines was associated with symptom improvement in mild-moderate cases (level B, class IIa).

Psychotherapy | An RCT by Faramarzi et al[42] (n = 86) compared psychotherapy treatment with standard care. All women received 40 mg of vitamin B_6 daily, and the treatment group received eight 50-minute psychotherapy sessions over a 3-week period. A greater change in the mean Rhodes score was seen in the treatment group (18.76 [SD, 5.48] to 7.06 [SD, 5.79] vs 19.18 [SD, 5.63] to 12.81 [SD, 6.88], $P < .001$).

In summary for psychotherapy: limited evidence indicated that psychotherapy plus vitamin B_6 was associated with greater benefit than vitamin B_6 alone (level B, class IIa,).

Dopamine Antagonists | Tan et al[43] (n = 159) compared metoclopramide (10 mg) with promethazine (25 mg) given intravenously 3 times over 24 hours. Symptoms improved in both treatment groups, with no difference between groups (episodes of vomiting, 1 [IQR, 0-5] for metoclopramide vs 2 [IQR, 0-3] for promethazine [$P = .81$], VAS [0-10 scale] for nausea, 2 [IQR, 1-5] vs 2 [IQR, 1-4], respectively [$P = .99$]).

In summary, evidence indicated that treatment with dopamine receptor antagonists was associated with improved symptoms (level A, class IIa).

Serotonin Antagonists (Ondansetron) | Two RCTs compared ondansetron with metoclopramide. Abas et al[44] (n = 160) compared ondansetron (4 mg intravenously) with metoclopramide (10 mg intravenously). Symptom improvement was seen in both groups, with no evidence of difference between groups at 24 hours. However, more women in the metoclopramide group reported adverse effects (drowsiness: 12.5% for ondansetron vs 30% for metoclopramide [$P = .011$]; dry mouth: 10% for ondansetron vs 23.8% for metoclopramide ($P = .03$). Kashifard et al[45] (n = 83) compared ondansetron with metoclopramide over 2 weeks. Ondansetron was associated with lower nausea scores on day 4 than metoclopramide (mean visual analog scale [VAS] score, 4.1 [SD, 2.9] for ondansetron vs 5.7 [SD, 2.3] for metoclopramide [$P = .023$]) but not episodes of emesis (5.0 [SD, 3.1] vs 3.3 [SD, 3], respectively [$P = .013$]). The ondansetron group had lower vomiting scores than the metoclopramide group calculated over 14 days ($P = .042$, raw data not provided), but there was no difference in trend in nausea scores over 14 days between groups.

In summary, treatment with serotonin receptor antagonists was associated with improvement in symptoms of all severities (level A, class IIa).

Intravenous Fluids | Tan et al[46] (n = 222) compared different compositions of intravenous solution. The intervention group received intravenous dextrose saline with antiemetics according to health care provider preference, whereas the comparator group received normal saline with antiemetics. Repeated-measures analysis of variance of nausea score found greater improvements in the dextrose saline group relative to the saline group ($P = .046$), but no difference in vomiting was reported.

In summary, limited evidence indicated that dextrose saline may be associated with better improvements than normal saline in moderate-severe cases (level B, class IIa).

Outpatient/Day-Case Management | Two RCTs compared day-care outpatient management with inpatient care.[47,48] McParlin et al[47]

Table 3. Dose, Common Adverse Effects, and Contraindications of Recommended Therapies by Severity of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum[a]

Therapy	Dose	Adverse Effects	Contraindications
Mild Symptoms			
Ginger	Most common regime: 250 mg every 6 h	Acid reflux	None apparent
Vitamin B_6 (pyridoxine)	10-25 mg every 8 h	Drowsiness; decreased sensation to touch, temperature, and vibration; loss of balance or coordination	
Antihistamines (eg, cyclizine)	50 mg every 8 h	Drowsiness; dizziness; muscle twitches; dry mouth; headache; rash; tachycardia	Glaucoma, high or low blood pressure, epilepsy
Moderate Symptoms			
Antihistamine/vitamin B_6 combination (doxylamine/pyridoxine)	10 mg doxylamine + 10 mg pyridoxine up to 4 times daily if needed	Drowsiness; somnolence; dizziness; nervousness; stomach pain; headache; diarrhea; irritability; insomnia	Taking monoamine oxidase inhibitors, antimuscarinic drugs
Metoclopramide	10 mg every 8 h	Dystonic movements; oculogyric crises; diarrhea; drowsiness; restlessness; irritability; dry mouth; insomnia; urinary problems; depression; rash	Kidney or liver disease, congestive heart failure, high blood pressure, diabetes, history of depression, epilepsy (or other seizure disorder)
Promethazine	25 mg every 8 h	Dizziness; drowsiness; excitation; rash; increased sensitivity of skin to sunlight; lack of coordination; loss of strength or energy; muscle pain or weakness; insomnia	Should be used with caution in persons with seizure disorders or in persons using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold
Ondansetron	4 mg every 8 h	Anxiety; dizziness; constipation; dry mouth; confusion, headache; hyperventilation; tachycardia; irritability; restlessness; muscle spasms; insomnia	Cardiac arrhythmias, history of prolonged QT interval, heart failure, hypokalaemia, hypomagnesemia, use of concomitant medications that lead to prolongation of QT interval
Severe Symptoms			
Ondansetron	4-8 mg every 8 h	Anxiety; dizziness; constipation; dry mouth; confusion, headache; hyperventilation; tachycardia; irritability; restlessness; muscle spasms; insomnia	Cardiac arrhythmias, history of prolonged QT interval, heart failure, hypokalaemia, hypomagnesemia, use of concomitant medications that lead to prolongation of QT interval
Corticosteroids	Hydrocortisone (100 mg intravenously twice daily) converting to oral prednisolone (40-50 mg daily), with the dose gradually tapered until the lowest maintenance dose is reached	Increased risk of infections; gestational diabetes mellitus	Systemic infections, unless specific anti-infective therapy is used Live virus immunization Hypersensitivity to any component

[a] Data obtained from searches of appropriate drug and therapeutic websites.

(n = 53) reported no difference in symptom severity over 7 days between women who received outpatient rehydration and an antiemetic (cyclizine, 50 mg intravenous/oral) vs inpatient care. McCarthy et al[48] (n = 98) also compared outpatient with inpatient care. The median number of nights spent in the hospital was lower in the outpatient group (0 [IQR, 0-2] vs 2 [IQR, 1-4] nights, $P < .001$).

In summary, evidence indicated that outpatient treatment was associated with benefits that are not better or worse than inpatient intravenous therapy in patients with moderate symptoms (level A, class IIa).

Third-Line Treatments for Moderate-Severe Symptoms

Corticosteroids | Three RCTs compared corticosteroids with placebo or other treatments. Nelson-Piercy et al[49] (n = 40) compared prednisolone with placebo. There was no difference in vomiting and nausea scores in the steroid group compared with placebo. Safari et al[50] (n = 40) compared methylprednisolone with promethazine. There was no difference in symptom improvement by 1 week. However, no patients from the methylprednisolone group were readmitted for recurrence of vomiting, compared with 5 patients from the promethazine group ($P < .01$).

Bondok et al[51] (n = 40) compared hydrocortisone with metoclopramide. Steroids were associated with a greater reduction in vomiting episodes compared with metoclopramide (emesis reduction, 40.9% vs 16.5% at day 2; 71.6% vs 51.2% at day 3; 95.8% vs 76.6% at day 7 [n = 40, $P < .001$]).

In summary, evidence indicated that benefits of corticosteroids were unclear. Treatment may be considered in severe cases (level A, class IIb)

Transdermal Clonidine | Transdermal clonidine patches were investigated in 1 randomized crossover trial by Maina et al[52] (n = 12) in patients unresponsive to other antiemetics. Either clonidine or placebo patches were worn for 5 days before the treatment was alternated. Intravenous fluids and rescue antiemetics were given as required. The mean improvement in symptom scores was greater for clonidine treatment (mean PUQE score, 6.3 [95% CI, 5.5-7.1] for clonidine and 8.5 [95% CI, 7.7-9.3] for placebo, $P = .001$), and there was less use of antiemetics and intravenous therapy in the clonidine group.

In summary, limited evidence indicated treatment with transdermal clonidine was associated with symptom improvements, but currently this is not an established treatment for nausea and vomiting in pregnancy in clinical practice (level B, class IIb).

Discussion

The review found low-quality evidence for therapies treating nausea and vomiting in pregnancy and hyperemesis gravidarum. Less than half of all studies were judged as being at low risk of bias.

Ginger, acupressure, and vitamin B_6 are appropriate initial over-the-counter therapies for mild symptoms. Treatment with nerve stimulation may be considered, but, as with acupuncture, the benefit is unclear.

When symptoms are mild-moderate, or if the above over-the-counter therapies were not beneficial, antihistamines (alone or combined with vitamin B_6) were associated with improved symptoms compared with placebo. Limited evidence indicated an association between psychotherapy, metoclopramide, and promethazine and improvements in moderate symptoms. There was no evidence to indicate that these treatments are unsafe, but more research is needed.

When symptoms are moderate-severe, outpatient, day-care management is feasible, acceptable, and does not result in worse outcomes compared with inpatient care. The serotonin receptor antagonist ondansetron improves symptoms at all severities, but benefit compared with metoclopramide or antihistamines is unclear. Ondansetron appears to be safe in pregnancy,[59] but evidence is limited and more research is needed. Large doses of intravenous ondansetron (more than 8 mg in 1 intravenous dose) are contraindicated in women at risk of cardiac arrhythmias (QT prolongation). In such circumstances, an electrocardiogram should be performed and electrolyte levels checked prior to treatment.[60] There is no evidence that oral administration of ondansetron causes QT prolongation in adults.[10]

When symptoms are more severe or persistent, corticosteroids are associated with improved symptom severity and may be more beneficial than metoclopramide and promethazine. However, use is generally limited to women with severe intractable symptoms with prior treatment failure, preferably after 10 weeks' gestation and during an inpatient admission. This arises from concerns regarding a small increase in incident oral clefts in fetuses exposed to corticosteroids in utero in pooled data from observational studies.[61] More evidence is needed comparing corticosteroids with other medications.

Comparison With Previous Literature

The American College of Obstetricians and Gynecologists published clinical management guidelines in August 2015,[2] recommending the use of vitamin B_6 or vitamin B_6 plus doxylamine as first-line pharmacotherapy, ginger as a nonpharmacological option, and methylprednisolone in refractory cases. Recommendations based on consensus include intravenous hydration and enteral tube feeding for women who are not responsive to medical therapy. Many of the findings in this review support recommendations in the guidelines. However, although pyridoxine plus doxylamine was more effective than placebo, there is no substantial evidence to suggest that the combination is more effective than other antiemetics such as antihistamines. Moreover, this review adds value by categorizing therapies depending on symptom severity. Two Cochrane reviews were published recently.[62,63] Matthews et al[62] included only RCTs focusing on nausea and vomiting and excluded trials involving hyperemesis gravidarum; the review by Boelig et al[63] only included RCTs of hyperemesis gravidarum. Neither review categorized therapies depending on symptom severity. However, both reviews were consistent in concluding that there is little good-quality evidence to support any available intervention.

Limitations

These recommendations are limited by the quality and heterogeneity of evidence. Quality was downgraded due to clinical heterogeneity, imprecision, sparseness of data, or a combination of these factors. There was also considerable variation in the initial assessment and subsequent reporting of nausea, vomiting, and other relevant outcomes in the identified studies. As a result, we were unable to conduct the planned meta-analysis stipulated in our original protocol.

One set of outcome measures likely to be important to women and practitioners is safety. We sought to assemble data on fetal outcomes and adverse events; however, no reliable safety data were identified in the included studies. Details of common adverse effects of the interventions recommended by this review are provided in **Table 3**, along with common dosage regimens. Available observational data (pregnancy-related but not specifically focused on nausea and vomiting) does not provide evidence of any safety concerns with antiemetic medications; this is not the same as ruling out any important differences in adverse outcomes.

Conclusions

For mild symptoms of emesis and nausea of pregnancy, ginger, pyridoxine, antihistamines, and metoclopramide were associated with greater benefit than placebo. For moderate symptoms, pyridoxine-doxylamine, promethazine, and metoclopramide were associated with greater benefit than placebo. Ondansetron was associated with symptom improvement for a range of symptom severity. Corticosteroids may be associated with benefit in severe cases. Overall, the quality of evidence was low.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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Supplementary Online Content

McParlin P, O'Donnell A, Robson S, et al. Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review. *JAMA*.
doi:10.1001/jama.2016.14337

eBox 1. List of All Sources Searched

Electronic databases:

MEDLINE (OVID) 1946 to 2016 May Week 4, searched 8th June 2016

MEDLINE(R) (OVID) In-Process & Other Non-Indexed Citations (7th June) searched 8th June 2016

EMBASE (OVID) 1980 to 2016 Week 23, searched 8th June 2016

CENTRAL (Wiley) issue 5 2016, searched 8th June 2016

CDSR (Wiley) issue 6 2016, searched 8th June 2016

DARE (Wiley) issue 2 2016, searched 8th June 2016

CINAHL (EBSCO) 1981 to June 2016, searched 8th June 2016

British Nursing Index (NHS Healthcare Databases) 1992 to October 2015, searched 3rd November 2015

PsycINFO (OVID) 1806 to June Week 1 2016, searched 8th June 2016

CAB Abstracts (OVID) 1910 to 2016 Week 21, searched 8th June 2016

LILACS http://regional.bvsalud.org, searched 3rd November 2015

AMED (NHS Healthcare Databases) 1985 to January 2014, searched 3rd November 2015

Science Citation Index (Web of Knowledge) 1970 to June 2016, searched 8th June 2016

Social Science Citation Index (Web of Knowledge) 1970 to June 2016, searched 3rd November 2015

Scopus, searched 3rd November 2015

Conference Proceedings Index – Science (Web of Knowledge) 1990 to June 2016, searched 3rd November 2015

Clinicaltrials.gov searched 3rd November 2015

NHS-EED (Wiley) issue 2 2015, searched 3rd November 2015

HEED (Wiley), searched 3rd November 2015

China National Knowledge Infrastructure CNKI http://eng.cnki.net/grid2008/index.htm, searched 3rd November 2015

Websites:

Motherisk http://www.motherisk.org/women/drugs.jsp

ACOG, the American Congress of Obstetricians and Gynecologists http://www.acog.org/

Pregnancy Sickness Support http://www.pregnancysicknesssupport.org.uk

NICE Clinical Knowledge Summaries http://cks.nice.org.uk/nauseavomiting-in-pregnancy

HER, Hyperemesis Education and Research http://www.helpher.org/health-professionals/treatments/index.php

UK Teratology Information Service http://www.uktis.org/

EMA, European Medicines Agency http://www.ema.europa.eu/ema/

Index to Theses http://www.theses.com/

ETHoS, Electronic theses online service http://ethos.bl.uk/

TRIP http://www.tripdatabase.com/

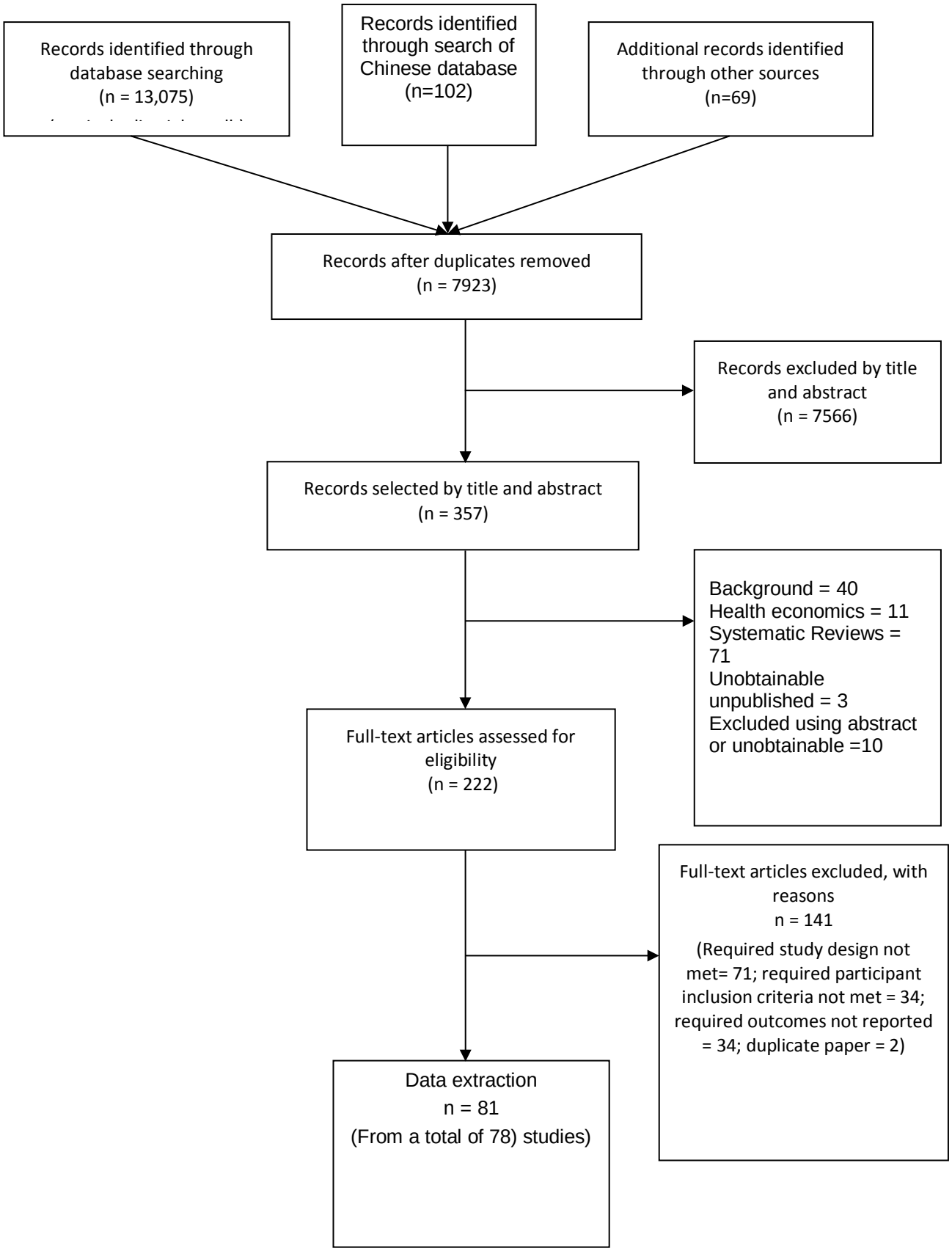
System for Information on Grey Literature in Europe http://www.opengrey.eu/

Google Scholar

Hand-searches

Obstetric Medicine vol 1(1) (September 2008) – vol 7(2) (November 2015).

eFigure 1. Systematic Review Flow-Chart



eBox 2. American Heart Association Grade of Evidence and Recommendation Grading Scale

A-I: conditions for which there is evidence and/or general agreement that a given treatment is useful and effective; data derived from multiple randomized clinical trials (RCTs)

A-II: conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a treatment; data derived from multiple randomized studies

A-III: conditions for which there is evidence and/or general agreement that the treatment is not useful/effective and in some cases may be harmful; data derived from multiple RCTs

B-I: conditions for which there is evidence and/or general agreement that a given treatment is useful and effective; data derived from a single randomized trial or nonrandomized studies

B-II: conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure/treatment, data derived from a single randomized trial or nonrandomized studies

B-III: conditions for which there is evidence and/or general agreement that the treatment is not useful/effective and in some cases may be harmful; data derived from a single randomized trial or nonrandomized studies

C-I: conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective; consensus opinion of experts

C-II: conditions for which there is conflicting evidence and/or divergence of opinion about usefulness/efficacy of a procedure or treatment; consensus opinion of experts

C-III: conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful; consensus opinion of experts

Source: American Heart Association [1]

eTable 1. Summary of Findings From Trials at Low Risk of Bias Evaluating the Effectiveness of First-Line Interventions for Nausea and Vomiting and Hyperemesis Gravidarum in Pregnancy

Note: References for eTable 1 are listed in the article.

Source	Study Details		Participants and Treatments			Outcome Measures and Results		*P* Value
	Study Design	Baseline Symptom Severity[a]	No. of Participants	Gestation, Mean (Range), wk	Dosage and Duration	Primary Outcome Measures	Results	
Ginger vs placebo (4 RCTs)								
Fischer-Rasmussen et al,[19] 1990 (Denmark)	Double-blind randomized crossover trial	Mild-moderate	Intervention: 15	11 (7-17)	Ginger capsules (250 mg powdered root ginger 4 times daily for 4 d, then 2-d washout)	Nausea severity change score	Intervention: 13.7 after first 5 d; 8.2 after second 5 d Comparator: 13.3 after first 5 d; 8.9 after second 5 d	Not significantly different
			Comparator: 15	10.8 (7-16)	Placebo capsules (250 mg lactose 4 times daily for 4 d, then 2-d washout)	Nausea and vomiting relief change score	Intervention: 4.1 after first 5 d; 3.7 after second 5 d Comparator: −0.1 after first 5 d; 0.9 after second 5 d	.035
Vutyavanich et al,[20] 2001 (Thailand)	Double-blind RCT	Mild	Intervention: 32	10.4 (SD, 2.3)	Ginger capsules (250 mg ginger 3 times daily following meals and another before	Decrease in VAS score for nausea	Intervention: 2.1 (SD, 1.9) Comparator: 0.9 (SD, 2.2)	.014

					bed for 4 d)			
			Comparator: 38	10.3 (SD, 2.6)	Placebo capsules (3 times daily after meals and another before bed for 4 d)	Decrease in episodes of vomiting	Intervention: 1.4 (SD, 1.3) Comparator: 0. (SD, 1.1)	<.001
Keating and Chez,[21] 2002 (United States)	Double-blind RCT	Mild	Intervention: 14	Range, 7-11	I250 mg ginger + honey and water, 4 times daily for 2 wk)	VAS score for nausea by day 9	Intervention: 10 women ≥4-point improvement Comparator: 2 women ≥4-point improvement	Not reported
			Comparator: 12		Placebo syrup of water, honey, and lemon oil 4 times daily for 2 wk)	Vomiting stopped by day 6	Intervention: 8 women Comparator: 2 women	1.
Basirat et al,[18] 2009 (Iran)	Double-blind RCT	Mild	Intervention: 35	Range, 7-17	Ginger biscuits (0.5 mg ginger 5 times daily for 4 d)	VAS score for nausea	Average change: Intervention: 2.57 (SD, 1.77) Comparator: 1.39 (SD, 1.62)	.01
			Comparator: 35		Nonginger biscuits (5 times daily for 4 d)	Episodes of vomiting	Average change: Intervention: 0.96 (SD, 0.2) Comparator: 0.62 (SD, 0.19)	.243
Ginger vs vitamin B_6 (4 RCTs)								

Sripramote and Lekhyananda,[25] 2003 (Thailand)	Double-blind RCT	Mild-moderate	Intervention: 68	10.1 (SD, 2.74)	Ginger capsules (500 mg 3 times daily for 3 d)	Mean change in VAS score	Intervention: 5.0 (SD, 1.99) to 3.6 (SD, 2.48) Comparator: 5.3 (SD, 2.08) to 3.3 (SD, 2.07)	<.001
			Comparator: 70	10.3 (SD, 2.95)	Vitamin B_6 capsules (10 mg 3 times daily for 3 d)	Episodes of vomiting	Intervention: 1.9 (SD, 2.06) to 1.2 (SD, 1.75) Comparator: 1.7 (SD, 1.81) to 1.2 (SD, 1.50)	<.01
Smith et al,[24] 2004 (Australia)	Randomized, controlled equivalence trial	Mild-moderate	Intervention: 146	Median, 8.5 (IQR, 8-15)	Ginger capsules (350 mg 3 times daily for 3 wk)	Mean difference in Rhodes Index score: Nausea	0.2 (90% CI, −0.3 to 0.8)	Not reported
			Comparator: 145	Median, 8.6 (IQR, 8-15)	Vitamin B_6 capsules (25 mg 3 times daily for 3 wk)	Vomiting	0.3 (90% CI, −0.0 to 0.6)	1.
						Retching	0.5 (90% CI, 0.0 to 0.9)	1.
Chittumma et al,[22] 2007 (Thailand)	Double-blind RCT	Mild	Intervention: 63	12 (SD, 2)	Ginger capsules (2x 325 mg 4 times daily for 4 d)	Mean change in combined Rhodes Index score	Intervention: 3.3 (SD, 1.5) Comparator: 2.6 (SD, 1.3)	<.05
			Comparator: 63	11 (SD, 2)	Vitamin B_6 capsules (2x 12.5 mg 4 times daily for 4 d)			
Ensiyeh & Sakineh et al,[23] 2009 (Iran)	Double-blind RCT	Mild	Intervention: 35	Not reported	Ginger capsules (500 mg 2 times	Mean change in VAS	Intervention: 2.2 (SD, 1.9) Comparator: 0.9	.024

					daily for 4 d)		(SD, 1.7)	
			Comparator: 35		Vitamin B_6 capsules (20 mg 2 times daily for 4 d)	Episodes of vomiting	Intervention: 0.6 (SD, 0.7) Comparator: 0.5(SD, 1.1)	1.101[b]
Ginger vs acupressure (1 randomized clinical trial)								
Saberi et al,[27] 2013 (Iran)	Three-group RCT	Mild-moderate	Intervention: 53	8.78 (SD, 2.32)	Ginger capsules (250 mg 3 times daily for 4 d)	Mean difference in combined Rhodes Index score	Intervention: 8.61 (SD, 5.24) Comparator: 4.17 (SD, 5.53) Control: 0.84 (SD, 3.72)	<.001
			Comparator: 53	9.32 (SD, 2.38)	Acupressure (sea bands worn continuously for 4 d)			
			Control: 53	9.11 (SD, 0.18)	No intervention			
Ginger vs vitamin B6 /Doxylamine combination (1 randomized clinical trial)								
Biswas et al,[26] 2011 (India)	Single-blind RCT	Mild	Intervention: 42	10.25 (SD, 2.8)	Ginger tablets (150 mg 3 times daily for 1 wk)	Median VAS score for nausea	Intervention: 3 to 0.43 Comparator: 4 to 0.6	Not reported
			Comparator: 36	9.3 (SD, 3.1)	Doxylamine (10 mg) + pyridoxine (10	Mean VAS score for vomiting	Intervention: 1 to 0.14 Comparator: 2 to 0	1.

					mg), 3 times daily for1 wk)			
Acupressure vs placebo (3 RCTs)								
Bayreuther et al,[28] 1994 (United Kingdom)	RCT	Mild	Intervention: 11	≤16	Sea bands at P6 point (7 consecutive d, then 2 d no treatment)	Treatment difference in mean VAS score	Paired *t* test: 1.69 Two-sample *t* test: 1.67 Wilcoxon: 1.65 Mann-Whitney U: 1.61	Not reported
			Comparator: 12		Sea bands at placebo position (7 consecutive d, then 2 d no treatment)			
Belluomini et al,[29] 1994 (United States)	RCT	Mild	Intervention: 30	8.5 (SD, 1.4)	3 d no treatment, then self-administered acupressure (10 min 4 times daily for 7 d at point P6)	Change in Rhodes index for: Nausea	Intervention: 5.80 (SD, 2.9) Comparator: 7.04 (SD, 2.6)	≤.001 ≤.001
			Comparator: 30	8.6 (SD, 1.4)	3 d no treatment, then self-administered acupressure (10 min 4 times daily for 7 d at placebo	Vomiting	Intervention: 1.28 (SD, 1.9) Comparator: 1.63 (SD, 2.3)	.03 Not reported
						Combined	Intervention: 8.69 (SD, 5.0) Comparator: 10.03 (SD, 4.6)	≤.001 .019

					point)			
Naeimi Rad et al,[30] 2012 (Iran)	RCT	Mild-moderate	Intervention: 40	9.55 (SD, 1.81)	Acupressure to KID21 points (20 min daily for 4 d and during nausea and vomiting episodes)	Median (IQR) VAS score at day 4 d for: Intensity of nausea	Intervention: 4 (5-2) Comparator: 7 (8-5)	<.001
			Comparator: 40	9.45 (SD, 2.02)	Acupressure to a false point (20 min daily for 4 d and during nausea and vomiting episodes)	Frequency of nausea	Intervention: 0 (0.75-0) Comparator: 1 (2-0)	<.001
Acupressure vs vitamin B_6 (1 RCT)								
Jamigorn and Phupong,[32] 2007 (Thailand)	RCT	Mild-moderate	Intervention: 33	6.2 (SD, 1.0)	Acupressure wristbands (sea bands at P6 point worn days 1-5) + placebo tablet	Difference in combined Rhodes Index score	No difference	>.05
			Comparator: 33	6.8 (SD, 1.5)	Dummy sea bands + 50-mg tablets of vitamin B_6 every 12 h for 5 d			
Nerve stimulation vs								

placebo (1 RCT)								
Rosen et al,[31] 2003 (United States)	Multicenter RCT	Mild-moderate	Intervention: 117	9.2 (SD, 1.7)	Nerve stimulation (for 3 wk via a relief band model)	Mean change in combined Rhodes Index Score	Intervention: 6.48 (95% CI, 5.31-7.66) Comparator: 4.65 (95% CI, 3.67-5.63)	.02
			Comparator: 113	9.0 (SD, 1.7)	Identical nonstimulating device (for 3 wk)			
Acupuncture vs placebo (3 RCTs)								
Carlsson et al,[34] 2000 (Sweden)	Randomized crossover study	Moderate-severe	Intervention: 17	9.9 (6-16)	Acupuncture at point P6 on days 1 and 2 (30 min, 3 times daily), no acupuncture on days 3 and 4 (washout period) and sham acupuncture on days 5 and 6	Reduction in VAS score for nausea	Between preactive and postactive acupuncture: Intervention: 4 Comparator: 3 Between preplacebo and postplacebo acupuncture: Intervention: 0.1 Comparator: 1.7	Not reported
			Comparator: 16		Sham acupuncture on days 1 and 2, no acupuncture	Incidence of vomiting after 2 d of acupuncture	Intervention: 7/17 women Comparator: 12/16 women	1.00

					on days 3 and 4 (washout period) and active acupuncture at point P6 on days 5 and 6 (30 min, 3 times daily)			
Knight et al,[35] 2001 (United Kingdom)	RCT	Mild-moderate	Intervention: 28	7.8 (SD, 1.0)	Participants allocated to a traditional Chinese medicine diagnosis and treated with acupuncture to a range of points, twice in the first wk and once weekly for 2 wk)	Median (IQR) VAS score	Intervention: day 1 = 85.5 (71.25-89.75); 3 d after session 1 = 63.0 (50.75-86.5); 3 d after session 2 = 65.0 (36.25-79.5); 3 d after session 3 = 44.0 (29.0-77.25); 3 d after session 4 = 47.5 (29.25-69.5 Comparator: day 1 = 87.0 (73.0-90.0); 3 d after session 1 = 69.0 (45.0-87.0): 3 d after session 2 = 61.0 (30.0-80.0); 3 d after session 3 = 53.0 (25.0-80.0); 3 d after session 4 = 48.0 (14.0-80.0)	Not reported
			Comparator: 27	8.0 (SD, 1.0)	Sham treatment (tapping a blunt cocktail stick, supported by a plastic guide tube, in the region of each acupuncture			

					point, twice in week 1 and once weekly for 2 wk).			
Smith et al,[33] 2002 (Australia)	RCT	Mild-moderate	Intervention: 148	Median, 8.3 (IQR, 5-13)	Serin (Japan) 0.2 × 30-mm needles inserted at range of points (0.5-1 cm with maximum of 6 needles per session, then manipulated and left for 20 min)	Rhodes index for: Nausea	Day 7: Intervention: 5.0 (SD, 3.0) Comparator: 5.4 (SD, 3.3) Sham treatment: 5.7 (SD, 2.8) Control: 6.1 (SD, 2.9)	.05
			Comparator: 148	Median, 8.3 (IQR, 4-14)	Acupuncture to p6 single point only (for a 20-min period, twice in week 1 then weekly for 3 wk)	Retching	Day 7: Intervention: 1.3 (SD, 1.4) Comparator: 1.6 (SD, 1.7) Sham treatment: 1.5 (SD, 1.8) Contro: 1.7 (SD, 1.7)	>.05
			Sham treatment: 148	Median, 8.0 (IQR, 4-13)	Sham acupuncture (over similar period)	Vomiting	Day 7: Intervention: 1.4 (SD, 2.0) Comparator: 1.2 (SD, 2.0) Sham treatment: 1.5 (SD, 2.2)	>.05

							Control: 1.5 (SD, 2.1)	
			Control: 149	Median, 8.4 (IQR, 5-14)	Standardized information sheet with diet, lifestyle, and use of vitamin B_6 advice plus telephone support		1.	1.
Vitamin B6 vs placebo (1 RCT)								
Vutyavanich et al,[36] 1995 (Thailand)	Double-blind RCT	Mild-moderate	Intervention: 173	10.9 (SD, 2.7)	Vitamin B_6 tablets (10 mg of pyridoxine hydrochloride 8 hourly for 5 d)	Mean change in VAS score for nausea	Intervention: 2.9 (SD, 2.2) Comparator: 2.0 (SD, 2.7)	<.001
			Comparator: 169	10.9 (SD, 2.8)	Placebo tablets (8 hourly for 5 d)	Mean change in episodes of vomiting	Intervention: 1.22 (SD, 2.0) Comparator: 0.65 (SD, 2.4)	.055
High vs low dose vitamin B_6 (1 RCT)								
Wibowo et al,[37] 2012 (Indonesia)	RCT	Mild	Intervention: 30	<12	Pyridoxine (5 mg mixed with 40 g of powdered milk 2 times daily for 2 wk)	PUQE score	Intervention: 3.86 (SD, 2.12) Comparator: 2.80 (SD, 1.78)	<.05

			Comparator: 30		Pyridoxine (0.64 mg mixed with 40 g of powdered milk twice daily for 2 wk)			

Abbreviations: IQR, interquartile range; PUQE, Pregnancy-Unique Quantification of Emesis and Nausea; RCT, randomized clinical trial; VAS, visual analog scale.

[a]Symptom severity was classified by 2 independent assessors (C.M.P., S.C.R.) as either mild, moderate, or severe, based on the description of severity reported in the study inclusion criteria and, if available, any severity score provided at baseline.

[b]*P* value as reported in report.

eTable 2. Summary of Findings From Trials at Low Risk of Bias Evaluating the Effectiveness of Second-Line Interventions for Nausea and Vomiting and Hyperemesis Gravidarum in Pregnancy

Note: References for eTable 2 are listed in the article.

Source	Study Details		Participants and Treatments			Outcome Measures and Results		*P* Value
	Study Design	Baseline Symptom Severity[1]	No. of Participants	Gestation, Mean (Range), wk	Dosage and Duration	Primary Outcome Measures	Results	
Pyridoxine/doxylamine vs placebo (2 RCTs)								
Koren et al,[38] 2010 (United States)	Double-blind RCT	Moderate	Intervention: 140	9.3 (2.0)	Pyridoxine + doxylamine (Diclectin) (2 tablets daily; up to 4 as needed)	Mean change in PUQE score	Intervention: 4.8 (SD< 2.7) Comparator: 3.9 (SD, 2.6)	.006
			Comparator: 140	9.3 (1.8)	Placebo tablets (2 tablets daily; up to 4 as needed)	Mean AUC of change in PUQE score	Intervention: 61.5 (SD, 36.9) Comparator: 53.5 (SD, 37.5)	<.0001
Maltepe & Koren et al,[40]* 2013 (Canada)	RCT	Not applicable	Intervention: 31	Not reported	Pyridoxine + doxylamine (Diclectin) (2 tablets daily) after pregnancy confirmation (gradual increase if symptoms escalate)	Reduction in hyperemesis gravidarum between pregnancies	Intervention: 43.3% Comparator: 17.2%	.047
			Comparator: 29		Pyridoxine + doxylamine	PUQE score ≥11	Intervention: 15.4%	<.04

					(Diclectin) (2 tablets daily) once symptomatic (with gradual increase if symptoms escalate)		Comparator: 39.1%	
Serotonin antagonist (ondansetron) vs pyridoxine/doxylamine (1 RCT)								
Oliveira et al,[39] 2014 (United States)	Double-blind RCT	Moderate	Intervention: 13	Median gestation, 8 (IQR, 7.1-8.9)	Ondansetron (1 4-mg tablet) + 1 placebo tablet (every 8 h for 5 d)	Median reduction in VAS score for nausea	Intervention: 51 (IQR, 37-64) Comparator: 20 (IQR, 8-51)	.019
			Comparator: 17	Median gestation, 8.1 (IQR, 7.2-9.9)	Pyridoxine (1 tablet, 25 mg) + doxylamine (1 tablet, 12.5 mg every 8 h for 5 d)	Median reduction in VAS score for vomiting	Intervention: 41 (IQR, 17-57) Comparator: 17 (IQR, −4 to 38)	.049
Psychotherapy vs usual treatment (1 RCT)								
Faramarzi et al,[42] 2015 (Iran)	RCT	Moderate	Intervention: 43	<12	Eight 50-min psychotherapy sessions over 3 wk + 40 mg vitamin B_6	Mean change in Rhodes Index Score combined	Intervention: 18.76 (SD, 5.48) to 7.06 (SD, 5.79) Comparator: 19.18 (SD, 5.63) to 12.81 (SD, 6.88)	<.001
			Comparator:		40 mg vitamin			

			43		B_6 over 3 wk			
Antihistamines vs placebo (1 RCT)								
Erez et al,[41] 1971 (Turkey)	RCT	Mild	Intervention: 100	<12	Hydroxyzine hydrochloride capsules (25 mg 2 times daily for 3 wk)	Partial or complete relief of symptoms	Intervention: 82% of patients Comparator: 22% of patients	<.01
			Comparator: 50		Placebo capsules (2 × daily for 3 wk)			
Dopamine antagonists—promethazine vs metoclopramide (1 RCT)								
Tan et al,[43] 2010 (Malaysia)	Double-blind RCT	Moderate	Intervention: 79	9.2 (2.3)	Metoclopramide (10 mg intravenously after randomization and at 8, 16, and 24 h)	Episodes of vomiting	Intervention: 1 (0–5) Comparator: 2 (0–3)	.81
			Comparator: 80	9.3 (2.6)	Promethazine (25 mg intravenously after randomization and at 8, 16, and 24 h)	VAS score for nausea at 24 h	Intervention: 2 (1–5) Comparator: 2 (1–4)	.99
Serotonin antagonist (ondansetron) vs metoclopramide (2								

RCTs)								
Kashifard et al,[45] 2013 (Iran)	Double-blind RCT	Mild-moderate	Intervention: 49	8.7 (2.6)	Ondansetron hydrochloride tablets (4 mg 3 times daily for 1 wk; dose gradually reduced and discontinued after wk 2)	Mean VAS score for nausea	Day 3: Intervention: 5.4 (2.9) Comparator: 6.0 (2.9) Day 4: Intervention: 4.1 (2.9) Comparator: 5.7 (2.3)	.024 .023
			Comparator: 34	8.7 (2.6)	Metoclopramide (10 mg 3 times daily for 1 wk; dose gradually reduced and discontinued after wk 2)	Episodes of vomiting	Day 3: Intervention: 5.3 (3) Comparator: 3.2 (3.4) Day 4: Intervention: 5 (3.1) Comparator: 3.3 (3)	.006 .013
Abas et al,[44] 2014 (Malaysia)	Double-blind RCT	Severe	Intervention: 80	≤16	Ondansetron (4 mg diluted in 100 mL normal saline)	VAS score for nausea (median (IQR) Episodes of vomiting	At 8 h: Intervention: 4 (3-6) Comparator: 5 (4-6) 16 h: Intervention: 3 (1-4) Comparator: 3 (2-4.75) 24 h: Intervention: 1	Repeated-measures ANOVA *P* = .22

							(1-3) Comparator: 2 (1-3)	
			Comparator: 80		Metoclopramide (10 mg diluted in 100 mL normal saline)	Episodes of vomiting	In first 24 h: Intervention: 1 (0-2) Comparator: 2 (0–2.75)	.38
Intravenous fluids D-saline vs N-saline (1 RCT)								
Tan et al,[46] 2013 (Malaysia)	Double-blind RCT	Moderate-severe	Intervention: 111	9.8 (2.8)	5% dextrose–0.9% saline by intravenous infusion (125 mL/h over 24 h)	Median vomiting episodes	Both groups: 0 (0-2)	.66
			Comparator: 111	9.8 (2.5)	0.9% saline by intravenous infusion (125 mL/h over 24 h) Both groups also given potassium chloride (9.5 mmol) as required plus multivitamin (containing 250 mg thiamine given intravenously)	Nausea score (0-10) at 24 h	Intervention: 2 (1-4) Comparator: 2 (2-4) Repeated-measures ANOVA of nausea score	.39 .046 in favor of intervention group
Day-case/Outpatient (2 randomized clinical								

trials)								
McCarthy et al,[48] 2014 (Ireland)	RCT	Mild-moderate	Intervention: 42	Median, 8 (IQR, 7-10)	Treatment in day-care unit (weekdays, 08:00-16:00; 2 L normal saline given intravenously over 5 h; antiemetics as required)	Hospital stay (median IQR)	Intervention: 0 (0-2) Comparator: 2 (1-4)	<.001
			Comparator: 56	Median, 8 (IQR, 7-11)	Usual inpatient treatment (1 L normal saline intravenously over 3 h, then 1 L every 6 h; antiemetics as required)			
McParlin et al,[47] 2016 (United Kingdom)	RCT	Moderate-severe	Intervention: 27	9.3 (2.8)	Cyclizine (50 mg intravenously followed by 3 L Hartman solution over 6 h + 50 mg of oral thiamine, discharged home with prescription for oral cyclizine (50 mg 3 times daily) +	Change in PUQE score	Intervention: 6.9 (4.1) Comparator: 6.2 (2.3)	>.05

					ongoing support and advice			
			Comparator: 26	10.3 (2.9)	Admission to antenatal ward for routine care, intravenous fluids, intravenous cyclizine, and oral thiamine			

Abbreviations: ANOVA, analysis of variance; AUC, area under the curve; IQR, interquartile range; PUQE, Pregnancy-Unique Quantification of Emesis and Nausea; RCT, randomized clinical trial; VAS, visual analog scale.

eTable 3. Summary of Findings From Trials at Low Risk of Bias Evaluating the Effectiveness of Third-Line Interventions for Nausea and Vomiting and Hyperemesis Gravidarum in Pregnancy

Note: References for eTable 3 are listed in the article.

Source	Study Details		Participants and Treatments			Outcome Measures and Results		*P* Value
	Study Design	Baseline Symptom Severity[a]	No. of Participants	Gestation, Mean (Range), wk	Dosage and Duration	Primary Outcome Measures	Results	
Corticosteroids vs placebo (1 RCT)								
Nelson-Piercy et al,[49] 2001 (United Kingdom)	Double-blind, placebo-controlled RCT	Moderate-severe	Intervention: 12	0.6 (2.1)	One-wk course of prednisolone tablets (20 mg, 12 hourly) Both groups: if symptomatic after 72 h, therapy was changed to intravenous equivalent	Episodes of vomiting median (range) Vomiting >5 times/d at 1 wk	No. participants: Intervention: 5 Comparator: 7 Relative risk (95% CI) = 1.4 (0.6-3.2) Intervention: 2 Comparator: 5 Relative risk (95% CI) = 2.5 (0.6-10.5).	Not reported
			Comparator: 13	8.3 (1.9)	One-wk course of placebo tablets (20 mg 12 hourly. Both groups: if symptomatic after 72 h, therapy was changed to IV equivalent.	VAS sore for vomiting median (range) VAS score for nausea median (range)	Intervention: 2.0 (−1.0 tp 4.0) Comparator: 1.5 (−3.0 to 4.0) Intervention: 6.5 (2.0-	

							10.0) Comparator: 4.0 (−5.0 to 9.0) Relative risk = 0.10 for proportion with nausea	
Corticosteroids vs phenothiazines/promethazine/phenergan (1 RCT)								
Safari et al,[50] 1998 (United States)	RCT	Moderate-severe	Intervention: 20	9.8 (2.1)	Methylprednisolone (16 mg orally 3 times daily for 3 d, followed by a tapering regimen, halving of dose every 3 d, to none during the course of 2 wk)	Improvement of symptoms or therapy failure within 2 d of starting therapy	Intervention: therapy failure in 3 patients Comparator: therapy failure in 2 patients	Not reported
			Comparator: 20	9.5 (2.7)	Promethazine (25 mg orally 3 times daily for 2 wk)	Readmitted to hospital	Intervention: 0 patients Comparator: 5 patients	.0001
Corticosteroids vs metoclopramide (1 RCT)								
Bondok et al,[51] 2006 (Egypt)	Prospective, double-blind RCT	Moderate-severe	Intervention: 20	10 (2.68)	Intravenous hydrocortisone (300 mg for 3 d, followed by a tapering regimen: 3 × 10 mL syringes, every 8 h, 1 × drug diluted in normal saline, 2 × normal saline)	Mean episodes of vomiting	Intervention: reduced 40.9% on day 2; 71.6% on day 3; 95.8% on day 7 Comparator: 16.5% on day 2;	<.001

							51.2% on day 3; 76.6% on day 7	
			Comparator: 20	11 (2.44)	Metoclopramide (10 mg in 10-mL syringe diluted in normal saline, intravenously every 8 h for the same 7-d period)			
Transdermal clonidine (1 RCT)								
Maina et al,[52] 2014 (Italy)	Double-blind, controlled, crossover RCT	Severe	12 in total	6 to 12	Transdermal clonidine patch (5 mg) 5-d period before crossover Other antiemetic drugs and intravenous fluids as needed plus thiamine supplement	Mean PUQE score (95% CI)	Intervention: 6.3 (5.5-7.1) Comparator: 8.5 (7.7-9.3)	.001
					Sham patch 5-d period before crossover Other antiemetic drugs and intravenous fluids as needed plus thiamine supplement	Mean (95% CI) VAS score	Intervention: 22 (19-26) Comparator: 29 (25-32)	.009

Abbreviation: RCT, randomized clinical trial; PUQE, Pregnancy-Unique Quantification of Emesis and Nausea; VAS, visual analog scale.

[a]Symptom severity was classified by 2 independent assessors (C.M.P., S.C.R.) as either mild, moderate, or severe, based on the description of severity reported in the study inclusion criteria and, if available, any severity score provided at baseline.

eTable 4. Studies Evaluating the Effectiveness of First-Line Interventions for Nausea and Vomiting or Hyperemesis Gravidarum in Pregnancy. All at High or Unclear Risk of Bias

Author, year (country)	Study Design	Number of participants	Gestation in weeks Mean (range)	Baseline symptom severity[1]	Dosage and duration	Primary Outcome Measures	Results	p value
Ginger versus placebo (2 studies)								
Willets et al, 2003[2] (Australia)	Double blind RCT	Intervention =60	All less than 20	Mild	Ginger capsules (125mg ginger extract, 4 x daily for 4 days)	Rhodes Index for: 1. Nausea 2. Vomiting 3. Retching	1. I < C from day one 2. No difference 3. I < C	p values not reported.
		Comparator =60			Placebo capsules (soya oil, 4 x daily for 4 days).			
Ozgoli et al., 2009[3] (Iran)	Single blind RCT	Iintervention =35	13 (8-19)	Mild-moderate	Ginger capsules (250mg ginger extract, 4 x daily for 4 days)	1. VAS for nausea	I = 85% score decrease C = 56%	p < 0.01
		Comparator =35			Placebo capsules (lactose, 4 x daily for 4 days).	VAS for vomiting	I = 50% score decrease C= 9%	p<0.05
Ginger versus vitamin B6 (3 studies)								
Narenji et al., 2012[4] (Iran)	RCT	Intervention =50	Less than 17	Mild-moderate	Ginger syrup (mix of ginger and honey, 1 teaspoon 2 x daily for 4 days)	Mean change in VAS	I = 1.0(1.32) v C = 0.7(1.99)	p=0.8

[1] Symptom severity was classified by two independent assessors (CMP and SCR) as either mild, moderate or severe, based on the description of severity reported in the study inclusion criteria and, if available, any severity score provided at baseline.

		Comparator =50			Vitamin B6 capsules (40mg 2 x daily for 4 days).	Episodes of vomiting	No difference	p not reported
Haji Seid Javadi et al., 2013[5] (Iran)	RCT	Intervention =47	62.9(8.1) days	Not clear	Ginger tablets (250mg, 6 hourly for 4 days)	Mean change in MPUQE	I = 8.32(2.19) C = 7.77(1.80)	p=0.172
		Comparator =48	62.9(8.6) days		Vitamin B6 tablets (40mg, 12 hourly for 4 days).			
Firouzbakht et al., 2014[6] (Iran)	Double blind three-arm RCT	Intervention =24	9.1(4.6)	Mild	Ginger capsules (250mg, 6 hourly for 4 days)	Likert scale for nausea	I = 6(3.3) to 0.8(0.4) (p<0.001); C=5.8(3.07) to 0.88(0.54) (p<0.001); P=5.21(3.15) to 0.88(0.54)	p<0.001
		Comparator =35	8.9(2.9)		Vitamin B6 capsules (40mg 6 hourly for 4 days)	Episodes of vomiting	I = 4.16(2.14) to 0.89(0.47) (p<0.001); C = 1.49(1.17) to 0.88(0.5) (p=0.022); P = 5.02(1.17) to 0.49(0.13)	p=0.013.
		Placebo (P)=28	9.1(3.6)		Capsules (40mg sugar, 6 hourly for 4 days).			
Ginger versus vitamin B6 / doxylamine combination (1 study)								
Biswas et al., 2011[7] (India)	Single blind RCT	Intervention =42	10.25(2.8)	Mild	Ginger tablets (150mg, 3 x daily for one week)	Median VAS for nausea	I = 3 to 0.43 v C = 4 to 0.6	p not reported
		Comparator =36	9.3(3.1)		Doxylamine 10mg plus pyridoxine 10mg, 3 x daily for one week).	Mean VAS for vomiting	I = 1 to 0.14 C = 2 to 0	p not reported

Ginger versus antihistamine (1 study)								
Pongrojpaw et al., 2007[8] (Thailand)	Double blind RCT	Intervention =85	10.25 (2.8)	Not clear	Ginger capsules (500mg, 2 x daily for one week)	VAS for nausea	No difference	p > 0.05
		Comparator =85	9.3 (3.1)		Dimenhydrinate capsules (50mg, 2 daily for one week).	Episodes of vomiting	C = more effective on days 1-2 (p < 0.05); no difference on days 3-7	p not reported
Ginger versus metoclopramide (1 study)								
Mohammadbeigi et al., 2011[9] (Iran)	Three-arm RCT	Intervention =34	9.5(2.02)	Mild	Ginger capsules (200mg, 3 x daily for 5 days)	Rhodes Index for: Nausea	I and C improved more than P but no difference between I and	I: p=0.003 C: p=0.001 I v C p=0.683
		Comparator =34	10.03 (1.99)		Metoclopramide capsules (10mg, 3 x daily for 5 days)	Vomiting	I and C improved more than P but no difference between I and C	I: p=0.046 C: p=0.018 I v C p= 0.718
		Placebo(P)=34)	10.32 (2.25)		Placebo capsules (200mg flour, for 5 days).			
Acupressure versus placebo (5 studies)								
Steele et al., 2001[10] (USA)	RCT	Intervention =68	Less than 13	Mild	Sea bands (7 days then 72 hour no-treatment control period)	**Mean rank days 1-4:** 1. Nausea frequency 2. Nausea severity 3. Vomiting frequency	1. I=40.30, C=72.82 2. I=40.13, C=73.09 3. I=41.51, C=70.94	No p values reported

						4. Vomiting severity **Mean rank days 5-7:** 5. Nausea frequency 6. Nausea severity 7. Vomiting frequency 8. Vomiting severity	4. I=39.28, C=73.65 5. I=47.18, C=58.47 6. I=49.46, C=54.79 7. I=50.44, C=53.22 8. I=46.63, C=58.24	
		Comparator =42			Placebo sea bands (7 day followed by 72 hour no-treatment control period).			
Werntoft & Dykes, 2001[11] (Sweden)	Three arm pilot RCT	Iintervention =20	9.8(1.9	Moderate-severe	Acupressure wristbands (at P6 point for two weeks)	Mean VAS: 1. Post-treatment 2. Post-day 1 3. Post-day 3 4. Post-day 6 5. Post-day 14	1. I=8.4(1.2) v C=8.4(1.4) v control=8.0(1.5) 2. I=5.2(2.7) v C=5.6(2.5) v control=7.6(1.6) 3. I=5.6(2.3) v C=5.5(2.8) v control=7.2(1.3) 4. I=4.9(2.4) v C=6.3(2.4) v control=6.9(2.0) 5. I=4.2(2.6) v C=5.9(2.4) v control=6.5(2.2)	No p values reported
		Comparator =20	9.6(1.6)		Acupressure wristbands (at placebo point for two weeks)			
		Control=20	10.8(2.2)		No treatment			

Hsu et al., 2003[12] (USA)	RCT	Intervention =38	9 (3-18)	Not clear	Acupressure device placed worn at P6 point (for 60 minutes)	McGill Nausea Questionnaire	No difference at baseline, 30 or 60 minutes	p<0.2
		Comparator =39	9 (3-18)		Acupressure device worn at sham site for (60 minutes).			
Heazell et al., 2006[13] (UK)	RCT	Intervention =40	8.5 (6-14)	Moderate	Acupressure bead at P6 point (8 hours a day, 09:00-17:00)	Number of women staying >4 days	I = 11 v C = 18	p < 0.05
		Comparator =40	9.0 (5-14)		Acupressure bead at sham site (8 hours a day, 09:00-17:00).	Median total no. anti-emetic doses (IQR)	I = 7.1(3-10) v C = 7.5 (4-9.8)	No p value reported
Can Gurkan & Arslan, 2008[14] (Turkey)	RCT	Intervention =26	11.46	Mild-moderate	I/C = days 1-3 no-treatment; days 4-6 acupressure wristbands applied at P6 point; days 7–9 no-treatment	Mean rank at day 4-6 for: 1. Frequency of nausea 2. Severity of nausea 3. Intensity of discomfort from nausea 4. Episodes of vomiting	1. I= 24.52 U= 286.5 P= 26.56 U= 286.5 2. I= 24.9 U= 296.5 P= 26.15 U= 296.5 3. I= 23.98 U= 272.5P = 27.15 U= 272.5 4. I= 22.67 U= 238.5 v P = 28.56 U= 238.5	p>0.05 p>0.05. p>0.05 p>0.05. p>0.05 p>0.05 p>0.05 p>0.05
		Comparator =25	11.52		C/P = days 1-3 no-treatment; days 4-6 acupressure wristbands applied to a placebo point; days 7–9 no-treatment.			

		Placebo(P)=24	10.04					
Acupressure – no comparaor (1 study)								
Markose et al., 2004[15] (India)	Case Series	35 recruited, 17 completed	<12	Mild-moderate	3 days no treatment control phase then acupressure at point P6 from day 4 (4 x daily for 10 min on each hand).	1. Frequency of nausea. 2. Frequency of vomiting. 3. Frequency of dry retches. 4. Distress due to dry retches. 5. Distress due to vomiting. 6. Distress due to nausea.	1. Day 1=52.9%, Day 3=58.8%, Day 7=11.7% 2. Day 1=88.2%, Day 3=100%, Day 7=17.6% 3. Day 1=58.8%, Day 3=58.8%, Day 7=5.8% 4. Day 1=70.5%, Day 3=64.7%, Day 7=23.5% 5. Day 1=82.3%, Day 3=76.4%, Day 7=29.4% 6. Day 1=58.8%, Day 3=70.5%, Day 7=11.7%	(p= 0.008). p<0.001 p= 0.004 p= 0.016 p= 0.008 p= 0.002
Nerve stimulation versus placebo (2 studies)								
Evans et al., 1993[16] (USA)	Randomized Crossover Trial	25	9.9(5-14)	Not clear	Intervention: Active SAS wrist unit (worn continually for 48 hours) Comparator: inactive SAS unit (worn continually for 48 hours)	Nausea score: Average Improvement	1. I= 2.4 v C = 2.7 I = 15 v C = 10	p < 0.05 p < 0.05
de Veciana et al., 2001[17] (USA)	Multicenter RCT	230	6 to 12	Not clear	Nerve stimulation device worn at P6 point	Combined Rhodes Index score	No difference	No p value reported

					Non-stimulating device worn at P6 point for 21 days.			
Acupuncture versus metoclopramide + vitamin B12 (1 study)								
Neri et al., 2005[18] (Italy)	RCT	Intervention =43 Comparator =38	Less than 12	Moderate-severe	Acupuncture (twice weekly for 2 weeks at points PC6, CV12 & ST36) plus acupressure device (Sea Band) at the PC6 point for 6-8 hours a day at home) Metoclopramide infusion (20 mg / 500 ml saline for 60 min twice a week for 2 weeks plus 30mg/day vitamin B12 complex (pyridoxine, hydroxycobalamine)	Nauseaintensity (no. cases improved (%)) Episodes of vomiting (no. cases improved (%))	I: 1st session =1 (2.3), 2nd session=11 (25.5), 3rd session=19 (44.1) v C: 1st=1 (2.3), 2nd=9 (23.6), 3rd=12 (31.5) I: 1st=7 (16.2), 2nd=15 (34.8), 3rd=24 (55.8) v C: 1st=4 (10.5), 2nd=12 (31.5), 3rd=14 (36.8)	No p value reported 1.
Acupuncture versus Chinese herbal medicine versus Western medicine (2 studies)								
Zhang, 2005[19] (China)	Three arm RCT	Intervention =50	6-8 (n=30), 8-12 (n=17), >12wk (n=3)	Moderate	Traditional Chinese acupuncture at specific points + gentle warming moxibustion (10-15 minutes twice daily for 7 days. If the first round of treatment ineffective a 3 day rest period was given before repeating the 7 days)	Self-reported symptom recovery, n(%)	I: complete recovery= 21 (42%), Obvious improvement= 13 (26%), Slight improvement= 9 (18%), no effect= 7 (14%)	No p value reported

		Comparator1 =50	6-8(n=28), 8-12 (n=20), >12wk(n=2)		Specific traditional formula of herbs boiled and made into drink (full daily dose given in 2 parts over 7 days and repeated if not effective for further 7 days)		C1: complete recovery= 9 (18%), Obvious improvement= 7 (14%), Slight improvement= 5 (10%), no effect= 29 (58%)	
		Comparator2 =50.	6-8 (n=25), 8-12 (n=22), >12(n=3)		2500-3000 mls IV fluids given daily to correct dehydration and electrolyte imbalance plus Phenobarbitol (30 mg given orally 3 times daily for 7 days. If not effective treatment repeated for another 7 days after a 3 day rest period).		C2: complete recovery= 5 (10%), Obvious improvement= 8 (16%), Slight improvement= 6 (12%), no effect= 31 (62%).	
Mao & Liang, 2009[20] (China)	Three arm RCT	Intervention =30	8.30(1.60)	Moderate-severe	Traditional Chinese acupuncture (twice daily for 7 days)	1. Symptom severity on Day 4, N(%); 2. Proportion of women with symptom relief on Day 4 (%); 3. Symptom severity on Day 8 N(%); 4. Proportion of women gaining some benefit on Day 8 N(%).	1. I: Obvious improvement= 8(26.7%), Slight improvement= 9(30.0%), no effect= 1(3.3%) v C1: complete recovery= 2(6.7%), Obvious improvement =10(10.0%), Slight improvement= 7(23.3%), no effect= 18(60.0%) v C2: complete recovery=3(10.0%), Obvious improvement= 1(3.3%), Slight improvement= 8(26.7%), no effect= 1 (60.0%) 2. I=96.7% v C1=40.0% v C2=40.0% 3. I: Complete recovery= 27(90.0%), Obvious	No p values reported

							improvement= 2(6.7%), Slight improvement= 0, no effect= 1(3.3%) v C1: Complete recovery= 1(3.3%), Obvious improvement= 6(20.0%), Slight improvement= 4(13.3%), no effect =16(53.4%) v C2: Complete recovery= 3(10.0%), Obvious improvement= 10(33.0%), Slight improvement= 5(16.7%), no effect= 12(40%). 4. I=96.7% v C1=46.6% v C2=60.0%.	
		Comparator1 =30	8.33(1.38)		Phenobarbitol (30 mg 3 x daily for 7 days)			
		Comparator2 =30	8.57 (1.66).		Traditional herbal remedy			
Aromatherapy versus placebo + control (2 studies)								
Pasha et al., 2011[21] (Iran)	Pilot RCT	Intervention =33	9.07(1.31)	Mild	4 drops of pure mint oil added to a bowl of water (placed on the floor near their beds for 4 consecutive nights before sleeping) plus dietary advice	VAS score for: Nausea	I=3.50(1.95) v C =4.38(2.18)	No p values reported
		Comparator =34	9.73(2.2)		4 drops of saline added to a bowl of water (placed on the floor near their beds for 4 consecutive nights	Vomiting	I =2.23(1.88) v C = 2.55(2.55)	

					before sleeping)			
Ghani & Ibrahim, 2013[22] (Saudi Arabia)	Pilot RCT	Intervention =50	10(2.6)	Mild-moderate	4 drops of lavender oils + 1 drop peppermint oil in 1 spoon of water (ratio 4:1:1, heated using an oil burner, 2 x daily for 3 days before sleep. Women were instructed to breathe deeply for 20 minutes)	Combined Rhodes Index Score	I = 23.06(6.37) to 17.60(6.08) C no results reported	p=0.0001 for improvement in intervention group
		Comparator =51	10.2(2.29)		Routine care, no treatment/oils given.			
Vitamin B6 versus placebo (2 studies)								
Sahakian et al., 1991[23] (USA)	Double blind RCT	Intervention =31	9.3 (6-15.5)	Mild-moderate	Vitamin B6 tablets (25 mg of pyridoxine 8 hourly for 3 days)	**1.** Mean change in VAS for nausea **2.** Mean change in severe nausea	**1.** I=2.9 (2.4) v C=1.9 (2.0), **2.** I=4.3 (2.1) v C=1.8 (2.2),	p.0.05 p<0.01
		Comparator =28	9.7 (6-19)		Placebo tablets (8 hourly for 3 days).	Odds ratio for vomiting	0.3014 (95% CI 0.1018-0.8926)	p<0.05
Tan et al., 2009[24] (Malaysia)	RCT	Intervention =48	10.5(3.1)	Moderate	Pyridoxine tablets (20 mg 3 x daily) + metoclopramide (10 mg 3 x daily) + oral thiamine (10 mg daily) + IV rehydration with saline (±KCl). Discharged with	Mean change in VAS for nausea after 2 weeks	I=2(3) v C=2.5±4	p=0.69

					pyridoxine, (2 tablets 3 x daily) + oral metoclopramide + thiamine			
		Comparator =46	9.6(2.8)		Mint tic tac (2 x 3 times daily) + metoclopramide (10 mg 3 x daily) + oral thiamine (10 mg daily) + IV rehydration with saline (±KCl). Discharged with mint tic tac (2 x 3 times daily) + oral metoclopramide + thiamine.	Mean change in episodes of vomiting after 2 weeks.	I=1.4(1.3) v C=1.4(1.6)	p=0.98
Vitamin B6 versus antihistamine (1 study)								
Babaei & Foghah a,2014[25] (Iran)	Double blind RCT	Intervention =70 Comparator =70	4to 17	Mild	Vitamin B6 tablet (50 mg daily for one week) Dimenhydrinate tablet (50 mg daily for one week).	Mean change in Rhodes Index score	I= 4.4(1.6) C=5.7(5.5)	p<0.05

Abbreviations: I, intervention; C, comparator; IQR, interquartile range; PUQE, Pregnancy-Unique Quantification of Emesis and Nausea; RCT, randomized clinical trial; VAS, visual analog scale.

eTable 5. Studies Evaluating the Effectiveness of Second-Line Interventions for Nausea and Vomiting or Hyperemesis Gravidarum in Pregnancy. All at High or Unclear Risk of Bias

Author, year (country)	Study Design	No. participants	Gestation in weeks Mean (range)	Baseline symptom severity[1]	Intervention (dosage/duration) v Comparator (dosage/duration)	Primary Outcome Measures	Results	p value
Serotonin antagonist (ondansetron) versus pyridoxine / doxylamine (2 studies)								
Capp et al., 2014[26] (USA)	Double blind RCT	36 recruited, 30 completed	Less than 16	Not clear;	Intervention = ondansetron (4 mg) + placebo (one tablet every 8 hours for 5 days) Comparator = pyridoxine (25 mg) + doxylamine (12.5 mg, every 8 hours for 5 days).	**VAS for nausea (median (IQR)** Episodes of vomiting	Intervention less than Comparator Intervention less than Comparator	p<0.05 p<0.05
Pyridoxine versus pyridoxine/doxylamine (1 study)								
Pope et al., 2015[27] (Canada)	Prospective, controlled cohort study	Intervention = 80	7.9	Mild-moderate	Women reporting NVP treatment with pyridoxine at least 3-4 days prior to the calling the helpline (mean daily dose 99.1± 62.9mg	**1.** Mean PUQE score improvement over 1 week **2.** Mean PUQE score improvement for women with moderate-severe NVP	**1.** I = -0.2, median 0 v C = 0.5, median 0 **2.** I = 2.6, median 2.8 v C = 0.4, median 0	p=0.002 p=0.02

		Comparator =80	8.1		Women reporting commencing NVP treatment with doxylamine succinate-pyridoxine HCl at least 3-4 days prior to calling the helpline (mean daily dose 37.9±11.0mg).	Number of . women with moderate-severe NVP after 1 week	I = 17 C = 7	p=0.03
Pyridoxine / doxylame versus metoclopramide (1 study)								
Ashkenazi-Hoffnung et al., 2013[28] (Israel)	Prospective case-controlled observational study	Intervenion =29 Comparator =29	Not reported	Not clear	Pyridoxine 50 mg 2 x daily. If vomiting persisted + doxylamine 25 mg once daily, with two additional doses of 12.5 mg if required **M**etoclopramide (10 mg, 8 hourly as needed).	Reported moderate-severe symptoms following treatment	I = 69% C = 72%	p=0.65
Antihistamines +/- vitamin B6 (2 studies)								
Monias, 1957[29] (USA)	RCT	Intervention =100	6 to 20	Mild	Cyclizine plus pyridoxine tablets (2 tablets of each, half an hour before breakfast + additional tablet before lunch if required, x 10 days. Dose not reported)	Relief of symptoms	Intervention: complete = 78, partial relief = 5, none = 17 Comparator: complete = 13, partial = 5, none = 82.	No p value reported
		Comparator =100			Placebo (2 tablets half an hour before breakfast and an additional tablet before lunch if required, for 10 days).			

Diggory & Tomkinson, 1962[30] (UK)	Four arm RCT	Group 1=29	Less than or equal to 14	Mild	Dietary info sheet only	Severity Scale based on disruption to life (good, fair, poor)	G1 = Good (n=6); Fair (n=4); Poor (n=19)	p<0.001
		Group 2=34			Dietary info sheet + placebo		G2 = Good (n=5); Fair (n=11); Poor (n=18)	p<0.001
		Group 3=41			Dietary info sheet + antihistamines (25 mg am, 50mg pm)		G3 = Good (n=28); Fair (n=12); Poor (n=1)	p<0.001
		Group 4=35			Dietary info sheet + antihistamines (25 mg am, 50mg am) plus pyridoxine (50 mg am, 100 mg pm).		G4 = Good (n=22); Fair (n=11); Poor (n=2)	p<0.001
Dopamine antagonists versus conventional treatment (1 study)								
Ferreira et al., 2003[31] (Canada)	Cohort study	Group A= 54	11.1(4.6)	Moderate	Retrospective control group (variety of antiemetic treatments (IM chlorpromazine, IV dimenhydrinate, IV metoclopramide, or a combination of doxylamine–pyridoxine (Diclectin) taken orally, according to the physicians' choice)	Mean National Cancer Institute's Common Toxicity Criteria scale for nausea on day 1 to during hospitalisation	GA= 2.24(0.87) to 1.48(0.49) v GB= 1.33(1.0) to 0.78(0.70) v GC =1.03(1.00) to 0.58(0.60)	p<0.001
		Group B= 67	10.3(3.9)		IV rehydration + multivitamins plus IV droperidol infusion (1 mg/h) plus IV	Mean National Cancer Institute's Common Toxicity Criteria scale for	GA= 1.06(1.00) to 0.62(0.54) v GB= 0.34(0.66) to 0.25(0.36) v GC= 0.41(0.74) to 0.24(0.39)	p<0.001 in favour of group B

					diphenhydramine (25–50 mg, 6 hourly)	vomiting on day 1 to during hospitalisation		
		Group C= 34	10.4(2.8)		IV rehydration + multivitamins plus IV droperidol (0.5 mg/h) plus IV diphenhydramine (50 mg, 6 hourly) plus gradually oral antiemetic treatment consisting of hydroxyzine and metoclopramide			
Serotonin antagonist (ondansetron) versus usual treatment (1 study)								
Einarson et al., 2004[32] (Australia)	Prospective, three arm comparative study	Group 1=188 Group 2=176 Group 3=176	Less than 12	Not clear	Callers taking ondansetron within a two year period Callers not exposed to ondansetron (but used other anti-emetics) Callers exposed to other prescribed drugs or no medication	PUQE score	No results reported	
Serotonin antagonist (ondansetron) versus antihistamines (2 studies)								
Sullivan et al., 1996[33] (USA)	RCT	Intervention =15	11.0 (2.7)	Moderate-severe	IV hydration plus ondansetron (10 mg via IV in 50 ml IV fluid over 30 mins. First dose mandatory, then as	VAS for nausea	No difference	No p value reported

					needed 8 hourly)			
		Comparator =15	10.2 (3.8)		IV hydration plus promethazine (50 mg via IVin 50 ml IV fluid over 30 mins. First dose mandatory, then as needed 8 hourly).			
Eftekhari& Mehralhasani, 2014[34] (Iran)	RCT	Intervention =30	71.56 days (15-125)	Moderate-severe	Rehydration with IV fluids plus ondansetron (8 mg IM 8 hourly for 48 hours)	Mean change in author defined severity scale	I=6.4(2.02) C=5.34(3.1)	p=0.46
		Comparator =30	80.06 days (35-128)		Rehydration with IV fluids plus promethazine (25 mg IM 6 hourly for 48 hours).	Mean change in author defined relief scale	I=12.16(3.7) C=11.65(3.4)	p=0.178.
Serotonin antagonist (ondansetron) versus metoclopramide (1 study)								
Ghahiri et al., 2012[35] (Iran)	RCT	Intervention =35	12 (3.8)	Mild-moderate;	Rehydration with IV fluids + metoclopramide (10 mg orally twice daily for 3 weeks)	Severity of nausea	At Days 3 or 7: no difference At 2 weeks: I greater than C for nausea	p=0.05;
		Comparator =35	10.8 (3.3)		Rehydration with IV fluids plus ondansetron (4 mg orally 2 x daily for 3 weeks).	Severity of vomiting	At 2 weeks I less than C At 3 weeks: I greater than C	p=0.04 p=0.02
IV fluids +/- Diazepam (1 study)								
Ditto et al., 1999[36] (Italy)	RCT	Intervention =50	11.2(3.17)	Moderate;	IV fluids + multivitamins plus diazepam (10mg IV twice daily. Discharged with oral diazepam tablets, 5 mg, twice daily)	VAS for nausea	Significant reduction intervention versus comparator	p<0.05

		Comparator =50	11.5(2.96)		IV fluids plus multivitamins only (discharged with placebo tablets).	Episodes of vomiting	No difference	p>0.05
Day-case / outpatient (1 study)								
Alalade et al., 2007[37] (UK)	Case series	27	8.8	Moderate-severe;	Direct admission to gynecological day ward. Two litres of normal saline infused over 4h with 20 mmol of KCl in each bag. Plus intramuscular /IV antiemetics given.	Hospital stay	All discharged within 24hrs and no re-admittance	No p value

Abbreviations: I, intervention; C, comparator; IQR, interquartile range; IV, intravenous; PUQE, Pregnancy-Unique Quantification of Emesis and Nausea; RCT, randomized clinical trial; VAS, visual analog scale.

eTable 6. Studies Evaluating the Effectiveness of Third-Line Interventions for Nausea and Vomiting or Hyperemesis Gravidarum in Pregnancy. All at High or Unclear Risk of Bias

Author, year (country)	Study Design	No. participants	Gestation in weeks Mean (range)	Baseline symptom severity[1]	Intervention (dosage/duration) v Comparator (dosage/duration)	Primary Outcome Measures	Results	p value
Corticosteroids versus placebo (1 study)								
Yost et al., 2003[38] (USA)	RCT	Intervention =64 Comparator =62	11.0(2.7) 10.8(2.7)	Moderate-severe	I = methylprednisolone (125 mg IV) followed by tapering regimen of oral prednisone (40 mg for 1 day, 20 mg for 3 days, 10 mg for 3 days, 5 mg for 7 days) All: IV re-hydration until ketonuria cleared plus usual treatment. IV placebo followed by the same tapering regimen of an identical appearing placebo. All: IV re-hydration until ketonuria cleared plus usual treatment.	Number requiring hospitalisation	I = 19(34%) C = 19 (35%)	p=0.89
Corticosteroids versus phenothiazines / promethazine / Phenergan (2 studies)								
Ziaei et al., 2004[39] (Iran)	RCT	Intervention =40	11(7-14)	Moderate	Prednisolone (5 mg once day for 10 days)	VAS for nausea	Mild-moderate: First 48h I=20 (50%) v C=30 (75%); 3rd to 10th day I= 6 (65%) v C=25 (62.5%); 17th day I= 17 (43.6%) v C= 12 (30.8%). Severe: First 48h I= 20 (50%) v C=10 (25%); 3rd to 10th day I= 14 (35%) v C=15 (37.5); 17th day I=22 (56.4%) v C=27 (69.2%)	P value not reported

		Comparator =40	11(7-14)		Promethazine (25 mg, 3 x daily for 10 days).	Episodes of vomiting (median (range))	First 48 hrs I=3 (1–7) v C=1 (0–4), p=0.04; 3-10th day I=1.5 (1–5) v C=1 (0–5), p=0.80; 10-17th day I=3 (0–6) v C=3 (0–5)	p=1.0
Adamc-zak et al., 2007[40] (USA)	RCT	Intervention =55	8-14	Not clear	Solumedrol dose pack (included 8mg 3 x daily tapered over 6 days)	Episodes of vomiting	Day 1: I=7.1(1.8) v C=6.6(1.9) Day 3: I=3.0(1.9) v C=4.7(1.8) Day 7: I=1.8(1.6) v C=3.9(1.7) Day 14: I=0.6(0.8) v C=2.5±1.4	p=0.2 p<0.05 p<0.05 p<0.05
		Comparator =55			Phenergan suppositories (25mg 4 x daily).			
Corticosteroids versus usual treatment (1 study)								
Moran & Taylor, 2002[41] (UK)	Retrospective case series	Intervention =25	9.6 (8.6-11.1)	Severe	Prednisolone tablets (10mg x 8 hourly followed by a tapering regime (or via IV hydrocortisone 50mg x 8 hourly if unable to tolerate tablets))	1. VAS for nausea 2. Use of steroids	1. Pattern of resolution in intensity for intervention group 2. 3 comparator group patients received steroids	No p values reported
		Comparator =25	Not reported		IV rehydration plus prophylactic thiamine support plus traditional anti-emetics (metoclopramide, prochlorperazine maleate, or cyclizine hydrochloride).	Median number of inpatient days	Pre-steroid treatment= 8 (4-14) and after commencement=3 (1-6.5)	No p value reported
Nasogastric feeding (2 studies)								

Hsu et al., 1996[42] **(USA)**	Case series	7	Not reported	Severe	Enteral feeding via 8-Fr Dobbhoff nasogastric tube, of Jevity or Osmolite incrementally to meet daily caloric requirements. Initial rate of 25mL/ hour, increasing as tolerated by 25mL/ hour/ day).	1. Improvement in nausea & vomiting symptoms 2. Hospital discharge	1. All improved within 24 hours 2. All discharged within 8 days (mean = 4.6 days)	No p values reported
Stokke et al., 2015[43] (Norway)	Retrospective cohort study	Group A = 273	Median: 8.0	Severe	Antiemetics + IV rehydration	Weight gain to discharge (kg) (95% CI)	GA = 0.0 (0.0–0.0) v GB = 0.0 (0.0–0.0) v GC = 0.8 (0.5–1.0)	p=0.005
		Group B = 177	9.3		Antiemetics + IV rehydration followed by peripheral parenteral nutrition if remained	No. hospital admissions (95% CI)	GA = 1.0 (1.0–1.0) v GB = 1.0 (1.0–2.0) v GC = 2.0 (1.0–2.0)	p= <0.001
		Group C= 107	8.4		Antiemetics (antihistamines or prochlorperazine) plus IV rehydration (saline or 5% glucose) followed by peripheral parenteral then enteral tube feeding if remained symptomatic	Median length hospitalization (days)	GA = 2 days v GB = 4 days v GC = 13 days	p < 0.001
Jejunostomy (1 study)								
Saha et al., 2009[44] (USA)	Case series	5	16.3	Severe	J tubes (placed 12-26 weeks' gestation for 19 weeks (8–28).	1. Resolution of nausea and vomiting 2. Retention of J tubes to delivery	1. Symptoms continued in all patients 2. 4 x J tubes remained in place until delivery. 1 x J tube removed at 34 weeks due to emotional distress; 1 x J tube fell out at 30 weeks	No p values reported

Gabapentin (1 study)								
Guttoso et al., 2010[45] (USA)	Case series	7	8	Moderat e-severe	Gabapentin (300mg orally, 3 x daily, increased by 300 mg to max 3600 mg/day if patient remained symptomatic). After 14 days, therapy discontinued for 2 days, resumed on day 17 & remainder of pregnancy if necessary).	1. Mean reduction in PUQE score from baseline 2. Mean emesis score on discharge	1. 80% to 94% at days 12–14; 84% at baseline to 98% at days 19–21 2. 3× increase in mean nausea and a 7× increase emesis associated with discontinuing gabapentin during days 15–16.	No p value reported

Abbreviations: I, intervention; C, comparator; IV, intravenous; PUQE, Pregnancy-Unique Quantification of Emesis and Nausea; RCT, randomized clinical trial; VAS, visual analog scale.

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