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

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

## **KEY POINTS**

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

**Findings:** Ginger, vitamin B6, antihistamines, metoclopramide (mild symptoms) and pyridoxine-doxylamine (moderate symptoms) are associated with improved nausea and vomiting in pregnancy as compared to placebo. Ondansetron is 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.

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

## **ABSTRACT**

**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 8<sup>th</sup> June 2016. Relevant websites and bibliographies were also searched. Results were narratively synthesised; planned meta-analysis was not possible due to heterogeneity and incomplete reporting of findings.

**Findings:** 78 studies were included; 67 randomized clinical trials and 11 non-randomized studies.

Evidence from 35 randomized clinical trials at low risk of bias indicated that ginger, vitamin B6, antihistamines, metoclopramide (mild symptoms), pyridoxine-doxylamine and ondansetron (moderate symptoms) were associated with improved symptoms as compared to placebo. One randomized clinical trial, (n=86), reported greater improvements in moderate symptoms following psychotherapy, change in Rhodes score (range 0=no symptoms to 40=worst possible symptoms) intervention: 18.76(5.48) to 7.06(5.79) versus comparator: 19.18(5.63) to 12.81(6.88) (p<0.001). For moderate-severe symptoms one randomized clinical trial (n=60) suggested that pyridoxine-doxylamine combination taken pre-emptively reduced risk of recurrence of moderate-severe symptoms (15.4%) compared to treatment once symptoms

begin (39.13%) ( $p < 0.04$ ). One randomized clinical trial, ( $n=83$ ), found that ondansetron was associated with lower nausea scores on day 4, (using a VAS where 0=no symptoms to 10=worst possible symptoms) than metoclopramide (mean (SD) nausea ondansetron: 4.1(2.9) versus metoclopramide: 5.7(2.3)( $p=0.023$ ), but not episodes of emesis 5.0(3.1) versus 3.3(3), respectively( $p = 0.013$ )). However there was no difference in trend in nausea scores over the 14 day study period but trend in vomiting scores was better in the ondansetron group ( $p=0.042$ ). Another randomized clinical trial ( $n=159$ ), found no difference between metoclopramide and promethazine after 24 hours, [(episodes of vomiting: 1(0–5) versus 2(0–3)( $p=0.81$ ), VAS (0-10) for nausea: 2 (1–5) versus 2 (1–4) ( $p=0.99$ )]. Three randomized clinical trials 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 and metoclopramide was reported (emesis reduction: corticosteroid group days 2, 3 and 7= 40.9%, 71.6%, 95.8% versus 16.5%, 51.2%, 76.6% ( $n=40$ ,  $p < 0.001$ )). For other interventions, evidence was sparse.

### **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.

## **INTRODUCTION**

Nausea and vomiting in pregnancy is a common but debilitating condition affecting up to 85% of women<sup>1</sup>. 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<sup>2</sup>. Symptoms usually start by six to eight weeks gestation and subside before 20 weeks<sup>1</sup>. In severe cases, women may require prolonged hospitalization and support from enteral or parenteral nutrition.

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

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 and non-randomized comparative studies of pharmacological or non-pharmacological intervention for nausea and vomiting in pregnancy or hyperemesis gravidarum, without language restriction, from inception to 8<sup>th</sup> June 2016, using terms describing: (1) nausea, vomiting or hyperemesis gravidarum; (2) pregnancy (see

eBox 1). 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 two reviewers (AO, CMP). 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; no relevant outcomes reported (either via a validated scale or author-defined scale, see Table 1). Discrepancies were resolved by consultation with another reviewer (AB). 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<sup>7</sup> for randomized clinical trials and the Effective Public Health Practice Project (EPHPP) tool<sup>8</sup> for non-randomized 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)<sup>9</sup>.

Both fixed- or random- effect model meta-analysis and a Bayesian mixed treatment comparison were planned, but were not performed due to 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**

13,075 titles were identified, of which 222 underwent full review. Seventy-eight studies met our inclusion criteria (see eFigure 1). Of these, 11 randomized clinical trials were classified as

having high within-study risk of bias, mainly due 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 due to poor reporting and lack of methodological detail. The quality of case series and non-randomised studies was weak (n=9) or moderate (n=2)<sup>8</sup>. The remaining 35 randomized clinical trials were at low risk of bias, and are presented below and summarised in Table 2a,b,c (see eTables 1-3 for details of all other included studies).

## **Treatment**

Treatment focuses on relieving symptoms and preventing serious morbidity such as Wernicke's encephalopathy, renal impairment and extreme weight loss.<sup>10-12</sup>. Treatments can be categorized in three broad yet overlapping groups. **First-line treatments**, including simple lifestyle changes, (such as eating small amounts often, avoiding dietary triggers and strong odours, eating high carbohydrate, low fat foods) and over-the-counter remedies, such as vitamin B6 (pyridoxine), ginger and sea bands ( an acupuncture toweling wrist band which stimulates the Pericardium P6 acupuncture point), and 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 anti-emetic 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<sup>13,14</sup>. An international on-line survey carried out by the Hyperemesis Education and

Research Foundation reported that of 808 respondents, 15.2% stated that they underwent at least one pregnancy termination for hyperemesis gravidarum<sup>13</sup>.

### ***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 anti-nausea properties were first described in traditional Chinese medicine<sup>15</sup>. Four randomized clinical trials compared ginger with placebo, and all reported an improvement in symptoms from baseline compared with placebo, regardless of the ginger dose and preparation<sup>16-19</sup>. Basirat et al (n=70) reported greater improvement in symptoms on a visual analogue scale (VAS, participants specify their level of symptom severity by indicating a position along a continuous line between zero (no symptoms) and ten (worst possible symptoms, see Table 1). The ginger group changed from a mean (SD) 5.88 (1.83) at baseline to 3.03 (2.19) on day 4 compared to from 4.67 (1.97) to 3.03 (2.47) for the placebo group (p=0.01) but there was no difference in episodes of vomiting. Fischer-Rasmussen et al<sup>17</sup> (n=30) reported that mean nausea and vomiting relief score, (a complex score designed by the authors which takes into account intensity of nausea, vomiting, weight loss, Ketonuria and haematocrit, range not provided), improved more for ginger (ginger improvement 4.1 and 3.7 for two, five day treatment periods compared to -0.1 and 0.9 for placebo p=0.035). Vutyavanich et al (n=70) reported a greater improvement in VAS for nausea (2.1 v 0.9, p=0.014) and vomiting episodes (1.4 v 0, p<0.001) in the ginger group compared to placebo; similarly Keating et al (n=26) reported greater improvements in a VAS for nausea (10 women in the ginger group had greater than a 4-point improvement compared to 2 in the placebo group by day 9), and a greater proportion stopped vomiting in the ginger group (8 women in the ginger group compared to 2 in the placebo group by day 6, p value not reported).

Four randomized clinical trials compared ginger capsules and vitamin B6. Chittumma et al (n=126) and Ensiyeh et al (n=70) reported greater improvements in nausea scores in women taking ginger capsules compared with vitamin B6 (Chittumma: improvement in Rhodes score 3.3 v 2.5,  $p<0.05$ ; Ensiyeh: change in VAS 2.2 v 0.9,  $p=0.024$ )<sup>20,21</sup>. Smith et al (n=291) and Sripramote et al (n=138) found no differences between the efficacy of ginger and vitamin B6. Sripramote reported improvements in symptoms within each group via VAS for nausea and episodes of vomiting, but no difference between groups<sup>22,23</sup>. Similarly Biswas et al, (n=78), compared ginger with a doxylamine-pyridoxine combination<sup>24</sup> and reported symptom improvement within each group via VAS, but no difference between groups. Compared with sea-bands, Saberi et al, (n=159), reported that ginger capsules were associated with a greater improvement in symptoms (Rhodes score improvement ginger 8.61, sea-bands 4.17.  $p<0.001$ )<sup>25</sup>.

In summary, treatment with ginger is 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 (the Pericardium 6 [P6] point lies one sixth of the distance up the arm from the inner aspect of the wrist between the two tendons. Pressure at this point is believed to reduced symptoms of nausea and vomiting). Three randomized clinical trials compared acupressure with placebo in women with mild symptoms. Bayreuther et al (n=23) and Belluominin et al (n=60)<sup>26,27</sup> reported improved symptoms from baseline following acupressure at P6 compared to pressure an alternative location (Bayreuther: improvement in VAS for nausea in the treatment group 3.23, placebo 4.92 ( $p=0.019$ ); Belluomini 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(2.5) to 1.28(1.9),  $p=0.03$  versus 1.83(2.7) to 1.63(2.3),  $p$  not reported in the placebo group). Naemi-Rad et al ( $n=80$ ) reported reduced symptoms of nausea and vomiting after two days when comparing acupressure at acupoint Kidney 21(KID21, a traditional Chinese point on the upper abdomen, 6cm above the umbilicus, 5cm lateral to the anterior midline) to non-stimulation<sup>28</sup> (median (IQR) VAS for nausea intensity acupoint group: 4 (2-5), comparator 7 (5-8) ( $p<0.001$ ) and vomiting 0 (0-0.75) v 1 (0=2) ( $p<0.001$ )).

Rosen et al ( $n=230$ ) compared nerve stimulation with placebo and reported a greater improvement in the Rhodes score in the treatment group, (mean change from baseline 6.48 (95% CI 5.31, 7.66) v 4.65 (95% CI 3.67, 5.63) ( $p=0.02$ ))<sup>29</sup>.

Jamigorn and Phupong ( $n=66$ ) compared five days treatment with acupressure, using sea-bands plus placebo tablet to treatment with bands at non-stimulating position plus vitamin B6 50mg twice daily<sup>30</sup>. Both were allowed to take Dimenhydrinate 50mg every six 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 randomized clinical trials compared acupuncture with other treatments. A four-group randomized clinical trial conducted by Smith et al ( $n=593$ ) compared traditional acupuncture, P6 acupuncture, sham treatment versus 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]: traditional =3.8; P6 =4.3; sham =4.4; control =5.8 ( $p=0.001$ ))<sup>31</sup>. No differences in vomiting scores were found between the groups over the three week study period. A crossover trial by Carlsson et al ( $n=33$ ) reported a reduction in symptoms over time but no difference between P6 and sham acupuncture in nausea symptoms after a six

day treatment period<sup>32</sup>. A similar outcome was found by Knight et al, (n=56), (final VAS score [range 0, no symptoms-100, worst possible symptoms] for nausea [median IQR] 3 days after session 4; P6=47.5 (29.25-69.5) v sham=48.0 (14.0–80.0))<sup>33</sup>.

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 is unclear (Level A Class IIb).

### Vitamin B6 (pyridoxine)

Two randomized clinical trials examined the association of vitamin B6 with improvement in people with mild to moderate symptoms. Vutyavanich et al<sup>34</sup> (n=342) compared vitamin B6 (one mg three times daily) with placebo. Vitamin B6 was associated with a greater reduction in nausea VAS score from baseline compared with a placebo tablet (2.9(2.2) v 2.0(2.7) [p<0.001]). There was no difference in reported vomiting<sup>34</sup>. When high and low dose vitamin B6 (10 mg versus 1.28 mg daily) were compared in 60 women, a greater change in PUQE score (three question scale, scoring from 0=no symptoms to 15=worst possible symptoms, see Table 1) was reported in the high dose group (high dose=3.86(2.12), low dose=2.80(1.78) (p<0.05))<sup>35</sup>.

In summary, treatment with vitamin B6 is associated with symptom improvement for mild cases (Level A Class IIa).

## *Second-line treatments for moderate-severe symptoms*

### Vitamin B6 (pyridoxine)/doxylamine combination

Three randomized clinical trials compared pyridoxine-doxylamine combinations with either placebo or ondansetron. Koren et al (n=280) compared pyridoxine 10mg plus doxylamine 10mg, slow release preparation, with placebo over 14 days<sup>36</sup>. 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= 0.006).

Oliveira et al (n=36) compared pyridoxine-doxylamine with ondansetron<sup>37</sup>. Symptom improvement occurred in both groups but was greater in the ondansetron group (median (IQR) change using a 0-100VAS for nausea: ondansetron=51(37-64), pyridoxine-doxylamine= 20 (8-51) (p=0.019) and vomiting ondansetron=41 (17-57), pyridoxine-doxylamine=17 (4-38), p=0.049). Maltepe et al (n=60) compared pre-emptive treatment with pyridoxine-doxylamine to treatment once symptoms started<sup>38</sup>. Moderate-severe symptoms were reduced in the pre-emptive group, 15.4%, compared to the post-symptom group, 39.1% (p<0.04).

In summary, treatment with vitamin B6 (pyridoxine)-doxylamine is associated with symptom improvement for women with mild-moderate symptoms (Level A Class IIa).

Erez et al (n=150) compared hydroxyzine hydrochloride (25 mg twice daily for three weeks) with placebo<sup>39</sup>. Symptom improvement occurred in the treatment group with partial or complete relief of symptoms in 82% of women, compared to only 22% in the placebo group (p<0.01).

In summary, limited quality evidence indicates that treatment with antihistamines is associated with symptoms improvements in mild-moderate cases (Level B Class IIa).

### Psychotherapy

A randomized clinical trial by Faramarzi et al (n=86) compared psychotherapy treatment with standard care<sup>40</sup>. All women received 40mg of vitamin B6 daily and the treatment group received eight 50 minute psychotherapy sessions over a three week period. A greater change in the mean Rhodes score was seen in the treatment group, (18.76 to 7.06 versus 19.18 to 12.81,  $p < 0.001$ ).

In summary for psychotherapy: limited evidence indicates that psychotherapy plus vitamin B6 is associated with greater benefit than vitamin B6 alone (Level B Class IIa).

### Dopamine antagonists

Tan et al (n=159) compared metoclopramide 10mg to promethazine 25mg given intravenously (IV) three times over 24 hours<sup>41</sup>. Symptoms improved in both treatment groups, with no difference between groups.

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

### Serotonin antagonists (ondansetron)

Two randomized clinical trials compared ondansetron with metoclopramide. Abas et al (n=160) compared ondansetron 4mg IV with metoclopramide 10mg IV<sup>42</sup>. 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 side effects (drowsiness: ondansetron 12.5% v metoclopramide 30% ( $p=0.011$ ), and dry mouth: ondansetron 10% v metoclopramide 23.8% ( $p=0.03$ ). Kashifard et al (n=83) compared ondansetron with metoclopramide over two weeks<sup>43</sup>. The ondansetron group had lower vomiting scores than the metoclopramide group calculated over 14-days ( $p=0.042$ , 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 (n=222) compared different compositions of IV solution<sup>44</sup>. The intervention group received IV dextrose saline with anti-emetics according to healthcare provider preference, while 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=0.046) but no difference in vomiting was reported.

In summary, limited evidence indicates 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 randomized clinical trials compared day-care outpatient management with inpatient care. McParlin et al (n=53) reported no difference in symptom severity over seven days between women who received outpatient rehydration and anti-emetics (Cyclizine 50mg IV/oral) versus inpatient care<sup>45</sup>. McCarthy et al (n= 98) also compared outpatient with inpatient care<sup>46</sup>. The median (IQR) number of nights spent in hospital was lower in the outpatient group (0 [0-2] versus 2 [1-4] nights, p<0.001).

In summary, evidence indicates that outpatient treatment was associated with benefits that are not better or worse than in-patient intravenous therapy in patients with moderate symptoms (Level A Class IIa).

### ***Third-line treatments for moderate-severe symptoms***

#### Corticosteroids

Three randomized clinical trials compared corticosteroids with placebo or other treatments. Nelson-Piercy et al (n=40) compared prednisolone with placebo<sup>47</sup>. There was no difference in vomiting and nausea scores in the steroid group compared with placebo. Safari et al (n=40) compared methylprednisolone with promethazine<sup>48</sup>. There was no difference in symptom improvement by one week. However, no patients from the methylprednisolone group were readmitted for recurrence of vomiting compared to five patients from the promethazine group (p<0.01).

Bondok et al (n=40) compared hydrocortisone with metoclopramide<sup>49</sup>. Steroids were associated with a greater reduction in vomiting episodes compared with metoclopramide (96% reduction in the steroid group v 77% in the metoclopramide group on day seven, p<0.001).

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 one randomized cross-over trial by Maina et al (n=12) in patients unresponsive to other anti-emetics<sup>50</sup>. Either clonidine or placebo patches were worn for five days before the treatment was alternated. IV fluids and rescue anti-emetics were given as required. The mean improvement in symptom scores was greater for clonidine treatment (mean PUQE score: clonidine=6.3(5.5-7.1), placebo= 8.5(7.7-9.3), p=0.001), and there was less use of anti-emetics and IV therapy in the clonidine group.

In summary, limited evidence indicates treatment with transdermal clonidine is associated with symptom improvements but currently this is not an established treatment (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 B6 are appropriate initial ‘over the counter’ (OTC) 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 OTC therapies were not beneficial, antihistamines (alone or combined with vitamin B6) were associated with improved symptoms compared with placebo. Limited evidence indicates an association between psychotherapy, metoclopramide and promethazine and improvements in moderate symptoms. There is 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 to inpatient care. The serotonin receptor antagonist, ondansetron, improves symptoms at all severities but benefit compared to metoclopramide or antihistamines is unclear. Ondansetron appears to be safe in pregnancy<sup>51</sup> but evidence is limited and more research is needed. Large doses of IV ondansetron (more than 8mg in one intravenous dose) are contraindicated in women at risk of cardiac arrhythmias (QT prolongation). In such circumstances an ECG should be performed and

electrolytes checked prior to treatment<sup>52</sup>. There is no evidence that oral administration of ondansetron causes QT prolongation in adults<sup>59</sup>.

**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(s), preferably after 10 weeks gestation and during an inpatient admission. This arises from concerns regarding a small increase in oral clefts in fetuses exposed to corticosteroids in utero in pooled data from observational studies<sup>53</sup>. More evidence is needed comparing corticosteroids to other medications.

### **Comparison with previous literature**

The American College of Obstetricians and Gynaecologists published clinical management guidelines in August 2015<sup>2</sup>, recommending the use of vitamin B6 or Vitamin B6 plus doxylamine as first line pharmacotherapy, ginger as a non-pharmacological 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 is 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<sup>54 55</sup>. Matthews et al<sup>54</sup> only focused on nausea and vomiting and randomized clinical trial's, excluded trials involving hyperemesis gravidarum, Boelig et al<sup>55</sup> only included randomized clinical trial's of hyperemesis gravidarum. Neither review categorized therapies depending on symptom

severity. However, both reviews are 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, a 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 (PROSPERO CRD42013006642).

One set of outcome measures that is likely to be very 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 side effects of the interventions recommended by this review are provided in Table 4 along with common dosage regimes. Available observational data (pregnancy-related but not specifically focused on nausea and vomiting) does not provide evidence of any safety concerns with anti-emetic medications, this is not the same as ruling out any important differences in adverse outcomes.

## **CONCLUSION**

For mild symptoms, ginger, pyridoxine, antihistamines and metoclopramide are associated with greater benefit than placebo. For moderate symptoms, pyridoxine-doxylamine, promethazine and metoclopramide are associated with greater benefit than placebo. Ondansetron is associated with symptom improvement at all severity levels and corticosteroids may be beneficial in severe cases. The quality of evidence for other interventions is low.

## ARTICLE INFORMATION

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**Author Contributions:** Professor Vale, Dr McParlin and Dr O'Donnell had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design: All authors.*

*Acquisition, analysis, or interpretation of data: All authors.*

*Drafting of the manuscript: McParlin and O'Donnell took the role as co-first authors and initial drafting of the manuscript.*

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**Table 1: Tools used to measure the severity of nausea and vomiting in pregnancy**

<b>Tool</b>	<b>Description</b>	<b>Scoring</b>	<b>Maximum score</b>	<b>Cut point for severe symptoms</b>
<b>Pregnancy Unique Quantification of Emesis and Nausea (PUQE and PUQE 24 score )</b> <sup>56-58</sup>	Three questions regarding nausea, vomiting and retching during previous 12 hours (original version), or 24 hours (most commonly used version).	For each question: 0 = no symptoms; 5 = worst possible symptoms.	15	Scores $\geq 13$ indicate severe symptoms
<b>The Rhodes Index of Nausea, Vomiting and Retching (RINVR)</b> <sup>59-61</sup>	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 $\geq 33$ indicated severe symptoms
<b>Nausea and vomiting of pregnancy Instrument (NVPI)</b> <sup>62,63</sup>	Three questions relating to nausea, retching and vomiting over the past 7 days.	For each component: 0 = no symptoms, 5 = worst possible symptoms.	15	Score $\geq 8$ indicates severe symptoms
<b>Visual analogue scale (VAS)</b>	Patients rate their symptoms on a scale of 0-10.	Visual analogue scale: 0 = no symptoms; 10 = extreme symptoms.	10	Not applicable

**Table 2a: 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**

Study details			Participants and treatments			Outcome measures and results		
Author, year (country)	Study Design	Baseline symptom severity <sup>1</sup>	Number of participants	Gestation in weeks Mean (range)	Dosage and duration	Primary Outcome Measures	Results	p value
<b>FIRST-LINE INTERVENTIONS</b>								
<b>Ginger versus placebo (4 Randomized Clinical Trials )</b>								
Fischer-Rasmussen et al., 1990 <sup>17</sup> (Denmark)	Double blind randomized crossover trial	Mild-moderate	Intervention=15	11 (7-17)	Ginger capsules (250mg powdered root ginger, 4 x daily for 4 days then 2 day washout)	Nausea severity change score	Intervention = 13.7 1 <sup>st</sup> 5 days 8.2 2 <sup>nd</sup> 5 days. Comparator = 13.3 1 <sup>st</sup> 5 days 8.9 2 <sup>nd</sup> 5 days.	p=not significantly different
			Comparator=15	10.8 (7-16)	Placebo capsules (250mg lactose, 4 x daily for 4 days then 2 day washout).	Nausea and vomiting relief change score	Intervention = 4.1 1 <sup>st</sup> 5 days and 3.7 2 <sup>nd</sup> 5 days Comparator = -0.1 1 <sup>st</sup> 5 days and 0.9 2 <sup>nd</sup> 5 days	p=0.035
Vutyavanch et al., 2001 <sup>18</sup> (Thailand)	Double blind Randomized Clinical Trial	Mild	Intervention=32	10.4 (2.3)	Ginger capsules (250mg ginger 3 times daily following meals and another before bed for 4 days)	Decrease in Visual Analogue Scale for nausea	Intervention = 2.1(1.9) Comparator = 0.9(2.2)	p=0.014.

<sup>1</sup> 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.

Study details			Participants and treatments			Outcome measures and results		
Author, year (country)	Study Design	Baseline symptom severity <sup>1</sup>	Number of participants	Gestation in weeks Mean (range)	Dosage and duration	Primary Outcome Measures	Results	p value
			Comparator=38	10.3 (2.6)	Placebo capsules (3 times daily following meals and another before bed for 4 days).	Decrease in episodes of vomiting	Intervention = 1.4(1.3) Comparator = 0.(±1.1)	p <0.001
Keating & Chez, 2002 <sup>19</sup> (USA)	Double blind Rando mized Clinical Trial	Mild	Intervention=14  Comparator=12	Range 7-11	I250mg ginger + honey and water, 4 x daily for 2 weeks)  Placebo syrup of water, honey and lemon oil, 4 x daily for 2 weeks).	Visual Analogue Scale for nausea by day 9  Vomiting stopped by day 6	Intervention=10 women ≥ 4-point improvement Comparator = 2 women ≥ 4-point improvement  Intervention=8 women Comparator=2 women	Not reported
Basirat et al., 2009 <sup>16</sup> (Iran)	Double blind Rando mized Clinical Trial	Mild	Intervention=35  Comparator=35	Range 7-17	Ginger biscuits (0.5mg ginger, 5 x daily for 4 days)  Non-ginger biscuits (5 x daily for 4 days).	Visual Analogue Scale for nausea  Episodes of vomiting	Average change: Intervention =2.57(1.77) Comparator =1.39(1.62) Average change: Intervention = 0.96(0.2) Comparator = 0.62(0.19)	p=0.01  p=0.243
<b>Ginger versus vitamin B6 (4 Randomized Clinical Trials )</b>								
Sripamote & Lekhyana	Double blind Rando mized	Mild-moderate	Intervention=68	10.1 (2.74)	Ginger capsules (500mg, 3 x daily for 3 days)	Mean change in Visual Analogue Scale	Intervention = 5.0(1.99) to 3.6(2.48) Comparator = 5.3(2.08) to 3.3(2.07)	p<0.001

Study details			Participants and treatments			Outcome measures and results		
Author, year (country)	Study Design	Baseline symptom severity <sup>1</sup>	Number of participants	Gestation in weeks Mean (range)	Dosage and duration	Primary Outcome Measures	Results	p value
nda, 2003 <sup>23</sup> (Thailand)	Clinical Trial		Comparator=70	10.3(2.95)	Vitamin B6 capsules (10mg, 3 x daily for 3 days).	Episodes of vomiting	Intervention = 1.9(2.06) to 1.2(1.75) Comparator = 1.7(1.81) to 1.2(1.50)	p<0.01
Smith et al., 2004 <sup>22</sup> (Australia)	Rando mized, controll ed equivalent trial.	Mild-moderate	Intervention=146	Median (IQR) 8.5 (8-15)	Ginger capsules (350mg, 3 x daily for 3 weeks)	Mean difference (Confidence Intervals) in Rhodes Index score: Nausea	0.2, (90% CI -0.3, 0.8)	p values not reported
			Comparator=145	8.6 (8-15)	Vitamin B6 capsules (25mg, 3 x daily for 3 weeks).	Vomiting	0.3 (90% CI -0.0, 0.6)	
Chittumma et al., 2007 <sup>20</sup> (Thailand)	Double blind Rando mized Clinical Trial	Mild	Intervention=63	12 (2)	Ginger capsules (2x 325mg 4 times daily for 4 days)	Mean change in combined Rhodes Index score	Intervention = 3.3(1.5) Comparator = 2.6(1.3)	p < 0.05
			Comparator=63	11 (2)	Vitamin B6 capsules (2x 12.5mg 4 times daily for 4 days).			
Ensiyeh & Sakineh, 2009 <sup>21</sup> (Iran)	Double blind Rando mized Clinical Trial	Mild	Intervention=35	Not reported	Ginger capsules (500mg 2 x daily for 4 days)	Mean change in VAS	Intervention = 2.2(1.9) Comparator = 0.9(1.7)	p=0.024
			Comparator=35		Vitamin B6 capsules (20mg 2 x daily for 4 days).	Episodes of vomiting	Intervention = 0.6(0.7) Comparator = 0.5(1.1)	p=1.101 <sup>2</sup>

<sup>2</sup> P value as reported in paper.

Study details			Participants and treatments			Outcome measures and results		
Author, year (country)	Study Design	Baseline symptom severity <sup>1</sup>	Number of participants	Gestation in weeks Mean (range)	Dosage and duration	Primary Outcome Measures	Results	p value
<b>Ginger versus acupressure (1 Randomized Clinical Trial)</b>								
Saberi et al., 2013 <sup>25</sup> (Iran)	Three-group Rando mized Clinical Trial	Mild-moderate	Intervention=53  Comparator=53  Control=53	8.78(2.32)  9.32( 2.38)  9.11(0.18)	Ginger capsules (250mg, 3 x daily for 4 days)  Acupressure (sea bands worn continuously for 4 days)  No intervention.	Mean difference in combined Rhodes Index score	Intervention = 8.61(5.24) Comparator = 4.17(5.53) Control = 0.84(3.72)	p<0.001
<b>Ginger versus vitamin B6 / doxylamine combination (1 Randomized Clinical Trial)</b>								
Biswas et al., 2011 <sup>24</sup> (India)	Single blind Rando mized Clinical Trial	Mild	Intervention=42  Comparator=36	10.25(2.8)  9.3(3.1)	Ginger tablets (150mg, 3 x daily for one week)  Doxylamine 10mg plus pyridoxine 10mg, (3 x daily for one week).	Median Visual Analogue Scale for nausea  Mean Visual Analogue Scale for vomiting	Intervention = 3 to 0.43 Comparator = 4 to 0.6  Intervention = 1 to 0.14 Comparator = 2 to 0	p value not reported
<b>Acupressure versus placebo (3 Randomized Clinical Trials )</b>								
Bayreuther et al., 1994 <sup>26</sup> (UK)	Rando mized Clinical Trial	Mild	Intervention=11  Comparator=12	≤16	Sea-bands at P6 point (7 consecutive days then 2 days no treatment)  Sea-bands at placebo position (7 consecutive days	Treatment difference in mean Visual Analogue Scale	Paired t-test=1.69 Two sample t-test=1.67 Wilcoxon=1.65 Mann Whitney U=1.61	p not reported

Study details			Participants and treatments			Outcome measures and results		
Author, year (country)	Study Design	Baseline symptom severity <sup>1</sup>	Number of participants	Gestation in weeks Mean (range)	Dosage and duration	Primary Outcome Measures	Results	p value
					followed by 2 days no treatment).			
Belluomini et al., 1994 <sup>27</sup> (USA)	Rando mized Clinical Trial	Mild	Intervention=30	8.5(1.4)	3 days no treatment then self-administered acupressure (10 minutes, 4 x daily for 7 days at point PC-6)	Change in Rhodes index for: Nausea	Intervention = 5.80(2.9) Comparator = 7.04(2.6)	p≤ 0.001 p≤ 0.001
			Comparator=30	8.6(1.4)	3 days no treatment followed by self-administered acupressure (10 minutes, 4 x daily for 7 days at placebo point).	Vomiting  Combined	Intervention = 1.28(1.9) Comparator= 1.63(2.3)  Intervention = 8.69(5.0) Comparator = 10.03(4.6)	p=0.03 p=not reported  p≤0.001 p=0.019
Naeimi Rad et al., 2012 <sup>28</sup> (Iran)	Rando mized Clinical Trial	Mild-moderate	Intervention=40	9.55(1.81)	Acupressure to KID21 points (20 minutes daily for 4 days + during nausea and vomiting episodes)	Median Visual Analogue Scale (IQR) at day 4 day for: Intensity of nausea	Intervention = 4(5-2) Comparator =7 (8-5)	p<0.001
			Comparator=40	9.45(2.02)	Acupressure to a false point (20 minutes daily for 4 days+ during	Frequency of nausea	Intervention = 0(0.75-0) Comparator = 1(2-0)	p<0.001

Study details			Participants and treatments			Outcome measures and results		
Author, year (country)	Study Design	Baseline symptom severity <sup>1</sup>	Number of participants	Gestation in weeks Mean (range)	Dosage and duration	Primary Outcome Measures	Results	p value
					nausea and vomiting episodes).			
<b>Acupressure versus vitamin B6 (1 Randomized Clinical Trial)</b>								
Jamigorn & Phupong, 2007 <sup>30</sup> (Thailand)	Randomized Clinical Trial	Mild-moderate	Intervention=33  Comparator=33	6.2(1.0)  6.8(1.5)	Acupressure wristbands (Sea-Bands at P6 point worn days 1-5) plus placebo tablet  Dummy Sea-Bands plus 50 mg tablets of vitamin B6 every 12 h for 5 days.	Difference in combined Rhodes Index score	No difference	p>0.05
<b>Nerve stimulation versus placebo (1 Randomized Clinical Trial)</b>								
Rosen et al., 2003 <sup>29</sup> (USA)	Multiple Randomized Clinical Trial	Mild-moderate	Intervention =117  Comparator =113	9.2(1.7)  9.0(1.7)	Nerve stimulation (for 3 weeks via a Relief Band Model)  Identical non-stimulating device (for 3 weeks).	Mean change (Confidence Intervals) in combined Rhodes Index Score	Intervention=6.48 (95% CI 5.31, 7.66) Comparator=4.65 (95% CI 3.67, 5.63)	p=0.02
<b>Acupuncture versus placebo (3 Randomized Clinical Trials )</b>								

Study details			Participants and treatments			Outcome measures and results		
Author, year (country)	Study Design	Baseline symptom severity <sup>1</sup>	Number of participants	Gestation in weeks Mean (range)	Dosage and duration	Primary Outcome Measures	Results	p value
Carlsson et al., 2000 <sup>32</sup> (Sweden)	Randomized Crossover Study	Moderate-severe	Intervention=17  Comparator=16	9.9 (6-16)	Acupuncture at point PC6 on days 1 & 2 (for 30 minutes, 3 times daily), no acupuncture on days 3 & 4 (wash-out-period) and sham acupuncture on days 5 & 6  Sham acupuncture on days 1 & 2, no acupuncture on days 3 & 4 (wash-out-period) and active acupuncture at point PC6 on days 5 & 6 (for 30 minutes, 3 times daily).	Reduction in Visual Analogue Scale score for nausea  Incidence of vomiting after 2 days of acupuncture	Between pre- and post- active acupuncture: Intervention=4 v Comparator=3; Between pre- and post- placebo acupuncture: Intervention=0.1 v Comparator=1.7  Intervention = 7 out of 17 Comparator = 12 out of 16 women	p value not reported).

Study details			Participants and treatments			Outcome measures and results		
Author, year (country)	Study Design	Baseline symptom severity <sup>1</sup>	Number of participants	Gestation in weeks Mean (range)	Dosage and duration	Primary Outcome Measures	Results	p value
Knight et al., 2001 <sup>33</sup> (UK)	Randomized Clinical Trial	Mild-moderate	Intervention=28  Comparator=27	7.8(1.0)  8.0(1.0)	Participants allocated to a traditional Chinese medicine diagnosis and treated with acupuncture to a range of points, twice in the first week and once weekly for two weeks)  Sham treatment (tapping a blunt cocktail stick, supported by a plastic guide tube in the region of each acupuncture point, twice in week one and once weekly for 2 weeks).	Median (IQR) Visual Analogue Scale score	Intervention: Day 1=85.5 (71.25-89.75); 3 days after session 1=63.0 (50.75-86.5); 3 days after session 2=65.0 (36.25-79.5); 3 days after session 3=44.0 (29.0-77.25); 3 days after session 4 =47.5 (29.25-69.5)  Comparator: Day 1=87.0 (73.0 –90.0); 3 days after session 1=69.0 (45.0–87.0); 3 days after session 2=61.0 (30.0–80.0); 3 days after session 3=53.0 (25.0–80.0); 3 days after session 4 =48.0 (14.0–80.0)	p value not reported

Study details			Participants and treatments			Outcome measures and results		
Author, year (country)	Study Design	Baseline symptom severity <sup>1</sup>	Number of participants	Gestation in weeks Mean (range)	Dosage and duration	Primary Outcome Measures	Results	p value
Smith et al., 2002 <sup>31</sup> (Australia)	Randomized Clinical Trial	Mild-moderate	I=148	Median: (IQR)8.3 (5-13)	Serin (Japan) 0.2 x 30 mm needles inserted at range of points (to 0.5-1 cm with maximum of 6 needles per session, then manipulated and left for a 20-minutes)	Rhodes index for: Nausea	Day 7: i Interventions = 5.0(3.0) Comparator = 5.4(3.3) Sham = 5.7(2.8) Control = 6.1(2.9)	=0.05
			Comparator =148	8.3 (4-14)	Acupuncture to p6 single point only (for a 20-minute period, twice in week 1 then weekly for 3 weeks)	Retching	Day 7: I = 1.3(1.4) v C = 1.6(1.7) v Sham = 1.5(1.8) v Control = 1.7(1.7)	p>0.05
			Sham=148	8.0 (4-13)	Sham acupuncture (over similar time period)	Vomiting	Day 7: Intervention = 1.4(2.0) Comparator = 1.2(2.0) Sham = 1.5 (2.2) Control = 1.5 (2.1)	p >0.05

Study details			Participants and treatments			Outcome measures and results		
Author, year (country)	Study Design	Baseline symptom severity <sup>1</sup>	Number of participants	Gestation in weeks Mean (range)	Dosage and duration	Primary Outcome Measures	Results	p value
			Control=149.	8.4 (5-14)	Standardized information sheet with diet, lifestyle, and use of vitamin B6 advice plus telephone support.			
<b>Vitamin B6 versus placebo (1 Randomized Clinical Trial)</b>								
Vutyavani ch et al., 1995 <sup>64</sup> (Thailand)	Double blind Rando mized Clinical Trial	Mild-moderate	Intervention =173	10.9(2.7)	Vitamin B6 tablets (10 mg of pyridoxine hydrochloride 8 hourly for 5 days)	Mean change in Visual Analogue Scale for nausea	Intervention=2.9(2.2) Comparator=2.0(2.7)	p<0.001
			Comparator=169	10.9 (2.8)	Placebo tablets (8 hourly for 5 days).	Mean change in episodes of vomiting	Intervention=1.22(2.0) Comparator=0.65(2.4) (p=0.055).	p=0.055
<b>High versus low dose Vitamin B6 versus (1 Randomized Clinical Trial)</b>								
Wibowo et al., 2012 <sup>35</sup> (Indonesia )	Rando mized Clinical Trial	Mild	I=30	Less than 12	Pyridoxine (5 mg mixed with 40 g of powdered milk 2 x daily for 2 weeks)	Pregnancy Unique Quantification of Emesis and nausea score	Intervention =3.86(2.12) Comparator =2.80(1.78)	p<0.05
			Comparator=30		Pyridoxine (0.64 mg mixed with 40 g of powdered milk twice daily for 2 weeks).			

**Table 2b: 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**

Study details			Participants and treatments			Outcome measures and results		
Author, year (country)	Study Design	Baseline symptom severity <sup>1</sup>	Number of participants	Gestation in weeks Mean (range)	Dosage and duration	Primary Outcome Measures	Results	p value
<b>SECOND-LINE INTERVENTIONS</b>								
<b>Pyridoxine / doxylamine versus placebo (2 Randomized Clinical Trials )</b>								
Koren et al., 2010 <sup>36</sup> (USA)	Double blind Randomized Clinical Trial	Moderate	Intervention =140	9.3(2.0)	Pyridoxine+ doxylamine (Diclectin) (2 tablets daily up to 4 as needed)	Mean change in Pregnancy Unique Quantification of Emesis and nausea score	Intervention =4.8(2.7) Comparator =3.9(2.6)	p= 0.006
			Comparator =140	9.3(1.8)	Placebo tablets (2 tablets daily up to 4 as needed).	Mean area under the curve of change in Pregnancy Unique Quantification of Emesis and nausea score	Intervention =61.5(36.9) Comparator =53.5(37.5)	p<.0001
Maltepe & Koren, 2013 <sup>38*</sup> (Canada)	Randomized Clinical Trial	Not applicable	Intervention=31	Not reported	Pyridoxine+ doxylamine (Diclectin) (2 tablets daily) following pregnancy confirmation (gradual increase if symptoms escalate)	Reduction in hyperemesis gravidarum between pregnancies	Intervention =43.3% Comparator =17.2%	p=0.047

Study details			Participants and treatments			Outcome measures and results		
Author, year (country)	Study Design	Baseline symptom severity <sup>1</sup>	Number of participants	Gestation in weeks Mean (range)	Dosage and duration	Primary Outcome Measures	Results	p value
			Comparator=29		Pyridoxine+ doxylamine (Diclectin) (2 tablets daily) once symptomatic (with gradual increase if symptoms escalate).	Pregnancy Unique Quantification of Emesis and nausea score $\geq 11$	Intervention =15.4% Comparator = 39.1%	p<0.04
<b>Serotonin antagonist (ondansetron) versus pyridoxine / doxylamine (1 Randomized Clinical Trial)</b>								
Oliveira et al., 2014 <sup>37</sup> (USA)	Double blind Randomized Clinical Trial	Moderate	Intervention=13	Median gestation (IQR): 8 (7.1-8.9)	Ondansetron (one tablet 4 mg) + one placebo tablet (every 8 hours for 5 days)	Median reduction in Visual Analogue Scale for nausea	Intervention = 51(IQR 37-64) Comparator = 20(IQR 8-51)	p=0.019
			Comparator=17	Median gestation (IQR): 8.1 (7.2-9.9)	Pyridoxine (one tablet 25 mg) + one tablet doxylamine (12.5 mg every 8 hours for 5 days).	Median reduction in Visual Analogue Scale for vomiting	Intervention =41(IQR 17-57) Comparator =17(IQR -4-38)	p=0.049
<b>Psychotherapy v usual treatment (1 Randomized Clinical Trial)</b>								
Faramarzi et al, 2015 <sup>40</sup> (Iran)	Randomized Clinical Trial	Moderate;	Intervention=43	Less than 12	8 x 50 minute psychotherapy sessions over 3 weeks + 40mg vitamin B6	Mean change in Rhodes Index Score combined	Intervention = 18.76(5.48) to 7.06(5.79) Comparator = 19.18(5.63) to 12.81(6.88)	p<0.001
			Comparator=43		40mg vitamin B6 over 3 weeks			
<b>Antihistamines versus placebo (1 Randomized Clinical Trial)</b>								

Study details			Participants and treatments			Outcome measures and results		
Author, year (country)	Study Design	Baseline symptom severity <sup>1</sup>	Number of participants	Gestation in weeks Mean (range)	Dosage and duration	Primary Outcome Measures	Results	p value
Erez et al., 1971 <sup>39</sup> (Turkey)	Randomized Clinical Trial	Mild	Intervention=100  Comparator=50	Less than 12	Hydroxyzine hydrochloride capsules (25mg 2 x daily for 3 weeks)  Placebo capsules (2 x daily for 3 weeks).	Partial or complete relief of symptoms	Intervention = 82% of patients Comparator = 22% patients	p<0.01
<b>Dopamine antagonists – promethazine versus metoclopramide (1 Randomized Clinical Trial)</b>								
Tan et al., 2010 <sup>41</sup> (Malaysia)	Double blind Rando mized Clinical Trial	Moderate	Intervention=79	9.2(2.3)	Metoclopramide (10 mg IV after randomization and at 8, 16 and 24 hours)	Episodes of vomiting 1.	Intervention =1 (0–5) Comparator =2 (0–3)	p=0.81
			Comparator=80	9.3(2.6)	Promethazine (25 mg IV after randomization and at 8, 16 and 24 hours).	Visual Analogue Scale for nausea at 24 hours	Intervention=2 (1–5) Comparator=2 (1–4)	p=0.99
<b>Serotonin antagonist (ondansetron) versus metoclopramide (2 Randomized Clinical Trials )</b>								
Kashifard et al., 2013 <sup>43</sup> (Iran)	Double blind Rando mized Clinical Trial	Mild-moderate	Intervention=49	8.7(2.6)	Ondansetron hydrochloride tablets (4 mg 3 x daily for 1 week. Dose gradually reduced and discontinued after 2 <sup>nd</sup> week)	Mean Visual Analogue Scale 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)	p=0.024  p=0.023

			Comparator=34	8.7(2.6)	Metoclopramide (10mg 3 times daily for 1 week. Dose gradually reduced and discontinued after 2 <sup>nd</sup> week)	Episodes of vomiting	<b>Day 3:</b> Intervention = 5.3(3) Comparator = 3.2(3.4) <b>Day 4:</b> Intervention = 5 (3.1) Comparator = 3.3(3)	p =0.006 p = 0.013
Abas et al., 2014 <sup>42</sup> (Malaysia)	Double blind Randomized Clinical Trial	Severe	Intervention=80  Comparator=80	Less than or equal to 16	Ondansetron (4 mg diluted in 100 ml normal saline)  Metoclopramide (10 mg diluted in 100 ml normal saline).	VAS for nausea (median (IQR)) Episodes of vomiting  Episodes of vomiting	At 8 hours: Intervention = 4 (3-6) Comparator = 5 (4-6); 16hours: Intervention = 3 (1-4) Comparator = 3(2-4.75) 24hours: Intervention = 1(1-3) Comparator = 2(1-3) <b>In first 24 hours:</b> Intervention=1 (0-2) Comparator=2 (0-2.75)	Repeated measures analysis of variance p=0.22  p=0.38
<b>IV fluids D-saline versus N-saline (1 Randomized Clinical Trial)</b>								
Tan et al., 2013 <sup>44</sup> (Malaysia)	Double blind Rando mized Clinical Trial	Moderate-severe	<b>Intervention =111</b>	<b>9.8(2.8)</b>	<b>5% dextrose–0.9% saline by IV infusion (125 mL/h over 24 hours)</b>	<b>Median vomiting episodes</b>	<b>Both groups=0 (0-2)</b>	<b>p=0.66</b>

			Comparator =111	9.8(2.5)	0.9% saline by IV infusion (125 mL/h over 24 hours). Both groups also given potassium chloride (9.5 mmol) as required plus multivitamin (containing 250 mg thiamine given IV).	Nausea score (0- 10) at 24 hrs	Intervention=2 (1-4) Comparator=2 (2-4)  Repeated measures analysis of variance of nausea score	p=0.39  p=0.046 in favour of intervention group
<b>Day-case / outpatient (2 Randomized Clinical Trials )</b>								
<b>McCarthy et al., 2014<sup>46</sup> (Ireland)</b>	<b>Rando mized Clinical Trial</b>	<b>Mild- moderate</b>	<b>Intervention=42</b>	<b>Median (IQR): 8 (7-10)</b>	<b>Treatment in day care unit (weekdays, 08:00- 16:00). Two litres normal saline given IV over 5 h. Antiemetics as required</b>	<b>Hospital stay (median IQR)</b>	<b>Intervention = 0(0-2) Comparator = 2(1-4)</b>	<b>p&lt;0.001</b>
			Comparator=56	Median (IQR): 8 (7-11)	Usual inpatient treatment (1 L normal saline IV over 3 h, then 1 L every 6h. Antiemetics as required).			
<b>McParlin et al., 2016<sup>45</sup> (UK)</b>	<b>Random ized Clinical Trial</b>	<b>Moderate- severe</b>	<b>Intervention=27</b>	<b>9.3(2.8)</b>	<b>Cyclizine (50 mg IV followed by 3 L Hartman's solution over 6 hours + 50 mg of oral thiamine, discharged home with prescription for oral cyclizine (50 mg 3 times daily) + plus ongoing support and advice</b>	<b>Change in Pregnancy Uniques Quantification of Emesis and nausea score</b>	<b>Intervention= 6.9(4.1) Comparator=6.2(2.3)</b>	<b>p&gt;0.05</b>

			Comparator=26	10.3(2.9)	Admission to antenatal ward for routine care, IV fluids, IV cyclizine and oral thiamine.			
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**Table 2c: 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**

Study details			Participants and treatments			Outcome measures and results		
Author, year (country)	Study Design	Baseline symptom severity <sup>3</sup>	Number of participants	Gestation in weeks Mean (range)	Dosage and duration	Primary Outcome Measures	Results	p value
<b>THIRD-LINE INTERVENTIONS</b>								
<b>Corticosteroids versus placebo (1 Randomized Clinical Trial)</b>								
Nelson-Piercy et al., 2001 <sup>47</sup> (UK)	Randomized, double blind, placebo - controlled trial	Moderate-severe	Intervention=12	0.6(2.1)	One week course of prednisolone tablets (20 mg 12 hourly) Both groups: if symptomatic after 72 hours, therapy was changed to IV equivalent.	Episodes of vomiting median (range)  Vomiting > 5 times /day at one week	Number participants: Intervention=5, Comparator=7, Relative risk (95% CI) =1.4 (0.6-3.2)  Intervention=2, Comparator=5,	p not reported

<sup>3</sup> 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=13	8.3(1.9)	One-week course of placebo tablets (20 mg 12 hourly. Both groups: if symptomatic after 72 hours, therapy was changed to IV equivalent.	Visual Analogue Scale for vomiting median (range)  Visual Analogue Scale for nausea median (range)	Relative risk (95% CI) =2.5 (0.6-10.5).  Intervention = 2.0 (-1.0-4.0), Comparator = 1.5 (-3.0- 4.0)  Intervention =6.5 (2.0-10.0), Comparator=4.0 (-5.0- 9.0), Relative risk 0.10 for proportion with nausea	
<b>Corticosteroids versus Phenothiazines / promethazine / Phenergan (1 RCT)</b>								
<b>Safari et al., 1998<sup>48</sup> (USA)</b>	<b>Rando mized Clinical Trial</b>	<b>Moderate -severe</b>	Intervention=20	9.8(2.1)	<b>Methylprednisolone (16 mg orally 3 x daily for 3 days, followed by a tapering regimen, halving of dose every 3 days, to none during the course of 2 weeks)</b>	<b>Improvement of symptoms or therapy failure within 2 days of starting therapy.</b>	Intervention = <b>therapy failure in 3 patients</b> Comparator = <b>therapy failure in 2 patients</b>	<b>p not reported</b>
			Comparator=20	9.5(2.7)	Promethazine (25 mg orally 3 times daily for 2 weeks).	Readmitted to hospital	Intervention = 0 patients Comparator = 5 patients	p=0.0001
<b>Corticosteroids versus metoclopramide (1 Randomized Clinical Trial)</b>								



**Table 3: Grade of evidence and recommendation**

Treatment <sup>1</sup>	Number of Studies <sup>2</sup>	Risk of bias / quality	AHA Rating
<b>First-line treatments for mild-moderate nausea and vomiting in pregnancy</b>			
Ginger	<ul style="list-style-type: none"> <li>17 Randomized clinical trials</li> </ul>	<ul style="list-style-type: none"> <li>10 = low<sup>17-25</sup>;</li> <li>3 = unclear<sup>65-67</sup>;</li> <li>4 = high<sup>68-71</sup></li> </ul>	Level A Class IIa
Acupressure	<ul style="list-style-type: none"> <li>10 Randomized clinical trials</li> <li>1 case series</li> </ul>	<ul style="list-style-type: none"> <li>5 = low<sup>25-28,30</sup>;</li> <li>4 = unclear<sup>72-75</sup>;</li> <li>1 = high<sup>76</sup></li> <li>1 = weak<sup>77</sup></li> </ul>	Level A Class IIa
Nerve Stimulation	<ul style="list-style-type: none"> <li>3 Randomized clinical trials</li> </ul>	<ul style="list-style-type: none"> <li>1 = low<sup>29</sup>;</li> <li>2 = unclear<sup>78,79</sup></li> </ul>	Level B Class IIb
Acupuncture	<ul style="list-style-type: none"> <li>6 Randomized clinical trials</li> </ul>	<ul style="list-style-type: none"> <li>3 = low<sup>31-33</sup>;</li> <li>3 = high<sup>80-82</sup></li> </ul>	Level A Class IIb
Aromatherapy	<ul style="list-style-type: none"> <li>2 Randomized clinical trials</li> </ul>	<ul style="list-style-type: none"> <li>2 = unclear<sup>83,84</sup></li> </ul>	Level B Class IIb
Vitamin B6 (pyridoxine)	<ul style="list-style-type: none"> <li>14 Randomized clinical trials</li> </ul>	<ul style="list-style-type: none"> <li>7 = low<sup>20-23,30,34,35</sup>;</li> <li>4 = unclear<sup>66,85-87</sup>;</li> <li>3 = high<sup>69,70,88</sup></li> </ul>	Level A Class IIa
<b>Second-line treatments for moderate-severe nausea and vomiting in pregnancy or hyperemesis gravidarum</b>			
Psychotherapy	<ul style="list-style-type: none"> <li>1 Randomized clinical trial</li> </ul>	<ul style="list-style-type: none"> <li>1 = low<sup>40</sup></li> </ul>	Level B Class IIa
Vitamin B6 (pyridoxine) / doxylamine combination	<ul style="list-style-type: none"> <li>5 Randomized clinical trials</li> <li>1 case-control study</li> <li>1 cohort-analytic</li> </ul>	<ul style="list-style-type: none"> <li>4 = low<sup>24,36-38</sup>;</li> <li>1 = unclear<sup>89</sup></li> <li>1 = weak<sup>90</sup></li> <li>1 = moderate<sup>91</sup></li> </ul>	Level A Class IIa
Antihistamines	<ul style="list-style-type: none"> <li>7 Randomized clinical trials</li> </ul>	<ul style="list-style-type: none"> <li>1 = low<sup>39</sup>;</li> <li>4 = unclear<sup>67,87,92,93</sup>;</li> <li>2 = high<sup>88,94</sup></li> </ul>	Level B Class IIa
Dopamine antagonists	<ul style="list-style-type: none"> <li>10 Randomized clinical trials</li> <li>1 case-control study</li> <li>1 cohort study</li> </ul>	<ul style="list-style-type: none"> <li>5 = low<sup>41-43,48,49</sup>;</li> <li>3 = unclear<sup>95-97</sup>;</li> <li>2 = high<sup>71,80</sup></li> <li>1 = weak<sup>90</sup></li> <li>1 = weak<sup>98</sup></li> </ul>	Level A Class IIa
Serotonin antagonists	<ul style="list-style-type: none"> <li>7 Randomized clinical trials</li> <li>1 cohort analytic study</li> </ul>	<ul style="list-style-type: none"> <li>3 = low<sup>37,42,43</sup>;</li> <li>4 = unclear<sup>89,92,93,95</sup></li> <li>1 = weak<sup>99</sup></li> </ul>	Level A Class IIa
Intravenous fluids	<ul style="list-style-type: none"> <li>1 Randomized clinical trial</li> </ul>	<ul style="list-style-type: none"> <li>1 = low<sup>44</sup></li> </ul>	Level B Class IIa
Intravenous fluids with or without Diazepam	<ul style="list-style-type: none"> <li>1 Randomized clinical trial</li> </ul>	<ul style="list-style-type: none"> <li>1 = unclear<sup>100</sup></li> </ul>	Level B Class III

<sup>1</sup> 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).

<sup>2</sup> Number of studies includes all those with an appropriate treatment group (either intervention or comparator).

Out-patient / day-case management	<ul style="list-style-type: none"> <li>• 2 Randomized clinical trials 1 case series study</li> </ul>	<ul style="list-style-type: none"> <li>• 2 = low<sup>45,46</sup></li> <li>• 1 = weak<sup>101</sup></li> </ul>	Level A Class IIa
<b>Third-line treatments for moderate-severe nausea and vomiting in pregnancy or hyperemesis gravidarum</b>			
Corticosteroids	<ul style="list-style-type: none"> <li>• 6 Randomized clinical trials</li> <li>• 1 case series</li> </ul>	<ul style="list-style-type: none"> <li>• 3 = low<sup>47-49</sup>;</li> <li>• 2 = unclear<sup>96,97</sup>;</li> <li>• 1 = high<sup>102</sup></li> <li>• 1 = weak<sup>103</sup></li> </ul>	Level A Class IIb
Nasogastric / assisted feeding	<ul style="list-style-type: none"> <li>• 2 case series</li> <li>• 1 cohort analytic</li> </ul>	<ul style="list-style-type: none"> <li>• 2 = weak<sup>104,105</sup></li> <li>• 1 = moderate<sup>106</sup></li> </ul>	Level C Class IIb
Gabapentin	<ul style="list-style-type: none"> <li>• 1 case series</li> </ul>	<ul style="list-style-type: none"> <li>• 1 = weak<sup>107</sup></li> </ul>	Level C Class III
Transdermal clonidine	<ul style="list-style-type: none"> <li>• 1 Randomized clinical trial</li> </ul>	<ul style="list-style-type: none"> <li>• 1 = low<sup>50</sup></li> </ul>	Level B Class IIb

**Table 1: Dose, common side effects and contra-indications of recommended therapies by severity of NVP and HG<sup>3</sup>**

Therapy	Dose	Side effects	Contra-indications
<b>Severity of symptoms: MILD</b>			
Ginger	Most common regime: 250mg every 6 hours	Acid reflux	None apparent
Vitamin B6 (pyridoxine)	10-25mg every 8 hours	Drowsiness; decreased sensation to touch, temperature, and vibration; loss of balance or coordination.	
Antihistamines e.g. Cyclizine	50mg every 8 hours	Drowsiness; dizziness; muscle twitches; dry mouth; headache; skin rash; tachycardia.	Glaucoma, high or low blood pressure, epilepsy,
<b>Severity of symptoms: MODERATE</b>			
Antihistamine/ vitamin B6 combination (doxylamine/ pyridoxine)	10mg doxylamine + 10mg pyridoxine up to 4 times daily if needed	Drowsiness; somnolence; dizziness; nervousness; stomach pain; headache; diarrhoea; irritability; insomnia.	Taking monoamine oxidase inhibitors, antimuscarinic drugs
Metoclopramide	10mg every 8 hours	Dystonic movements; oculogyric crises; diarrhoea; drowsiness; restlessness; irritability; dry mouth; insomnia; urinary problems; depression; skin rash.	Kidney or liver disease, congestive heart failure, high blood pressure, diabetes, history of depression, epilepsy (or other seizure disorder)
Promethazine	25mg every 8 hours	Dizziness; drowsiness; excitation; skin 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 who are using concomitant medications, such as narcotics or local anaesthetics, which may also affect seizure threshold.
Ondansetron	4mg every 8 hours	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.
<b>Severity of symptoms: SEVERE</b>			
Ondansetron	4-8 mg every 8 hours	As above	As above
Corticosteroids	Hydrocortisone 100mg i.v. twice daily, converting to oral prednisolone 40-50mg 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 employed. Live virus immunization. Hypersensitivity to any component.

<sup>3</sup> Data obtained from searches of appropriate drug and therapeutic websites.