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 B6, 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, 3.0], 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.

Nausea and vomiting in pregnancy is a common but debilitating condition affecting up to 85% of women. 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. Symptoms usually start by 6 to 8 weeks’ gestation and subside before 20 weeks. In severe cases, women may require prolonged hospitalization and support from enteral or parenteral nutrition.

Symptoms can affect day-to-day functioning, ability to work, and interactions with offspring, family, and friends. 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.

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

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 for RCTs and the Effective Public Health Practice Project (EPHPP) tool 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).

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 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. 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 B6 (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...
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.\textsuperscript{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.\textsuperscript{56}

First-Line Treatments for Mild to Moderate Symptoms

Ginger | Ginger (\textit{Zingiber officinale}) is available in several preparations: powdered fresh root, tablets, capsules, and syrup. Its antinausea properties were first described in traditional Chinese medicine.\textsuperscript{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.\textsuperscript{18-21} Basirat et al\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 B6.\textsuperscript{22-25} Chittumma et al\textsuperscript{22} (n = 126)\textsuperscript{22} and Ensiyeh and Sakineh\textsuperscript{23} (n = 70) reported greater improvements in nausea scores in women taking ginger capsules compared with vitamin B6 (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\textsuperscript{24} (n = 291) and Sripramote and Lekhyananda\textsuperscript{25} (n = 138) found no differences between the efficacy of ginger and vitamin B6. Sripramote and Lekhyananda reported improvements in symptoms within each group via VAS for nausea and episodes of vomiting but no difference between groups.\textsuperscript{24,25} Similarly, Biswas et al\textsuperscript{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\textsuperscript{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 Ia).

Acupressure, Acupuncture, and Nerve Stimulation | Acupressure involves the application of physical pressure to specific acupunc- ture 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 symp- toms of nausea and vomiting). Three RCTs compared acupressure with placebo in women with mild symptoms.\textsuperscript{28-30} Bayreuther et al\textsuperscript{28} (n = 23) and Belluomini et al\textsuperscript{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\textsuperscript{30} (n = 80) reported reduced symptoms of nausea and vomiting after 2 days when comparing acupressure at acupoint Kidney 21 (KI21), 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\textsuperscript{31} (n = 230) compared nerve stimulation with placebo and reported a greater improvement in the Rhodes score in the

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

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

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Jamigorn and Phupong32 (n = 66) compared 5 days of treatment with acupressure using sea bands plus placebo tablet vs treatment with bands at nonstimulating position plus vitamin B6 (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 al33 (n = 593) compared 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]).

### Table 2. Grade of Evidence and Recommendation

<table>
<thead>
<tr>
<th>Treatmenta</th>
<th>No. of Studiesb</th>
<th>Risk of Bias/Quality</th>
<th>AHA Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Line Treatments for Mild-Moderate Nausea and Vomiting in Pregnancy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginger</td>
<td>17 Randomized clinical trials</td>
<td>10 = low19-27 3 = unclear64-66 4 = high77-79</td>
<td>Level A, class IIa</td>
</tr>
<tr>
<td>Acupressure</td>
<td>10 Randomized clinical trials</td>
<td>5 = low27-30,32 4 = unclear71-74 1 = high75</td>
<td>Level A, class IIa</td>
</tr>
<tr>
<td>Nerve stimulation</td>
<td>3 Randomized clinical trials</td>
<td>1 = low11 2 = unclear77,78</td>
<td>Level B, class IIb</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>6 Randomized clinical trials</td>
<td>3 = low73-75, 3 = high79-81</td>
<td>Level A, class IIb</td>
</tr>
<tr>
<td>Aromatherapy</td>
<td>2 Randomized clinical trials</td>
<td>2 = unclear83,83</td>
<td>Level B, class IIb</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;6&lt;/sub&gt; (pyridoxine)</td>
<td>14 Randomized clinical trials</td>
<td>7 = low22-25,32,36,37 4 = unclear65,84-86 3 = high89,91,92</td>
<td>Level A, class IIa</td>
</tr>
<tr>
<td><strong>Second-Line Treatments for Moderate-Severe Nausea and Vomiting in Pregnancy or Hyperemesis Gravidarum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>1 Randomized clinical trial</td>
<td>1 = low42</td>
<td>Level B, class IIa</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;6&lt;/sub&gt; (pyridoxine)/doxylamine combination</td>
<td>5 Randomized clinical trials</td>
<td>4 = low36-38,40 1 = unclear88</td>
<td>Level A, class IIa</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>7 Randomized clinical trials</td>
<td>1 = low41 4 = unclear66,68,91,92 2 = high77,79</td>
<td>Level B, class IIa</td>
</tr>
<tr>
<td>Dopamine antagonists</td>
<td>10 Randomized clinical trials</td>
<td>5 = low41-45,50,51 3 = unclear94-96 2 = high70,79</td>
<td>Level A, class IIa</td>
</tr>
<tr>
<td>Serotonin antagonists</td>
<td>7 Randomized clinical trials</td>
<td>3 = low39,44,45 4 = unclear88</td>
<td>Level A, class IIa</td>
</tr>
<tr>
<td>Intravenous fluids</td>
<td>1 Randomized clinical trial</td>
<td>1 = low96</td>
<td>Level B, class IIa</td>
</tr>
<tr>
<td>Intravenous fluids with or without diazepam</td>
<td>1 Randomized clinical trial</td>
<td>1 = unclear65</td>
<td>Level B, class III</td>
</tr>
<tr>
<td>Outpatient/day-case management</td>
<td>2 Randomized clinical trials 1 case series study</td>
<td>2 = low47,48 1 = weak100</td>
<td>Level A, class IIa</td>
</tr>
<tr>
<td><strong>Third-Line Treatments for Moderate-Severe Nausea and Vomiting in Pregnancy or Hyperemesis Gravidarum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>6 Randomized clinical trials</td>
<td>3 = low49-51 2 = unclear59,96 1 = high101</td>
<td>Level A, class IIb</td>
</tr>
<tr>
<td>Nasogastric/assisted feeding</td>
<td>2 Case series 1 Cohort analytic</td>
<td>2 = weak103-104 1 = moderate105</td>
<td>Level C, class IIb</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1 Case series</td>
<td>1 = weak106</td>
<td>Level C, class III</td>
</tr>
<tr>
<td>Transdermal clonidine</td>
<td>1 Randomized clinical trial</td>
<td>1 = low32</td>
<td>Level B, class IIb</td>
</tr>
</tbody>
</table>

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).
bNumber of studies includes all those with an appropriate treatment group (either intervention or comparator).
after a 6-day treatment period. A similar outcome was found by Knight et al (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 acupuncture: treatment with acupuncture was associated with symptom improvement for mild cases (level A, class Ia).

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

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

Vitamin B<sub>6</sub> (Pyridoxine) | Two RCTs examined the association of vitamin B<sub>6</sub> with improvement in people with mild to moderate symptoms. Vutyavanich et al (n = 342) compared vitamin B<sub>6</sub> (1 mg 3 times daily) with placebo. Vitamin B<sub>6</sub> 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. When high- and low-dose vitamin B<sub>6</sub> (10 mg vs 1.28 mg daily) were compared in 60 women, a greater change in PUQE score, 4.8 v 3.9; vomiting: 14.0-80.0] for sham treatment).

In summary, treatment with vitamin B<sub>6</sub> was associated with symptom improvement for mild cases (level A, class IIa).

Second-Line Treatments for Moderate-Severe Symptoms

Vitamin B<sub>6</sub> (Pyridoxine)/Doxylamine Combination | Three RCTs compared pyridoxine-doxylamine combinations with either placebo or ondansetron. Koren et al (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 (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 (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<sub>6</sub> (pyridoxine)-doxylamine was associated with symptom improvement for women with mild-moderate symptoms (level A, class Ia).

Erez et al (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 Ila).

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

Psychotherapy | An RCT by Faramarzi et al (n = 86) compared psychotherapy treatment with standard care. All women received 40 mg of vitamin B<sub>6</sub> 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<sub>6</sub> was associated with greater benefit than vitamin B<sub>6</sub> alone (level B, class Ila).

Dopamine Antagonists | Tan et al (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 (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 (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 Ila).

Intravenous Fluids | Tan et al (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 Ila).

Outpatient/Day-Case Management | Two RCTs compared day-care outpatient management with inpatient care. McParlin et al
Safari et al50 (n = 40) compared methylprednisolone with pro-
pared prednisolone with placebo. There was no difference in vom-

McCarthy et al48 (n = 98) also compared outpatient with inpa-
tient intravenous therapy in patients with moderate symptoms (level

A, class IIa).

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

Third-Line Treatments for Moderate-Severe Symptoms

Corticosteroids | Three RCTs compared corticosteroids with pla-

cebo or other treatments. Nelson-Piercy et al49 (n = 40) com-
pared prednisolone with placebo. There was no difference in vom-
iting and nausea scores in the steroid group compared with placebo. Safari et al50 (n = 40) compared methylprednisolone with pro-
methazine. 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 pa-
tients from the promethazine group (P < .01).

Bondok et al51 (n = 40) compared hydrocortisone with meto-
clopramide. Steroids were associated with a greater reduction in
vomiting episodes compared with metoclopramide (emesis reduc-
tion, 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 corticoste-
roids were unclear. Treatment may be considered in severe cases
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In summary, limited evidence indicated treatment with trans-
dermal clonidine was associated with symptom improvements, but
currently this is not an established treatment for nausea and vom-
iting in pregnancy in clinical practice (level B, class IIb).

(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 al48 (n = 98) also compared outpatient with inpa-
tient 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,

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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, acupuncture, and vitamin B₆ 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 B₆) were associated with improved symptoms compared with placebo. Limited evidence indicated an association between psychotherapy, metoclopromide, 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 metoclopromide or antihistamines is unclear. Ondansetron appears to be safe in pregnancy, but evidence is limited and more research is needed. Large doses of intravenous ondansetron (more than 8 mg in an 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. There is no evidence that oral administration of ondansetron causes QT prolongation in adults.

When symptoms are more severe or persistent, corticosteroids are associated with improved symptom severity and may be more beneficial than metoclopromide 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. 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, recommending the use of vitamin B₆ or vitamin B₆ plus doxylamine as first-line pharmacotherapy, ginger as a nonpharmacological option, and methylerelpridnilsolone 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. Matthews et al included only RCTs focusing on nausea and vomiting and excluded trials involving hyperemesis gravidarum; the review by Boelig et al 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 metoclopromide were associated with greater benefit than placebo. For moderate symptoms, pyridoxine-doxylamine, promethazine, and metoclopromide 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.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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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 McGee McDermott, MD, at mmd608@northwestern.edu.

REFERENCES


nausea and vomiting of pregnancy: a randomized controlled trial.


