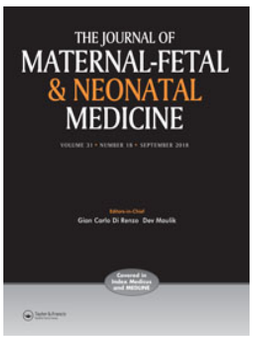

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REVIEW ARTICLE

Interventions for treating hyperemesis gravidarum: a Cochrane systematic review and meta-analysis

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ABSTRACT

Introduction: While nausea and vomiting in early pregnancy are very common, affecting approximately 80% of the pregnancies, hyperemesis gravidarum is a severe form affecting 0.3–1.0% of the pregnancies. Although hyperemesis gravidarum is rarely a source of mortality, it is a significant source of morbidity. It is one of the most common indications for hospitalization in pregnancy. Beyond the maternal and fetal consequences of malnutrition, the severity of hyperemesis symptoms causes a major psychosocial burden leading to depression, anxiety, and even pregnancy termination. The aim of this meta-analysis was to examine all randomized controlled trials of interventions specifically for hyperemesis gravidarum and evaluate them based on both subjective and objective measures of efficacy, maternal and fetal/neonatal safety, and economic costs.

Material and methods: Randomized controlled trials were identified by searching electronic databases. We included all randomized controlled trials for the treatment of hyperemesis gravidarum. The primary outcome was intervention efficacy as defined by severity, reduction, or cessation in nausea/vomiting; number of episodes of emesis; and days of hospital admission. Secondary outcomes included other measures of intervention efficacy, adverse maternal/fetal/neonatal outcomes, quality of life measures, and economic costs.

Results: Twenty-five trials (2052 women) met the inclusion criteria but the majority of 18 different comparisons described in the review include data from single studies with small numbers of participants. Selected comparisons reported below: No primary outcome data were available when acupuncture was compared with placebo. There was insufficient evidence to identify clear differences between acupuncture and metoclopramide in a study with 81 participants regarding reduction/cessation in nausea or vomiting (risk ratio (RR) 1.40, 95% CI 0.79–2.49 and RR 1.51, 95% CI 0.92–2.48, respectively). Midwife-led outpatient care was associated with fewer hours of hospital admission than routine inpatient admission (mean difference (MD) −33.20, 95% CI −46.91 to −19.49) with no difference in pregnancy-unique quantification of emesis and nausea (PUQE) score, decision to terminate the pregnancy, miscarriage, small-for-gestational age infants, or time off work when compared with routine care. Women taking vitamin B6 had a slightly longer hospital stay compared with placebo (MD 0.80 days, 95% CI 0.08–1.52). There was insufficient evidence to demonstrate a difference in other outcomes including mean number of episodes of emesis (MD 0.50, 95% CI −0.40–1.40) or side effects. A comparison between metoclopramide and ondansetron identified no clear difference in the severity of nausea or vomiting (MD 1.70, 95% CI −0.15–3.55, and MD −0.10, 95% CI −1.63–1.43; one study, 83 women, respectively). However, more women taking metoclopramide complained of drowsiness and dry mouth (RR 2.40, 95% CI 1.23–4.69, and RR 2.38, 95% CI 1.10–5.11, respectively). There were no clear differences between groups for other side effects. In a single study with 146 participants comparing metoclopramide with promethazine, more women taking promethazine reported drowsiness, dizziness, and dystonia (risk ratio (RR) 0.70, 95% CI 0.56–0.87, RR 0.48, 95% CI 0.34–0.69, and RR 0.31, 95% CI 0.11–0.90, respectively). There were no clear differences between groups for other important outcomes including quality of life and other side effects. In a single trial with 30 women, those receiving ondansetron had no difference in duration of hospital admission compared to those receiving promethazine (mean difference (MD) 0.00, 95% CI −1.39–1.39), although there was increased sedation with promethazine (RR 0.06, 95% CI 0.00–0.94). Regarding corticosteroids, in a study with 110 participants there was no difference in days of hospital admission compared to placebo (MD −0.30, 95% CI −0.70–0.10), but there was a decreased

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Supplemental data for this article can be accessed here.

readmission rate (RR 0.69, 95% CI 0.50–0.94; 4 studies, 269 women). For hydrocortisone compared with metoclopramide, no data were available for primary outcomes and there was no difference in the readmission rate (RR 0.08, 95% CI 0.00–1.28; one study, 40 women). In a study with 80 women, compared to promethazine, those receiving prednisolone had increased nausea at 48 h (RR 2.00, 95% CI 1.08–3.72), but not at 17 days (RR 0.81, 95% CI 0.58–1.15). There was no clear difference in the number of episodes of emesis or subjective improvement in nausea/vomiting.

Conclusions: While there were a wide range of interventions studied, both pharmaceutical and otherwise, there were a limited number of placebo controlled trials. In comparing the efficacy of the commonly used antiemetics, metoclopramide, ondansetron, and promethazine, the results of this review do not support the clear superiority of one over the other in symptomatic relief. Other factors such as side effect profile medication safety and healthcare costs should also be considered when selecting an intervention.

Introduction

While nausea and vomiting in early pregnancy are very common, affecting approximately 80% of the pregnancies, hyperemesis gravidarum is a severe form affecting 0.3–1.0% of the pregnancies [1,2]. The definition of hyperemesis gravidarum varies but generally includes intractable nausea/vomiting, signs of dehydration such as ketonuria, high urine specific gravity, electrolyte imbalances, and weight loss of at least 5% of prepregnancy weight, excluding other diagnoses [3–16]. The onset is generally in the first trimester at six to eight weeks, peaking by 12 weeks, with most women having resolution of symptoms by 20 weeks' gestation [5,17–30].

Although hyperemesis gravidarum is rarely a source of mortality, it is a significant source of morbidity. It is one of the most common indications for hospitalization in pregnancy [3]. Beyond the maternal and fetal consequences of malnutrition, the severity of hyperemesis symptoms causes a major psychosocial burden leading to depression, anxiety, and even pregnancy termination [3,6–9,31–45]. The socioeconomic costs of hyperemesis are also significant, stemming from treatment expense, lost job productivity, and high healthcare costs [8].

The objective of this review is to examine all the randomized controlled trials of interventions specifically for hyperemesis gravidarum and evaluate them based on both subjective and objective measures of efficacy, maternal and fetal/neonatal safety, and economic costs.

Materials and methods

This review was performed according to a protocol designed a priori and recommended for systematic review by the Cochrane Library, and validated in prior non-Cochrane meta-analyses [45–85]. We searched the Cochrane Pregnancy and Childbirth Group's (PCG) Trials Register by contacting the Trials Search Co-ordinator (up to date as of 20 December, 2015).

Briefly, the Cochrane PCG Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed, Central email alerts.
7. The World Health Organization International Clinical Trial Registry Platform (ICTRP) and ClinicalTrials.gov

In addition, we contacted the Cochrane Complementary Medicine Field to search their Trials Register (20 September 2014) and checked again via The Cochrane Register of Studies (20 December 2015).

We included all randomized controlled trials of any intervention for hyperemesis gravidarum. Trials that reported in abstract were included, provided that there was sufficient information in the abstract or available from the author to allow us to assess eligibility and risk of bias. We excluded quasi-randomized trials and trials using a cross-over design. Multiarmed trials were included and pair-wise comparisons were conducted separately. We excluded trials on nausea and vomiting of pregnancy that were not specifically studying the more severe condition of hyperemesis gravidarum.

The outcomes below are slightly different from what was initially published in the protocol for this

review [10]. Severity of nausea/vomiting was added as a primary outcome because it was found that this was often what was reported in the included studies. Similarly, rather than reporting the number of women requiring additional antiemetics, the outcome "number of antiemetics required" was used instead as this was more often reported.

Primary outcomes

Intervention efficacy:

1. Severity, reduction, or cessation in nausea/vomiting
2. Number of episodes of emesis
3. Days of hospital admission

Secondary outcomes

Intervention efficacy:

1. Hospital readmission
2. Number of women requiring additional antiemetics
3. Need for enteral or parenteral nutrition

Adverse maternal outcomes:

1. Pregnancy complications (i.e. antepartum hemorrhage, preeclampsia, gestational hypertension)
2. Weight loss

Adverse fetal/neonatal outcomes:

1. Spontaneous abortion
2. Stillbirth and neonatal death
3. Congenital abnormalities
4. Low birthweight
5. Preterm birth

Quality of life:

1. Quality of life outcomes including emotional, psychological, and physical well-being
2. Intervention side effects
3. Decision to terminate the pregnancy

Economic costs:

1. Direct financial costs to women
2. Productivity costs
3. Healthcare system costs

Data extraction

Selection of studies

Two review authors (RB and SB) independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion, or if required, we consulted a third author (AK).

Data extraction and management

We designed a form to extract data. Three review authors (RB, SB, GS) extracted data using the agreed form and resolved discrepancies either through discussion or with consultation with a fourth author (AK). We entered data into Review Manager software [11] and checked for accuracy. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (RB and SB) independently assessed the risk of bias for each study using the criteria outline in the *Cochrane Handbook for Systematic Reviews of Interventions* [12]. We resolved any disagreement by discussion or by involving an additional assessor (AK).

Assessment of the quality of evidence using the GRADE approach

The quality of the evidence has been assessed using the GRADE approach as outlined in the GRADE handbook [13] in order to assess the quality of the body of evidence relating to the following outcomes.

1. Severity, reduction or cessation in nausea/vomiting
2. Number of episodes of emesis
3. Days of hospital admission
4. Intervention side effects
5. Quality of life outcomes including emotional, psychological, and physical well-being
6. Pregnancy complications (i.e. antepartum hemorrhage, preeclampsia, gestational hypertension)
7. Adverse fetal/neonatal outcomes (i.e. spontaneous abortion, stillbirth and neonatal death, congenital abnormalities, low birthweight, preterm birth).

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we planned to use the mean difference if outcomes were measured in the same way between trials and the standardized mean difference to combine trials that measured the same outcome, but used different methods. We were unable to pool continuous data because most trials had a unique comparison, thus only the mean difference was used.

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either the T^2 was greater than zero, or there was a low *p* value (less than 0.10) in the Chi^2 test for heterogeneity.

We carried out statistical analysis using the Review Manager software [11]. We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged to be sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.

Where we used random-effects analyses, we presented the results as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

Results

The search strategy identified 78 total reports representing 67 distinct studies (some studies were resulted in more than one publication). Of these 67 studies, 25 met inclusion criteria for the review, 35 were excluded, 2 are awaiting translation and 5 studies are ongoing (Figure 1). See supplementary Appendix A for a full table of descriptions of the included studies.

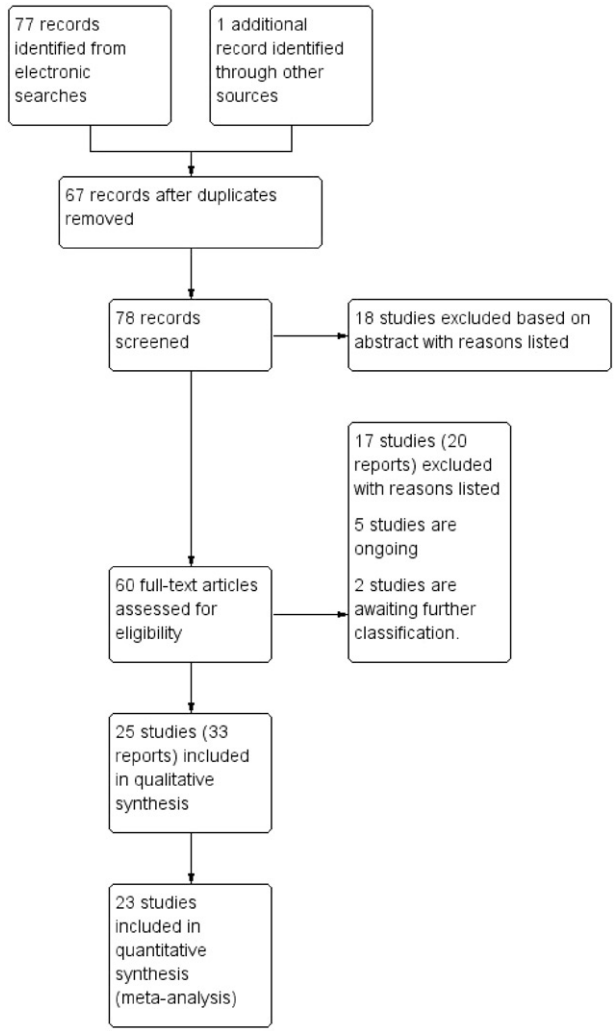

Figure 1. Study flow diagram.

This review included 25 studies (involving 2052 women), but the majority of our analyses are based on data from single studies with small numbers of participants. The included studies covered a range of interventions (both pharmacologic and nonpharmacological, such as acupressure/acupuncture, outpatient care, intravenous fluids, and various pharmaceutical interventions) for treating hyperemesis gravidarum. The methodological quality of the included studies varied (Figure 2).

Table 1 lists all 18 comparisons with all primary outcomes and selected secondary outcomes. For a full report of all comparisons and outcomes, see supplementary Appendix B.

A broad range of interventions for hyperemesis gravidarum were examined in the included trials and so to summarize findings, we selected those nonpharmacological and pharmacologic comparisons that we considered to be most clinically relevant to be reported here.

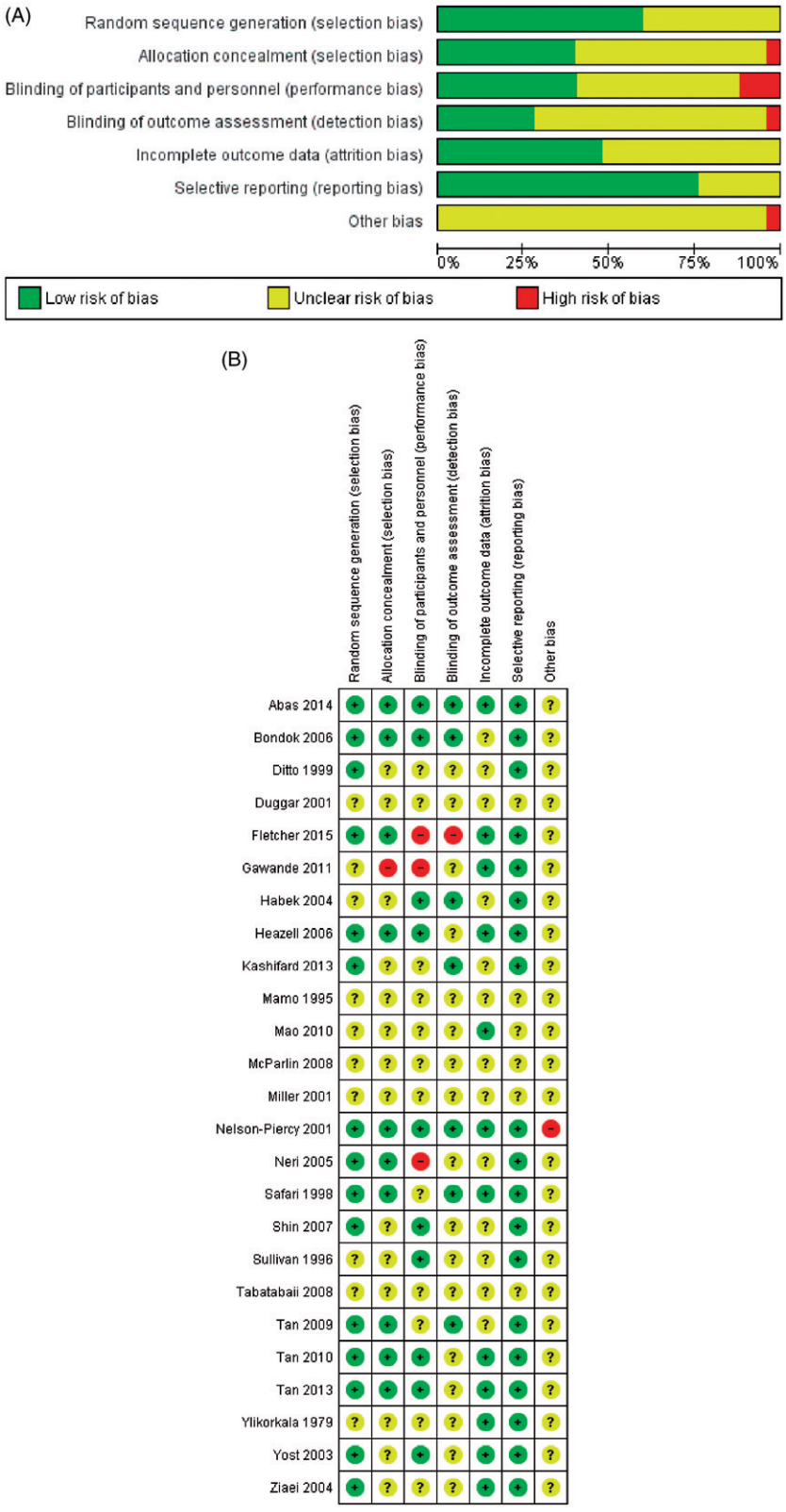

Figure 2. (A) Risk of bias graph about each risk of bias item presented as percentages across all included studies. (B) Assessment of risk of bias in included studies.

Table 1. Table of all comparisons and selected outcomes for interventions for hyperemesis gravidarum.

Comparison	Studies	Number of patients in each group	Selected Outcomes RR or MD (95% CI)
Acupuncture/Acupressor versus Placebo	Habek et al. [15]	21/15	Fewer women with acupuncture requiring additional antiemetics; one study, Habek 2004, RR 0.20 (0.08, 0.50)
	Shin et al. [14]	23/21	
	Heazell et al. [16]	29/28	
	Miller et al. [17]	45/28	
	Mamo et al. [18]	Total 38	
Acupuncture versus Metoclopramide	Neri et al. [19]	43/38	No difference in reduction or cessation of nausea (RR 1.40 (0.79, 2.49)) or vomiting (RR 1.51 (0.92, 2.48))
Pyridoxine versus placebo	Tan et al. [21]	47/45	Pyridoxine associated with longer hospital admission (days); MD 0.80 (0.08,1.52). No difference in number of episodes of emesis; MD 0.50 (−0.40, 1.40)
Metoclopramide versus ondansetron	Kashifard et al. [23]	34/49	No difference in severity of nausea (MD 1.70 (−0.015, 3.55)) or vomiting (MD-0.10 (−1.63, 1.43)) (one study, Kashifard 2013).
	Abas et al. [22]	80/80	Increased drowsiness (RR 2.40 (1.23,4.69)) and dry mouth (RR 2.38 (1.10, 5.11)) with metoclopramide (one study, Abas 2014).
Metoclopramide versus promethazine	Tan et al. [24]	76/76	Decreased drowsiness (RR 0.70 (0.56 − 0.87)), dizziness (RR 0.48 (0.34, 0.69)), and dystonia (RR 0.31 (0.11, 090)) with metoclopramide. No difference in quality of life (MD 0.50 (−0.22, 1.22)).
Ondansetron versus promethazine	Sullivan et al. [25]	15/15	No difference in days of hospital admission; MD 0.0 (−1.36, 1.39). Decreased sedation with ondansetron; RR 0.06 (0.00,0.94)
Corticosteroid versus placebo	Yost et al. [29]	56/54	No difference in days of admission (one study, Yost et al 2003, MD −0.30 (−0.70, 0.10)).
	Nelson-Piercy et al. [27]	12/12	Decreased risk of readmission with corticosteroids; RR 0.69 (0.50, 0.94).
	Duggar et al. [26]	14/25	
	Tabatabaii et al. [28]	48/48	
Hydrocortisone versus metoclopramide	Bondok et al. [32]	20/20	No difference in hospital readmission; RR 0.80 (0.00–1.28)
Corticosteroid versus promethazine	Ziaei et al. [31]	40/40	Increased severe nausea at 48 h (RR 2.00 (1.08, 3.72)) but not at 17 d (RR 0.81 (0.58, 1.15)) with corticosteroids. No difference in severity of vomiting at 48 h (RR 3.00 (0.33, 27.63)) or 17 d (RR 1.00 (0.21, 4.65)) (one study, Ziaei 2004).
	Safari et al. [30]	20/20	No difference in hospital readmission (one study Safari 1998; RR 0.09 (0.01, 1.53))
Adrenocorticotropic hormone versus placebo	Ylikorkala et al. [40]	16/16	No difference in reduction or cessation in nausea/vomiting MD0.60 (-1.65,2.85).
Acupuncture versus Phenobarbital	Mao et al. [41]	30/30	More women with complete recovery with acupuncture; RR 6.75 (2.69, 16.94)
Acupuncture versus Chinese Medicine	Mao et al. [41]	30/30	More women with complete recovery with acupuncture; RR 9.00 (3.06, 26.51)
Chinese medicine versus Phenobarbital	Mao et al. [41]	30/30	No difference in women with complete recovery; RR 0.75 (0.18, 3.07)
Diazepam with parenteral fluid versus parenteral fluid alone	Ditto et al. [42]	25/25	Decreased duration of hospital admission (days) with diazepam; MD −1.10 (−2.07, −0.13)
Dextrose saline versus normal saline rehydration	Tan et al. [43]	102/101	No difference in hours of hospital admission MD −5.00 (−10.78, 0.78)
Midwife led outpatient care versus routine care	McParlin et al. [20]	27/26	Decreased hours of hospital admission with outpatient care; MD −33.20 (−46.91, −19.49). No difference in subjective nausea and vomiting score; MD −0.70 (−3.17, 1.77).
Holistic assessment versus standard care alone	Fletcher et al. [44]	93/107	No difference in subjective nausea and vomiting score; MD −0.20 (−1.10, 0.70).
Muscle relaxation and pharmacotherapy versus pharmacotherapy	Gawande et al. [45]	15/15	Improved global improvement with muscle relaxation MD −0.54 (−1.04, −0.04).

The comparisons selected for presentation here are:

1. Acupuncture versus placebo
2. Acupuncture versus metoclopramide
3. Midwife led outpatient care versus routine care
4. Pyridoxine versus placebo
5. Metoclopramide versus ondansetron
6. Hydrocortisone versus metoclopramide
7. Metoclopramide versus promethazine
8. Ondansetron versus promethazine
9. Corticosteroid versus placebo
10. Corticosteroids versus promethazine

Acupuncture and acupressure versus placebo

Three studies (182 women) compared P6 acupressure or acupuncture versus placebo and were included in the analysis [14–16].

Two additional studies were in abstract form only and did not have data that could be entered into the analysis. Miller et al. compared nerve stimulation with a watch-like device at P6 versus placebo and reported lower symptoms in the intervention group, without specific data reported [17].

Mamo et al. compared acupressure Sea-band applied to each wrist versus control with no acupressure and reported more women required additional antiemetics than in the control group, again without specific data reported [18].

Primary outcomes

Severity, reduction, or cessation in nausea/vomiting. Only one study reported a decreased mean nausea score (using Rhodes index of nausea vomiting or retching), however, no standard deviation was reported so this could not be entered into our data and analysis tables [14].

Secondary outcomes

The number of women requiring additional antiemetics was lower in the acupuncture/acupressure group compared to placebo (RR 0.20, 95% confidence interval (CI) 0.08–0.50) [15]. However, there was no difference between the treatment group and placebo control with regard to spontaneous abortion (RR 0.48, 95% CI 0.05–5.03, *low-quality evidence*) [16], preterm birth less than 37 weeks (RR 0.12, 95% CI 0.01–2.26 *low-quality evidence*), stillbirth or neonatal death (RR 0.57, 95% CI 0.04–8.30, *low-quality evidence*) [16], decision to terminate the pregnancy (RR 0.72, 95% CI 0.18–2.95) [16], or anxiodepressive symptomology (RR 1.01, 95% CI 0.73–1.40, *very low-quality evidence*) [15].

Acupuncture versus metoclopramide

One study (81 women), evaluated the efficacy of acupuncture twice weekly versus metoclopramide infusion [19].

Primary outcomes

Severity, reduction, or cessation in nausea/vomiting. After the cessation of the last treatment, there was no difference in the rate of women who experienced a reduction of nausea (RR 1.40, 95% CI 0.79–2.49, *very low-quality evidence*) or the rate of women who experienced a reduction in vomiting (RR 1.51, 95% CI 0.92–2.48, *very low-quality evidence*).

Midwife led outpatient care versus routine care

One study (53 women) randomized women to midwife led outpatient care versus routine care with hospital admission. Data were obtained from communication with the authors [20].

Primary outcomes

Severity, reduction, or cessation in nausea/vomiting. There was no clear differences in the mean PUQE (pregnancy-unique quantification of emesis and nausea) score between the group of women who received midwife-led outpatient care and women who received routine care with admission (MD −0.70 points, 95% CI −3.17–1.77).

Days of hospital admission. Women who received midwife-led care remained in the hospital for fewer hours (MD −33.20 h, 95% CI −46.91 to −19.49)

Secondary outcomes

There was no clear difference in the rate of women who decided to terminate the pregnancy (RR 2.89, 95% CI 0.12–67.96). There was also no clear difference in spontaneous miscarriage (RR 0.96, 95% CI 0.15–6.34), or in the rate of small-for-gestational-age infants (RR 1.44, 95% CI 0.26–7.96). In terms of economic costs there was also no evidence of a difference between groups in relation to the rate of women who lost time from paid employment (RR 1.04, 95% CI 0.28–3.87).

Pyridoxine versus placebo

One study (94 women) randomized women to receive pyridoxine 20 mg orally three times a day versus placebo, in addition to all women receiving standard care

with intravenous rehydration, metoclopramide, and oral thiamine. Interventions were continued for 2 weeks, outcomes examined at the one- and 2-week mark, results reported here are at the 1-week mark due to significant attrition by two weeks [21].

Primary outcomes

Severity, reduction, or cessation in nausea/vomiting

Tan, et al reported nausea score as a median rather than a mean score – so the data could not be used for the RevMan tables, however the trialist reported no significant difference in nausea scores [21].

Number of episodes of emesis

There was no strong evidence of a difference in the daily mean vomiting episodes (MD 0.50 vomiting episodes, 95% CI −0.40–1.40, *low-quality evidence*).

Days of hospital admission

There was a slightly longer hospital stay associated with B6 compared with placebo (MD 0.80 days, 95% CI 0.08–1.52, *moderate-quality evidence*).

Secondary outcomes

There was no clear difference in hospital readmission (RR 1.78, 95% CI 0.85–3.71) or in weight loss after 1 week (MD 0.00 kg, 95% CI −0.93–0.93). Quality of life was reported as a median and therefore could not be included in the analysis, however, the authors reports no difference between groups in well-being score. Tan et al. did report on intervention side effects, and there was no differences in the rate of dizziness (RR 1.67, 95% CI 0.85–3.26, *low-quality evidence*), headaches, (RR 1.33, 95% CI 0.52–3.42, *low-quality evidence*), diarrhea (RR 3.00, 95% CI 0.13–71.07), palpitations (RR 1.00, 95% CI 0.22–4.60, *low-quality evidence*) and dry mouth (RR 0.82, 95% CI 0.49–1.38, *low-quality evidence*) in the pyridoxine group compared to placebo after 1 week of treatment. There were also no cases of rash or photosensitivity in either group.

Metoclopramide versus ondansetron

There were two studies (243 women) that compared metoclopramide with ondansetron. Abas et al. used 10 mg intravenous metoclopramide every 8 h for four doses versus 4 mg ondansetron intravenous every 8 h for four doses, while Kashifard et al. used oral medications in the same doses for 2 weeks and assessed severity of nausea and vomiting during the treatment period and 2 days 1 week after completion of therapy [22,23].

Primary outcomes

Severity, reduction, or cessation in nausea/vomiting.

Abas et al. reported nausea score as a median so it could not be analyzed in combination with the other study, but they report no significant difference between groups [22]. Kashifard, et al reported no significant difference between the metoclopramide and ondansetron groups in severity of nausea (MD 1.70 point, 95% CI −0.15–3.55, *very low-quality evidence*), or in severity of vomiting according to a 10-point VAS rating score on the second day 1 week after completion of therapy (MD −0.10 points, 95% CI −1.63–1.43, *very low-quality evidence*) [23].

Secondary outcomes

Abas et al. provided data (from 160 women) in relation to intervention side effects. The number of women who felt drowsy (RR 2.40, 95% CI 1.23–4.69 *moderate-quality evidence*), and who had a dry mouth (RR 2.38, 95% CI 1.10–5.11, *moderate-quality evidence*) was higher in the metoclopramide group compared to the group of women who received ondansetron. There were no clear differences in the rate of women unable to sleep (RR 1.29, 95% CI 0.50–3.28), felt dizzy (RR 2.33, 95% CI 0.94–5.77, *low-quality evidence*), had diarrhea (RR 9.00, 95% CI 0.49–164.46), had headache (RR 1.22, 95% CI 0.54–2.79), experienced palpitations (RR 2.50, 95% CI 0.50–12.51), or noticed skin rash (RR 1.00, 95% CI 0.06–15.71); no cases of dystonia in both groups were reported [22]. Kashifard et al. reported no side effects in either the metoclopramide or the ondansetron group, although the side effects examined were not specified [23]. In addition, Abas, et al reported no difference in the well-being VNRS score about quality of life outcome (MD −0.40 points, 95% CI −0.83–0.03, *moderate-quality evidence*) [22].

Metoclopramide versus promethazine

One study (152 women) compared 10 mg intravenous metoclopramide versus 25 mg intravenous promethazine given eight hourly for 24 h [24].

Primary outcomes

Severity, reduction, or cessation in nausea/vomiting.

Nausea score was reported by as a median so data could not be included in our analysis, but the trialist

reported no significant difference in nausea score between groups [24].

Number of episodes of emesis. The number of vomiting episodes were as a median so these data could not be included in our analysis, but the trialist reported no significant difference in the number of vomiting episodes between groups [24].

Secondary outcomes

In relation to quality of life, the mean well-being VNRS score was similar in the metoclopramide group and the promethazine groups (MD 0.50 points, 95% CI −0.22–1.22, *low-quality evidence*). Tan et al. also provided data on the intervention side effects – the number of women who felt drowsy (RR 0.70, 95% CI 0.56–0.87, *moderate-quality evidence*), dizzy (RR 0.48, 95% CI 0.34–0.69, *moderate-quality evidence*) and experienced dystonia (RR 0.31, 95% CI 0.11–0.90) was lower in the metoclopramide group compared to the promethazine group. Aside from that, there was no strong evidence showing any differences in the number of women unable to sleep (RR 0.78, 95% CI 0.40–1.53), had a dry mouth (RR 0.91, 95% CI 0.62–1.34), had diarrhea (RR 1.39, 95% CI 0.32–5.99), had headache (RR 0.81, 95% CI 0.47–1.38) (*low-quality evidence* for the aforementioned side effects), experienced palpitations (RR 0.61, 95% CI 0.25–1.46), and noticed skin rash (RR 1.39, 95% CI 0.32–5.99).

Ondansetron versus promethazine. One study (30 women) randomized women to receive either 10 mg intravenous ondansetron or 50 mg intravenous promethazine for one dose then every 8 h as needed [25].

Primary outcomes

Severity, reduction, or cessation in nausea/vomiting. Specific subjective nausea scores were not reported and could not be entered into our RevMan tables. However, the trialist reported no significant difference in the severity of nausea between the two groups [25].

Days of hospital admission. There was no difference between the ondansetron and promethazine groups in terms of the number of days of hospital admission (MD 0.00 days, 95% CI −1.39–1.39 *very low-quality evidence*).

Secondary outcomes

Regarding secondary outcomes, the rate of sedation (adverse effect) was increased with promethazine (RR 0.06, 95% CI 0.00–0.94, *low-quality evidence*), no other side effects were observed.

Corticosteroids versus placebo

There were four studies (271 women) that evaluated the efficacy of steroids versus placebo in hyperemesis gravidarum [26–29]. The specific medication and dose varied by study – Duggar, et al studied oral methylprednisone 12 tablets of 4 mg methylprednisone daily for 3 days followed by a 10-day taper [26]; Nelson-Piercy et al. studied 20 mg of oral prednisolone every 12 h for 1 week; they also provided additional antiemetics as deemed necessary by the providers [27]; and both Tabatabaii et al. and Yost et al. studied 125 mg of intravenous methylprednisolone followed by an oral prednisone taper; in the former study the women also received B6, in the latter study the women also received metoclopramide and promethazine as standard of care [28,29].

Primary outcomes

Severity, reduction, or cessation in nausea/vomiting. Nelson-Piercy et al reported a nonsignificant reduction in severity of nausea in the steroid versus placebo group, however this was reported as a median and could not be included into the analysis [27].

Days of hospital admission

Days of hospital admission were available only from Yost et al.; there was no clear difference (MD −0.30 days, 95% CI −0.70–0.10, *very low-quality evidence*) in the number of days of hospital admission between groups [29].

Secondary outcomes

Regarding secondary outcomes, the rate of hospital readmission was lower in the steroid hormone group compared to the placebo group of women (RR 0.69, 95% CI 0.50–0.94, four studies, 269 women) [26–29]. There was no difference in the rate of pregnancy complications (pregnancy hypertension or gestational diabetes (RR 0.61, 95% CI 0.26–1.47, *very low-quality evidence*) based on one study (110 women) [29]. There was no significant difference in the rate of spontaneous abortion (RR 0.64, 95% CI 0.11–3.70 (one study, 110 women, *very low-quality evidence*) [29]. There was no difference in the rate of stillbirth or neonatal death (RR 0.70, 95% CI 0.09–5.29, 2 studies, 134 women, *very low-quality evidence*) [27,29]. Only one study reported on congenital abnormalities, and there was no

difference between groups (RR 0.32, 95% CI 0.01–7.73, one study 110 women, *very low-quality evidence*) [29]. One study reported on low birthweight (RR 1.35, 95% CI 0.46–4.00, 110 women), *very low-quality evidence*) [29] and another study reported on small-for-gestational-age infants (RR 1.00, 95% CI 0.07–14.21, 24 women) [27] and there was no significant difference between groups for either outcome. One study reported on preterm birth less than 36 weeks and another reported on preterm birth less than 37 weeks, when we combined these data using a random-effects analysis (due to substantial statistical heterogeneity) there was no difference between groups (average RR 1.01, 95% CI 0.31–3.28; two studies, 134 women, $Tau^2 = 0.27$, $I^2 = 37\%$), *very low-quality evidence*) [27,29]. Duggar et al. reported intervention side effects (specifics side effects not reported) and found no difference in the rate of side effects (RR 0.79, 95% CI 0.06–11.20, 25 women, *very low-quality evidence*) [26]. One study reported on the number of women requiring additional antiemetics and there was no clear difference between groups for this outcome (RR 0.56, 95% CI 0.26–1.17, 24 women) and there was also no difference in the number of women who decided to terminate the pregnancy (RR 0.33, 95% CI 0.01–7.45, 24 women) [27].

Corticosteroids versus promethazine

Two studies (120 women) were involved in this comparison. One study evaluated oral methylprednisolone 16 mg three times daily versus oral promethazine 25 mg three times daily [30], while another one compared 5 mg oral prednisolone with 75 mg oral promethazine daily for 10 days [31].

Primary outcomes

Severity, reduction, or cessation in nausea/vomiting. In one study the number of women with severe nausea at 48 h was higher in the prednisolone group compared to the promethazine group (RR 2.00, 95% CI 1.08–3.72, *low-quality evidence*) and at day 17 was not significantly different between groups (RR 0.81, 95% CI 0.58–1.15, *very low-quality evidence*) [31]. We did not find any difference in the number of episodes of vomiting at 48 h (RR 3.00, 95% CI 0.33–27.63) and at 17 days (RR 1.00, 95% CI 0.21–4.65, *very low-quality evidence*) [31].

Another study reported on therapy failure as defined by persistence of vomiting more than five times/day, inability to tolerate liquids, and the women's impression that they were not better, and there was no difference between groups (RR 1.50, 95% CI 0.28–8.04) [30].

Number of episodes of emesis. Ziaei et al. reported increased number of episodes of emesis in the prednisolone group at 48 h, but no difference at day 17; however, data were reported as a median so were not able to be analyzed [31].

Secondary outcomes

Regarding secondary outcomes, there was no strong evidence of differences in the rate of hospital readmission (RR 0.09, 95% CI 0.01–1.53), in the number of women requiring additional antiemetics (RR 1.50, 95% CI 0.28–8.04), or in the rate of stillbirth/neonatal death (RR 3.00, 95% CI 0.13–69.52, *low-quality evidence*), in the rate of preterm birth (RR 3.00, 95% CI 0.13–69.52, *low-quality evidence*), or in the rate of women who decided to terminate the pregnancy (RR 3.00, 95% CI 0.13–69.52) [30]. In terms of side effects, there was no difference in the rate of women who felt abdominal pain during the first 48 h (RR 0.33, 95% CI 0.07–1.55), and between the third and 10th day (RR 0.11, 95% CI 0.10–2.00). The rate of drowsiness was also not substantially different (RR 0.08, 95% CI 0.00–1.32, *low-quality evidence*). Regarding quality of life, the number of women who reported becoming well or partially well by 48 h was lower in the prednisolone group compared to promethazine (RR 0.67, 95% CI 0.47–0.95), while no difference was identified in the number of women who reported becoming well or partially well by 17 days (RR 1.67, 95% CI 0.95–2.92) [31].

Hydrocortisone versus metoclopramide

There was one study (40 women) that compared women receiving 300 mg intravenous hydrocortisone daily for 3 days, tapered over the week, versus 10 mg of metoclopramide intravenously three times daily for one week [32].

Primary outcomes

Number of episodes of emesis. Mean number of daily episodes of emesis were reported by as significantly decreased in the hydrocortisone group, although the actual numbers were not available to be included into the analysis [32].

Secondary outcomes

Regarding secondary outcomes, there was no difference in the rate of hospital readmission between the

metoclopramide and hydrocortisone groups (RR 0.08, 95% CI 0.00–1.28, *moderate-quality evidence*). Similarly, there was no clear difference in the number of women requiring enteral or parenteral nutrition between the two groups (RR 0.33, 95% CI 0.01–7.72) [32].

Comment

On the basis of this review, there is little high-quality and consistent evidence supporting any one intervention over another, which should be taken into account when making management decisions. Few interventions were compared with placebo, and most were compared with another intervention. While studies on nonpharmacological interventions were limited, the finding that midwife-led outpatient care compared to inpatient hospitalization had similar outcomes with decreased hours in the hospital warrants further investigation. The commonly used antiemetics ondansetron, metoclopramide, and promethazine were not found to have significant differences compared to each other in symptomatic relief with differences primarily seen in side-effect profile.

Limited data were available regarding adverse maternal and neonatal outcomes, thus the lack of report on adverse events or the lack of statistical significance does not necessarily mean no harm is present. Larger studies on individual interventions need to be examined to determine the safety of these many interventions.

There was also very limited reporting on the economic impact of hyperemesis gravidarum and the impact on this economic burden that interventions may have. Although studies often reported an overall well-being score, this does not necessarily equate with ability to return to work.

There are a number of strengths to this review. The main strength of this review is its comprehensive approach to analyzing interventions specific to hyperemesis gravidarum. There are several other reviews and overviews on hyperemesis gravidarum, with varying degrees of support from the literature [5,33–39]. This review is unique in the breadth of the interventions examined, the limitation to only randomized controlled trials, and examination interventions specifically for hyperemesis gravidarum, versus the more common and milder condition of nausea and vomiting in pregnancy. In addition, we attempted to be as inclusive as possible in the search strategy and have included studies in languages other than English.

This review has some limitations. The studies reported are predominantly from European and North American journals, which may limit the external validity of these results. Interpreting and comparing the findings of the studies included was difficult because of the variation in the reporting of the subjective outcome of severity of nausea and vomiting, thus the meta-analysis component of this review is limited. In addition, even within a comparison, often dosages or route of administration varied between studies, we treated them as equivalent which is not necessarily clinically true. Finally, inclusion criteria were defined by the study authors and varied by study as there is no single standard definition or clinical criteria for the diagnosis of hyperemesis gravidarum.

The difficulty in interpreting the results of this review highlights the importance of having a specific definition of hyperemesis gravidarum for use in trials, conducting randomized controlled trials in comparing interventions, and using validated instruments for the measurement of severity of nausea and vomiting. There should be an agreed-upon set of clearly-defined and measurable outcomes in trials of interventions for hyperemesis gravidarum, so that outcomes of trials can be combined in future meta-analyses. Furthermore, the clinical practice of managing patients with hyperemesis gravidarum often employs combinations of interventions, which have not been well studied.

While there are a wide range of interventions studied, both pharmaceutical and otherwise, the most common antinausea medications studied and found to have some benefit in the treatment of hyperemesis gravidarum are metoclopramide, ondansetron, and promethazine. The results of this review do not support the clear superiority of one over the other in symptomatic relief, as such, other factors such as side effect profile, medication safety, and healthcare costs should also be considered when selecting an intervention.

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