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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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