ClinicalEvidence

Nausea and vomiting in early pregnancy

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ABSTRACT

INTRODUCTION: More than half of pregnant women suffer from nausea and vomiting, which typically begins by the fourth week and disappears by the 16th week of pregnancy. The cause of nausea and vomiting in pregnancy is unknown, but may be due to the rise in human chorionic gonadotrophin concentration. In 1 in 200 women, the condition progresses to hyperemesis gravidarum, which is characterised by prolonged and severe nausea and vomiting, dehydration, and weight loss. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatment for nausea and vomiting in early pregnancy? What are the effects of treatments for hyperemesis gravidarum? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2013 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 32 studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: acupressure; acupuncture; corticosteroids; ginger; metoclopramide; ondansetron; prochlorperazine; promethazine; and pyridoxine (vitamin B6).

QUESTIONS

INTERVENTIONS

Key points

- More than half of pregnant women suffer from nausea and vomiting, which typically begins by the fourth week and disappears by the 16th week of pregnancy.

  The cause of nausea and vomiting in pregnancy is unknown, but may be due to the rise in human chorionic gonadotrophin concentration.

  In 1 in 200 women, the condition progresses to hyperemesis gravidarum, which is characterised by prolonged and severe nausea and vomiting, dehydration, and weight loss.

- In general, the trials we found were small and of limited quality. There is a need for other large high-quality trials in this condition with consistent outcomes.

- For nausea and vomiting in early pregnancy:

  Ginger may reduce nausea and vomiting in pregnancy compared with placebo, although studies used different preparations of ginger and reported varying outcome measures.

  Pyridoxine may be more effective than placebo at reducing nausea but we don't know about vomiting, and evidence was weak.

  Pyridoxine may be as effective as ginger in reducing nausea and vomiting, although evidence was limited.

Acupressure may be more effective than sham acupressure at reducing nausea and vomiting. However, evidence was weak, and interventions and outcomes varied between trials.

We don't know whether acupressure is more effective than pyridoxine at reducing nausea or vomiting as we found insufficient evidence.

We don't know whether acupuncture is more effective than sham acupuncture at reducing nausea and vomiting.

We don't know whether prochlorperazine, promethazine, or metoclopramide reduce nausea or vomiting compared with placebo.

- In hyperemesis gravidarum:

We don't know whether acupressure, acupuncture, corticosteroids, ginger, metoclopramide, or ondansetron are effective in treating hyperemesis gravidarum.

Hydrocortisone may be more effective than metoclopramide at reducing vomiting episodes and reducing readmission to the intensive care unit in women with hyperemesis gravidarum.

DEFINITION

Nausea and vomiting are common problems in early pregnancy. Although often called 'morning sickness', nausea and vomiting can occur at any time of day and may persist throughout the day. [1] Symptoms usually begin between four weeks' and seven weeks' gestation (one study found this to be the case in 70% of affected women) [2] and disappear by 16 weeks' gestation in about 90% of women. [1] [2] [3] One study found that less than 10% of affected women suffer nausea, vomiting, or both before the first missed period. [3] Most women do not require treatment, and complete the pregnancy without any special intervention. However, if nausea and vomiting are severe and persistent, the condition can progress to hyperemesis, especially if the woman is unable to maintain adequate hydration, fluid and electrolyte balance, and nutrition. **Hyperemesis gravidarum** is a diagnosis of exclusion, characterised by prolonged and severe nausea and vomiting, dehydration, and weight loss. [1] Laboratory investigation may show ketosis, hyponatraemia, hypokalaemia, hypouricaemia, metabolic hypochloraemic alkalosis, and ketonuria.

INCIDENCE/ PREVALENCE

Nausea affects about 70% and vomiting about 60% of pregnant women. [1] The true incidence of hyperemesis gravidarum is not known. It has been documented to range from 3 in 1000 to 20 in 1000 pregnancies. However, most authors report an incidence of 1 in 200. [2]

AETIOLOGY/ RISK FACTORS

The causes of nausea and vomiting in pregnancy are unknown. One theory, that they are caused by the rise in human chorionic gonadotrophin concentration, is compatible with the natural history of the condition, its severity in pregnancies affected by hydatidiform mole, and its good prognosis (see prognosis below). [4] The cause of hyperemesis gravidarum is also uncertain. Again, endocrine and psychological factors are suspected, but evidence is inconclusive. [4] Female fetal sex has been found to be a clinical indicator of hyperemesis. [5] One prospective study found that *Helicobacter pylori* infection was more common in pregnant women with hyperemesis gravidarum than in pregnant women without hyperemesis gravidarum (number of women with positive serum *Helicobacter pylori* immunoglobulin G concentrations: 95/105 [91%] with hyperemesis gravidarum *v* 60/129 [47%] without hyperemesis gravidarum). [6] However, it was not clear whether this link was causal.

PROGNOSIS

One systematic review (search date 1988) found that nausea and vomiting were associated with a reduced risk of miscarriage (six studies, 14,564 women; OR 0.36, 95% CI 0.32 to 0.42) but found no association with perinatal mortality. [7] Hyperemesis gravidarum is thought by some to induce nutrient partitioning in favour of the fetus, which could explain the association with improved outcome in the fetus. [8] Nausea and vomiting and hyperemesis usually improve over the course of pregnancy, but in one cross-sectional observational study 13% of women reported that nausea and vomiting persisted beyond 20 weeks' gestation. [9] Although death from nausea and vomiting during pregnancy is rare, morbidities, including Wernicke's encephalopathy, splenic avulsion, oesophageal rupture, pneumothorax, and acute tubular necrosis, have been reported. [10] [11]

AIMS OF INTERVENTION

To reduce the incidence and severity of nausea and vomiting in early pregnancy; to reduce the incidence and severity of hyperemesis gravidarum; to minimise adverse effects of treatment and possible teratogenic effects on the fetus.

OUTCOMES

All women: **severity of nausea and vomiting episodes** (as measured on validated scales); **maternal mortality**; *in women with hyperemesis gravidarum, we also report*: **rates of admission or readmission to hospital (includes duration of hospital stay)**; *all women*: **incidence and severity of adverse effects of treatment**; **incidence of teratogenic effects of treatments on the fetus**; and **fetal loss/spontaneous abortion**.

METHODS *Clinical Evidence* search and appraisal September 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to September 2013, Embase 1980 to September 2013, and The Cochrane Database of Systematic Reviews 2013, issue 9 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search run by an Information Specialist were first assessed against predefined criteria by an Evidence Scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an Evidence Analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an Evidence Analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in English language, at least single blinded, and containing at least 20 individuals (at least 10 per arm) of whom at least 80% were followed up. There was no minimum length of follow-up. We included studies consisting of populations of women in early pregnancy (four to 16 weeks' gestation) in Question 1 and women with hyperemesis gravidarum in Question 2. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 34). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatment for nausea and vomiting in early pregnancy?

OPTION ACUPRESSURE FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 34 .
- Acupressure may be more effective than sham acupressure at reducing nausea and vomiting. However, evidence was weak, and interventions and outcomes varied between trials.
- We don't know whether acupressure is more effective than pyridoxine at reducing nausea or vomiting as we found insufficient evidence.

Benefits and harms

Acupressure versus placebo or control:

We found four systematic reviews, [12] [13] [14] [15] and one subsequent RCT. [16] The first systematic review (search date 2010, 27 RCTs) included all RCTs identified by the other three systematic reviews that met the inclusion criteria for this *Clinical Evidence* review. As it did not perform a meta-analysis, individual RCT data are reported. [17] [18] [19] The second, third, and fourth systematic reviews [13] [14] [15] did not include any additional RCTs that met inclusion criteria for this *Clinical Evidence* review so are not discussed further.

Severity of nausea and vomiting

Acupressure compared with sham acupressure or no treatment Acupressure may be more effective than sham acupressure at improving nausea and vomiting in women with nausea and vomiting in early pregnancy. However, evidence was weak and inconsistent (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[17] RCT	60 women, mean gestational age ranged from 9.6–10.8 weeks	**Mean nausea score assessed on visual analogue scale (0 = no nausea, 10 = extreme**	P = 0.002 acupressure *v* no treatment		P6 acupressure

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	In review [12]	**nausea) , 1 day post treatment commencement** 5.2 with P6 wristband acupressure for 2 weeks 5.6 with placebo wristband acupressure on upper surface of wrist for 2 weeks 7.6 with no treatment Baseline gestation at study entry was statistically significantly different among the 3 groups (P = 0.035)			
[17] RCT **3-armed trial**	60 women, mean gestational age ranged from 9.6–10.8 weeks In review [12]	**Mean nausea score assessed on visual analogue scale (0 = no nausea, 10 = extreme nausea) , 3–6 days** 5.6–4.9 with P6 wristband acupressure for 2 weeks 5.5–6.3 with placebo wristband acupressure on upper surface of wrist for 2 weeks Baseline gestation at study entry was statistically significantly different among the 3 groups (P = 0.035)	P = 0.013		P6 acupressure
[16] RCT	80 pregnant women within the first trimester with moderate to severe nausea and vomiting	**Median nausea score assessed on 10 cm visual analogue scale (0 = lack of nausea, 10 = severe nausea) , 1 day** 7 with acupressure at KID21 point applied for 4 consecutive days 7 with sham acupressure (non-acupuncture point) applied for 4 consecutive days All women also took vitamin B6	P = 0.473	⟷	Not significant
[16] RCT	80 pregnant women within the first trimester with moderate to severe nausea and vomiting	**Median nausea score assessed on 10 cm visual analogue scale (0 = lack of nausea, 10 = severe nausea) , 2 days** 6 with acupressure at KID21 point applied for 4 consecutive days 7 with with sham acupressure (non-acupuncture point) applied for 4 consecutive days All women also took vitamin B6	P = 0.012		acupressure
[16] RCT	80 pregnant women within the first trimester with moderate to severe nausea and vomiting	**Median nausea score assessed on 10 cm visual analogue scale (0 = lack of nausea, 10 = severe nausea) , 3 days** 5 with acupressure at KID21 point applied for 4 consecutive days 7 with sham acupressure (non-acupuncture point) applied for 4 consecutive days All women also took vitamin B6	P <0.001		acupressure
[16] RCT	80 pregnant women within the first trimester with moderate to severe	**Median nausea score assessed on 10 cm visual analogue scale (0 = lack of nausea, 10 = severe nausea) , 4 days**	P <0.001		acupressure

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	nausea and vomiting	4 with acupressure at KID21 point applied for 4 consecutive days 7 with sham acupressure (non-acupuncture point) applied for 4 consecutive days All women also took vitamin B6			
Vomiting					
[16] RCT	80 pregnant women within the first trimester with moderate to severe nausea and vomiting	**Median frequency of vomiting , 1 day** 1 with acupressure at KID21 point applied for 4 consecutive days 1 with sham acupressure (non-acupuncture point) applied for 4 consecutive days All women also took vitamin B6	P = 0.012		acupressure
[16] RCT	80 pregnant women within the first trimester with moderate to severe nausea and vomiting	**Median frequency of vomiting , 2 days** 0 with acupressure at KID21 point applied for 4 consecutive days 1 with sham acupressure (non-acupuncture point) applied for 4 consecutive days All women also took vitamin B6	P = 0.003		acupressure
[16] RCT	80 pregnant women within the first trimester with moderate to severe nausea and vomiting	**Median frequency of vomiting , 3 days** 0 with acupressure at KID21 point applied for 4 consecutive days 1 with sham acupressure (non-acupuncture point) applied for 4 consecutive days All women also took vitamin B6	P = 0.001		acupressure
[16] RCT	80 pregnant women within the first trimester with moderate to severe nausea and vomiting	**Median frequency of vomiting , 4 days** 0 with acupressure at KID21 point applied for 4 consecutive days 1 with sham acupressure (non-acupuncture point) applied for 4 consecutive days All women also took vitamin B6	P <0.001		acupressure
Nausea and vomiting (composite)					
[18] RCT	97 women, 8–12 weeks' gestation In review [12]	**Mean change from baseline in hours of nausea and vomiting , 12 days** –2.74 with active wristband acupressure –0.85 with sham wristband acupressure 71% in active group reported shorter duration of symptoms *v* 63% in the sham group	MD 1.89 95% CI 0.33 to 3.45 P = 0.018	○○○	active wristband acupressure
[18] RCT	97 women, 8–12 weeks' gestation In review [12]	**Mean change from baseline in nausea and vomiting assessed on visual analogue scale , 12 days**	MD +0.25 95% CI –0.12 to +0.62	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		–0.50 with active wristband acupressure –0.25 with sham wristband acupressure 71% in active group reported less intensity in morning sickness *v* 59% in the sham group			
[12] Systematic review	97 women, 8–12 weeks' gestation Data from 1 RCT	**Proportion of participants reporting no improvement in intensity of symptoms** 15/53 (28%) with active wristband acupressure 16/44 (36%) with sham wristband acupressure	RR 0.78 95% CI 0.44 to 1.39 P = 0.40	⟷	Not significant
[19] RCT	98 pregnant women, <14 weeks' gestation, with symptoms of nausea and vomiting In review [12]	**Mean Rhodes Index Scale , day 4** 8.7 with bilateral auricular acupressure (to the concha ridge zone of the inner auricle surface for 30 seconds 4 times a day on days 3–6) 10.6 with no treatment Both groups were allowed to take 1 tablet of dimenhydrinate every 6 hours when symptoms were intolerable	P = 0.387	⟷	Not significant
[19] RCT	98 pregnant women, <14 weeks' gestation, with symptoms of nausea and vomiting In review [12]	**Mean Rhodes Index Scale , day 5** 8.0 with bilateral auricular acupressure (to the concha ridge zone of the inner auricle surface for 30 seconds 4 times a day on days 3–6) 11.6 with no treatment Both groups were allowed to take 1 tablet of dimenhydrinate every 6 hours when symptoms were intolerable	P = 0.274	⟷	Not significant
[19] RCT	98 pregnant women, <14 weeks' gestation, with symptoms of nausea and vomiting In review [12]	**Mean Rhodes Index Scale , day 6** 7.7 with bilateral auricular acupressure (to the concha ridge zone of the inner auricle surface for 30 seconds 4 times a day on days 3–6) 11.3 with no treatment Both groups were allowed to take 1 tablet of dimenhydrinate every 6 hours when symptoms were intolerable	P = 0.252	⟷	Not significant

Maternal mortality

No data from the following reference on this outcome. [12] [16]

Hospital admission/readmission rates

No data from the following reference on this outcome. [12] [16]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] RCT	97 women, 8–12 weeks' gestation In review [12]	**Proportion of participants reporting adverse effects , 12 days** 63% with active wristband acupressure 90% with sham wristband acupressure The most common reported adverse effects were pain, numbness, soreness, and hand-swelling. Two women in the active group and 1 woman in the placebo group reported worsening of symptoms. There were no serious adverse effects reported	P = 0.004		active wristband acupressure

No data from the following reference on this outcome. [12] [16]

Acupressure versus pyridoxine (vitamin B_6):

We found one systematic review (search date 2010), [12] which included one RCT [20] comparing acupressure with pyridoxine over seven days in women with mild to moderate nausea and vomiting in early pregnancy. The data reported below for the longer term follow-up were taken from the individual RCT, [20] as the systematic review did not include these data.

Severity of nausea and vomiting

Acupressure compared with pyridoxine We don't know how acupressure and pyridoxine compare at reducing nausea or vomiting at 3 to 7 days (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea and vomiting					
[12] Systematic review	66 women with mild to moderate nausea and vomiting in early pregnancy, gestational age range 6–12 weeks Data from 1 RCT	**Mean Rhodes Index scores , day 3** 7.8 with wristband acupressure on the P6 acupoint (instruction to wear the wristband continuously from day 1 to the evening of day 5) plus placebo tablet 7.6 with pyridoxine (vitamin B6 twice daily for 5 days) plus placebo acupressure (dummy point) Absolute results not reported	MD +0.20 95% CI –2.24 to +2.64 P = 0.87 Women were also allowed to take a rescue drug which may have influenced results (see comment)	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[20] RCT	66 women with mild to moderate nausea and vomiting in early pregnancy, gestational age range 6–12 weeks In review [12]	**Rhodes Index scores , 5th day** with wristband acupressure on the P6 acupoint (instruction to wear the wristband continuously from day 1 to the evening of day 5) plus placebo tablet with pyridoxine (vitamin B_6 twice daily for 5 days) plus placebo acupressure (dummy point) Absolute results not reported See further information on studies for full details on Rhodes Index scores	P >0.05 Women were also allowed to take a rescue drug which may have influenced results (see comment)	⟷	Not significant
[20] RCT	66 women with mild to moderate nausea and vomiting in early pregnancy, gestational age range 6–12 weeks In review [12]	**Rhodes Index scores , 7th day after discontinuation of treatments** with wristband acupressure on the P6 acupoint (instruction to wear the wristband continuously from day 1 to the evening of day 5) plus placebo tablet with pyridoxine (vitamin B_6 twice daily for 5 days) plus placebo acupressure (dummy point) Absolute results not reported See further information on studies for full details on Rhodes Index scores	P >0.05 Women were also allowed to take a rescue drug which may have influenced results (see comment)	⟷	Not significant

Maternal mortality

No data from the following reference on this outcome. [20]

Hospital admission/readmission rates

No data from the following reference on this outcome. [20]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[20] RCT	66 women with mild to moderate nausea and vomiting in early pregnancy, gestational age range 6–12 weeks	**Adverse effects** with wristband acupressure on the P6 acupoint (instruction to wear the wristband continuously from day 1 to the evening of day 5) plus placebo tablet with pyridoxine (vitamin B_6 twice daily for 5 days) plus placebo acupressure (dummy point) The RCT reported that both acupressure and vitamin B_6 were	Not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		well tolerated, and only one person complained of irritation on wearing the wristband and withdrew from treatment in the acupressure group			

Further information on studies

[20] Rhodes Index scores, 8-item form: three items measure nausea (scores ranging from 3–15) and five items measure vomiting and retching (scores ranging from 5–25).

Comment: In the RCT comparing acupressure and pyridoxine, women were also advised to take dimenhydrinate in the event of nausea and vomiting. Women were asked to record whether they took dimenhydrinate and, if so, how often. However, it is not clear how many women actually took dimenhydrinate or how often it was taken. It is possible that the reduction in symptoms was largely due to the effects of the rescue drug. [20]

OPTION PROMETHAZINE FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 34 .
- We don't know whether promethazine reduces nausea and vomiting compared with placebo as we found no RCTs.
- We don't know how promethazine and prochlorperazine compare as we found insufficient evidence.

Benefits and harms

Promethazine versus placebo:

We found two systematic reviews (search date 1998, [21] and search date 2010 [12]), which found no RCTs which met inclusion criteria for this *Clinical Evidence* review.

Promethazine versus prochlorperazine:

See option on prochlorperazine, p 20 .

Comment: None.

OPTION GINGER FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 34 .
- Ginger may reduce nausea and vomiting in pregnancy compared with placebo, although studies used different preparations of ginger and reported varying outcome measures.
- We don't know whether ginger is more effective at reducing nausea or vomiting compared with pyridoxine or metoclopramide.
- Ginger may cause heartburn and may be a gastric irritant (in quantities >6 g). In addition, inhalation of ginger dust may lead to immunoglobulin E-mediated allergy.

Benefits and harms

Ginger versus placebo:

We found three systematic reviews (search date 2004, [22] search date 2009, [23] search date 2010 [12]), and two additional RCTs. [24] [25] As there was substantial overlap of RCTs identified in the three systematic reviews, and no meta-analysis was performed, when the systematic review did not report an outcome of interest for this review, data have been reported directly from the individual RCTs. [26] [27] [28] [29]

Severity of nausea and vomiting

Ginger compared with placebo Ginger may be more effective at reducing nausea and vomiting in early pregnancy (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[12] Systematic review	70 women, <17 weeks' gestation Data from 1 RCT	**Mean improvement in nausea score , 4 days of treatment** 2.1 with ginger 1.5 with placebo Ginger group, n = 32; placebo group, n = 38	MD +0.60 95% CI –0.51 to +1.71 P = 0.29 Per-protocol analysis demonstrated a significant difference in favour of placebo: MD 1.20; 95% CI 0.22 to 2.18; P = 0.017 (ginger group, n = 32; placebo group, n = 35)	⟷	Not significant
[12] Systematic review	23 women, gestational age 7–11 weeks Data from 1 RCT	**Proportion of women reporting little improvement in nausea , day 9** 3/13 (23%) with ginger 8/10 (80%) with placebo	RR 0.29 95% CI 0.10 to 0.82 P = 0.019	●●○	ginger
[27] RCT	99 women, mean gestational age of 9 weeks In review [12] [22]	**Mean nausea experience scores assessed by Rhodes Index of Nausea, Vomiting and Retching , day 1–day 4** with ginger in oral capsules taken 4 times daily for 4 days with placebo taken 4 times daily for 4 days Absolute results reported graphically	Reported as significant P value not reported	○○○	ginger
[24] RCT	62 women, 7–17 weeks' gestation	**Mean change from baseline in nausea score assessed by 10 cm visual analogue scale (0 = no nausea, 10 = severe nausea) , over 4 days** 2.57 with ginger powder in biscuit, 5 biscuits per day for 4 days 1.39 with placebo biscuits, 5 biscuits per day for 4 days Ginger group, n = 32; placebo group, n = 30	P = 0.01		ginger
[12] Systematic review	67 women, mean gestational age 13±3 weeks Data from 1 RCT	**Improvement in nausea intensity assessed by visual analogue scale (0 = absence of nausea, 10 = most severe condition of nausea) , 4 days** 27/32 (84%) with ginger capsule taken 4 times daily for 4 days 20/35 (56%) with placebo taken 4 times daily for 4 days	RR 1.48 95% CI 1.07 to 2.04 P = 0.018	●○○	ginger

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[29] RCT	70 women, less than or equal to 17 weeks' gestation In review [12] [22]	**Proportion of women with vomiting , 4 days** 12/32 (38%) with ginger in oral capsules taken 4 times daily 23/35 (66%) with placebo	RR 0.57 95% CI 0.34 to 0.95 NNT 4 95% CI 2 to 12	●○○	ginger
[12] Systematic review	26 women, gestational age 7–11 weeks Data from 1 RCT	**Proportion of women who continued vomiting , 6 days** 4/12 (33%) with ginger 8/10 (80%) with placebo	RR 0.42 95% CI 0.18 to 0.98 P = 0.046	●●○	ginger
[27] RCT	99 women, mean gestational age of 9 weeks In review [12] [22]	**Retching , day 1–day 2** with ginger in oral capsules taken 4 times daily for 4 days with placebo taken 4 times daily for 4 days Absolute results not reported	Reported as significant P value not reported	○○○	ginger
[27] RCT	99 women, mean gestational age of 9 weeks In review [12] [22]	**Vomiting , day 1–day 4** with ginger in oral capsules taken 4 times daily for 4 days with placebo taken 4 times daily for 4 days Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[24] RCT	62 women, 7–17 weeks' gestation	**Mean change from baseline in number of vomiting episodes , over 4 days of treatment** 0.96 with ginger powder in biscuit, 5 biscuits per day for 4 days 0.62 with placebo biscuits, 5 biscuits per day for 4 days Ginger group, n = 32; placebo group, n = 30	P = 0.243	⟷	Not significant
[28] RCT	67 women, mean gestational age 13±3 weeks In review [12]	**Decrease in vomiting frequency , 4 days** 50% with ginger capsule 4 times daily for 4 days 9% with placebo taken 4 times daily for 4 days Absolute numbers not reported	P <0.05		ginger
Nausea and vomiting (composite)					
[25] RCT **3-armed trial**	68 women, mean gestational age ranged from 9.5–10.3 weeks The remaining arm assessed metoclopramide	**Mean Rhodes Index , baseline and over 4 days of treatment** with ginger essence 3 times daily for 5 days with placebo 3 times daily for 5 days	P = 0.004 P value represents between group comparison for intensity of change in nausea and vomiting		ginger
Symptom improvement					
[29] RCT	70 women, less than or equal to 17 weeks' gestation In review [12] [22]	**Proportion of women with improved symptoms (non-specifically described) , 7 days** 28/32 (88%) with ginger in oral capsules taken 4 times daily 10/35 (29%) with placebo	RR 0.18 95% CI 0.07 to 0.45	●●●	ginger

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[24] RCT	62 women, 7–17 weeks' gestation	**Proportion of women reporting improvement of symptoms (Likert scale better or much better responses) , 4 days** 28/32 (88%) with ginger powder in biscuit, 5 biscuits per day for 4 days 21/30 (70%) with placebo biscuits, 5 biscuits per day for 4 days Remaining individuals reported no change in symptoms: n = 4 in ginger group *v* n = 9 in placebo group	P = 0.043		ginger

Maternal mortality

No data from the following reference on this outcome. [12] [22] [24] [25]

Hospital admission/readmission rates

No data from the following reference on this outcome. [12] [22] [24] [25]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] [22] Systematic review	70 women, less than or equal to 17 weeks' gestation Data from 1 RCT	**Spontaneous abortions** 1/32 (3%) with ginger 3/38 (9%) with placebo	P = 0.4 RCT may have been too small to detect a clinically important difference.	⟷	Not significant
[26] RCT	26 women, <13 weeks' gestation In review [22]	**Adverse effects** with ginger syrup (taken 4 times daily) with placebo The RCT identified by the review found no adverse effects associated with ginger			
[27] RCT	120 women, 5.5–18.0 weeks' gestation In review [22]	**Adverse effects** with ginger in oral capsules taken 4 times daily with placebo The RCT found that the most serious adverse effect was heartburn and reflux (no data reported to establish a comparison between groups)			

Ginger versus metoclopramide:

We found one RCT that compared ginger with metoclopramide. [25]

Severity of nausea and vomiting

Ginger compared with metoclopramide We don't know whether ginger is more effective than metoclopramide at reducing nausea and vomiting in women in early pregnancy as we found insufficient evidence from one small RCT (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea and vomiting (composite)					
[25] RCT **3-armed trial**	68 women, mean gestational age ranged from 9.5–10 weeks The remaining arm evaluated placebo	**Mean Rhodes Index , baseline and over 4 days of treatment** with ginger essence 3 times daily for 5 days with metoclopramide 3 times daily for 5 days	P = 0.509 P value represents between group comparison for intensity of change for nausea and vomiting	⟷	Not significant

Maternal mortality

No data from the following reference on this outcome. [25]

Hospital admission/readmission rates

No data from the following reference on this outcome. [25]

Adverse effects

No data from the following reference on this outcome. [25]

Ginger versus pyridoxine (vitamin B_6):

We found one systematic review (search date 2010 [12]).

Severity of nausea and vomiting

Ginger compared with pyridoxine We don't know whether ginger and pyridoxine differ in effectiveness at reducing nausea and vomiting (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[12] Systematic review	251 women, less than or equal to 16 weeks' gestation 2 RCTs in this analysis	**Mean nausea vomiting score assessed by Rhodes Index or 10 cm visual analogue scale , day 3** with ginger with vitamin B6	SMD 0.00 95% CI –0.25 to +0.25 P = 0.99	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[12] Systematic review	128 women, less than or equal to 16 weeks' gestation Data from 1 RCT	**Mean number of vomiting episodes , day 3** 1.1 with oral ginger capsules, taken 3 times daily for 3 days 1.1 with vitamin B6 capsule, taken 3 times daily for 3 days	MD 0.00 95% CI –0.60 to +0.60 P = 0.10	⟷	Not significant
Symptoms (includes composite of nausea and vomiting)					
[12] Systematic review	360 women, less than or equal to 17 weeks' gestation 2 RCTs in this analysis	**No improvement in symptoms** 84/181 (46%) with ginger 87/179 (49%) with vitamin B6	RR 0.84 95% CI 0.47 to 1.52 P = 0.57	⟷	Not significant

Maternal mortality

No data from the following reference on this outcome. [12]

Hospital admission/readmission rates

No data from the following reference on this outcome. [12]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] Systematic review	360 women, less than or equal to 17 weeks' gestation 2 RCTs in this analysis	**Spontaneous abortion** 5/181 (3%) with ginger 10/179 (6%) with vitamin B6	RR 0.49 95% CI 0.17 to 1.42 P = 0.19	⟷	Not significant
[12] Systematic review	146 women Data from 1 RCT	**Stillbirth** 0/146 (0%) with ginger 3/145 (2%) with vitamin B6	RR 0.14 95% CI 0.01 to 2.72 P = 0.20	⟷	Not significant
[12] Systematic review	146 women Data from 1 RCT	**Congenital abnormality** 3/146 (2%) with ginger 6/145 (4%) with vitamin B6	RR 0.50 95% CI 0.13 to 1.95 P = 0.32	⟷	Not significant

Further information on studies

[29] The ginger used in the RCT was derived from fresh ginger roots and given in capsules. The authors of the RCT warn that different preparations of ginger may have different potencies and therefore different magnitudes of effects. The active ingredient that improves nausea and vomiting has not been isolated.

Comment: A review of the literature on the effects of ginger reported that ginger may cause heartburn and may be a gastric irritant (in quantities >6 g). In addition, inhalation of ginger dust may lead to immunoglobulin E-mediated allergy. [30]

OPTION PYRIDOXINE (VITAMIN B6) FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 34 .
- Pyridoxine may be more effective than placebo at reducing nausea, but we don't know about vomiting, and evidence was weak.
- Pyridoxine may be as effective as ginger in reducing nausea and vomiting, although evidence was limited.
- We don't know how pyridoxine and acupressure compare at reducing nausea or vomiting as we found insufficient evidence.

Benefits and harms

Pyridoxine (vitamin B_6) versus placebo:

We found two systematic reviews (search dates 1998 [21] and 2010 [12]). Two RCTs were common to both reviews.

Severity of nausea and vomiting

Pyridoxine compared with placebo Pyridoxine may be more effective than placebo at reducing nausea, but we don't know about vomiting or about reducing subjectively defined failure rates (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[12] Systematic review	395 women 2 RCTs in this analysis	**Mean change in nausea scores** 3 with pyridoxine 2.1 with placebo	MD 0.92 95% CI 0.40 to 1.44 P = 0.00049 The method of randomisation was unclear in 1 RCT	○○○	pyridoxine
Vomiting					
[12] Systematic review	392 women 2 RCTs in this analysis	**Number of patients with emesis post-therapy , 3 days** 69/199 (35%) with vitamin B6 71/193 (37%) with placebo	RR 0.76 95% CI 0.35 to 1.66 P = 0.50 Heterogeneity: I^2 = 77%	⟷	Not significant
Failure rate					
[21] Systematic review	949 women 3 RCTs in this analysis	**Failure rates** 145/579 (25%) with pyridoxine 106/370 (29%) with placebo 'Failure rates' in 2 RCTs were defined in subjective ways and included failure to achieve resolution or a clinically important improvement in symptoms	RR 0.97 95% CI 0.78 to 1.20 The method of randomisation was unclear in 1 RCT	⟷	Not significant

Maternal mortality

No data from the following reference on this outcome. [12] [21]

Hospital admission/readmission rates

No data from the following reference on this outcome. [12] [21]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] Systematic review	1369 women Data from 1 cohort study	**Major fetal malformations** 18/458 (4%) with pyridoxine 34/911 (4%) with placebo	RR 1.05 95% CI 0.60 to 1.84	⟷	Not significant

No data from the following reference on this outcome. [12]

Pyridoxine (vitamin B_6) versus acupressure:
See option on acupressure, p 3 .

Pyridoxine (vitamin B_6) versus ginger:
See option on ginger, p 9 .

Comment: None.

OPTION ACUPUNCTURE FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 34 .
- We don't know whether acupuncture is more effective than sham acupuncture at reducing nausea and vomiting.

Benefits and harms

Acupuncture compared with sham acupuncture or no treatment:
We found two systematic reviews (search date 2010, [12] and search date 2005 [13]). The first systematic review examined the effects of acupressure and acupuncture in treating nausea or vomiting in early pregnancy, and identified two RCTs comparing acupuncture versus sham acupuncture or no treatment. [12] The second systematic review examined the effects of acupressure, acupuncture, and electrical stimulation, and identified two RCTs comparing acupuncture versus control (no treatment) in treating nausea or vomiting in early pregnancy. [13] Two RCTs were identified by both reviews. [31] [32] We report the results of these RCTs separately, see the Further information on studies and Comment sections.

Severity of nausea and vomiting

Acupuncture compared with sham acupuncture or no treatment We don't know whether acupuncture is more effective at reducing nausea and retching in early pregnancy (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[31] RCT **4-armed trial**	593 women with nausea and vomiting in early pregnancy In review [12] [13] The remaining arms evaluated weekly PC6 acupuncture and weekly 8 sham acupuncture, both for 4 weeks	**Improvement in nausea , 1 week** 13/135 (10%) with weekly traditional acupuncture for 4 weeks 4/127 (3%) with no acupuncture for 4 weeks Result between the 2 groups was significant after 1 week of treatment	RR 0.93 95% CI 0.88 to 0.99 See further information on studies for details on possible placebo effect However, the review [12] reanalysed the results at 7 days (see further information on studies)	●○○	traditional acupuncture
[31] RCT **4-armed trial**	593 women with nausea and vomiting in early pregnancy In review [12] [13] The remaining arms evaluated weekly traditional acupuncture and weekly 8 sham acupuncture, both for 4 weeks	**Improvement in nausea , 2 weeks** with weekly PC6 acupuncture for 4 weeks with no acupuncture for 4 weeks Absolute results not reported Result between the 2 groups was significant after 2 weeks of treatment	P <0.05 for PC6 acupuncture *v* no acupuncture See further information on studies for details on possible placebo effect However, the review [12] reanalysed the results at 7 days (see further information on studies)	○○○	PC6 acupuncture
[32] RCT	55 women, 6–10 weeks' gestation In review [12] [13]	**Proportion of women who reported nausea** with multisite acupuncture with sham acupuncture Absolute numbers not reported	P = 0.9	⟷	Not significant
Vomiting					
[31] RCT **4-armed trial**	593 women with nausea and vomiting in early pregnancy In review [12] [13] The remaining arms evaluated weekly traditional acupuncture and weekly 8 sham acupuncture, both for 4 weeks	**Dry retching** with weekly PC6 acupuncture for 4 weeks with no acupuncture for 4 weeks	P <0.001 See further information on studies for details on possible placebo effect However, the review [12] reanalysed the results at 7 days (see further information on studies)	○○○	PC6 acupuncture

Maternal mortality

No data from the following reference on this outcome. [12] [31] [32]

Hospital admission/readmission rates

No data from the following reference on this outcome. [12] [31] [32]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[34] RCT **4-armed trial**	593 women with nausea and vomiting in early pregnancy Further report of reference [31]	**Perinatal outcome, congenital abnormalities, pregnancy complications, or other infant outcomes** with weekly traditional acupuncture for 4 weeks with weekly PC6 acupuncture for 4 weeks with weekly 8 sham acupuncture for 4 weeks with no acupuncture for 4 weeks The follow-up study found no differences between study groups in perinatal outcome, congenital abnormalities, pregnancy complications, or other infant outcomes			

No data from the following reference on this outcome. [32]

Further information on studies

[31] The RCT noted a significant improvement in nausea in all groups receiving an intervention (traditional acupuncture, PC6 acupuncture, or sham acupuncture), which makes it difficult to establish whether the results for this RCT were influenced by a placebo effect. The RCT reported that sham acupuncture significantly improved nausea and dry retching compared with no acupuncture after three weeks (P <0.01). Results between the two groups were significant after three weeks of treatment.

[12] The review re-analysed data from the RCT. It found no significant difference between traditional acupuncture and placebo in mean dry retching score or mean vomiting score on day 7. It also found no significant difference between P6 acupuncture and placebo in mean nausea score, mean dry retching score, and mean vomiting score on day 7.

Comment: The second systematic review compared three different types of acustimulation (acupressure, acupuncture, and electrical stimulation). The acupuncture intervention did not reduce nausea. It may not be acceptable for studies to compare interventions as varied as these. The number of acupuncture trials is limited for pregnant women, perhaps because it is impossible to self-administer acupuncture, and acupuncture may also be inconvenient for women experiencing chronic symptoms of nausea and vomiting. The review reported inconsistencies in frequencies of acupuncture, which varied from three times daily for two days to once weekly for four weeks. [13]

OPTION METOCLOPRAMIDE FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 34 .
- Metoclopramide may reduce nausea and vomiting compared with placebo for women in early pregnancy. However, evidence was weak.
- We don't know how metoclopramide and ginger compare as we found insufficient evidence from one small RCT.

Benefits and harms

Metoclopramide compared with placebo:

We found one RCT (68 women) comparing metoclopramide with placebo. [25]

Severity of nausea and vomiting

Metoclopramide compared with placebo Metoclopramide may reduce nausea and vomiting for women in early pregnancy. However, evidence was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea and vomiting (composite)					
[25] RCT **3-armed trial**	68 women, mean gestational age ranged from 9.5–10 weeks The remaining arm evaluated ginger essence	**Intensity of change of Mean Rhodes Index , baseline and over 4 days of treatment** with metoclopramide 3 times daily for 5 days with placebo 3 times daily for 5 days The study reported mean for all study points days 1–5, but only reported the P value demonstrating the significant difference in the trend of change in nausea and vomiting between the 2 groups	P = 0.025 Method of randomisation unclear		metoclopramide

Maternal mortality

No data from the following reference on this outcome. [25]

Hospital admission/readmission rates

No data from the following reference on this outcome. [25]

Adverse effects

No data from the following reference on this outcome. [25]

Metoclopramide compared with ginger:

See option on ginger, p 28 .

Comment: Studies of the teratogenic potential of metoclopramide are limited. One review of the safety of drugs for the treatment of nausea and vomiting reported no malformations among four first-trimester exposures to metoclopramide. [21] [35] The risk of tardive dyskinesia associated with long-term or high-dose use of metoclopramide has been highlighted by the FDA (http://www.fda.gov).

Clinical guide:
Metoclopramide is commonly used in clinical practice in some countries, but clinical trials are needed to evaluate its effect on nausea and vomiting in pregnancy fully.

OPTION PROCHLORPERAZINE FOR TREATING NAUSEA AND VOMITING IN EARLY PREGNANCY

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 34 .
- We don't know whether prochlorperazine reduces nausea or vomiting as we found no RCTs.
- We don't know how prochlorperazine and promethazine compare as we found insufficient evidence.

Benefits and harms

Prochlorperazine versus placebo:

We found one systematic review (search date 2010; 2 RCTs, 300 women). [12] Neither of the RCTs fulfilled the inclusion criteria for this *Clinical Evidence* review, so are not reported here.

Prochlorperazine versus promethazine:

We found one systematic review (search date 2010), [12] which included one relevant RCT. [36]

Severity of nausea and vomiting

Prochlorperazine compared with promethazine We don't know how prochlorperazine and promethazine compare at reducing nausea and vomiting (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[36] RCT **3-armed trial**	102 outpatient women in the first trimester of a singleton pregnancy In review [12] The remaining arm evaluated pyridoxine (intramuscularly) plus metoclopramide (orally every 6 hours)	**Mean number of emesis episodes , 3 days** 1.1 with prochlorperazine 0.8 with promethazine Prochlorperazine group, n = 50; promethazine group, n = 52	Significance not assessed		
Symptoms (global)					
[36] RCT **3-armed trial**	102 outpatient women in the first trimester of a singleton pregnancy In review [12] The remaining arm evaluated pyridoxine plus metoclopramide	**Proportion of women reporting no improvement or worsening of symptoms (5-point scale ranging from 'much worse' to 'much better') , 3 days** About 60% with prochlorperazine About 60% with promethazine Absolute results reported graphically Prochlorperazine group, n = 50; promethazine group, n = 52	Significance not assessed		

Maternal mortality

No data from the following reference on this outcome. [36]

Hospital admission/readmission rates

No data from the following reference on this outcome. [36]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[36] RCT **3-armed trial**	102 outpatient women in the first trimester of a singleton pregnancy In review [12] The remaining arm evaluated pyridoxine plus metoclopramide	**Neonatal anomaly** 1/50 (2%) with prochlorperazine 0/52 (0%) with promethazine The neonatal anomaly in the prochlorperazine group was ventricular septal defect			

Comment: None.

QUESTION What are the effects of treatments for hyperemesis gravidarum?

OPTION ACUPRESSURE FOR TREATING HYPEREMESIS GRAVIDARUM

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 34 .
- We found evidence from one small RCT that acupressure may be more effective than placebo at reducing nausea and vomiting. However, evidence was weak.

Benefits and harms

Acupressure versus placebo or control:

We found three systematic reviews (search dates 2005, [13] 2010, [14] and 2008 [15]) examining the effects of acupressure, acupuncture, and electrical stimulation in women with nausea and vomiting during pregnancy. The first review identified one RCT for acupressure in women with hyperemesis, but pooled data for a mixed population of women with nausea and vomiting and women with hyperemesis; hence it is not discussed further. [13] The second and third reviews both identified the same RCT, [37] which is reported here.

Severity of nausea and vomiting

Acupressure compared with placebo or control P6 acupressure may be more effective at reducing nausea and vomiting in women with hyperemesis gravidarum. However, evidence was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea and vomiting					
[37] RCT **3-armed trial**	66 women diagnosed with hyperemesis gravidarum; gestational age range 5–30 weeks	**Mean nausea and vomiting scores (assessed using modified form of full Rhodes Index score) , third day after admission** 17.57 with acupressure at the Neiguan point (P6) applied using	P = 0.014 for among-group difference See further information on studies for data on placebo *v* control Weak methods (see further information on studies)		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	23 people with acupressure 21 people with placebo 22 people with control	the thumb for 10 minutes 3 times daily for 5–7 days 22.05 with placebo (acupressure applied around the radial pulse at the wrist) for 5–7 days 21.59 with control for 5–7 days All 3 groups also received conventional IV fluid therapy See further information on studies for details of Rhodes Index score and baseline differences among patients			
[37] RCT **3-armed trial**	66 women diagnosed with hyperemesis gravidarum; gestational age range 5–30 weeks 23 people with acupressure 21 people with placebo 22 people with control	**Mean nausea and vomiting scores , fourth day after admission** 12.48 with acupressure at the Neiguan point (P6) applied using the thumb for 10 minutes 3 times daily for 5–7 days 19.38 with placebo (acupressure applied around the radial pulse at the wrist) for 5–7 days 17.91 with control for 5–7 days All 3 groups also received conventional IV fluid therapy See further information on studies for details of Rhodes Index score and baseline differences among patients	P <0.001 for among-group difference See further information on studies for data on placebo *v* control Weak methods (see further information on studies)		
[37] RCT **3-armed trial**	66 women diagnosed with hyperemesis gravidarum; gestational age range 5–30 weeks 23 people with acupressure 21 people with placebo 22 people with control	**Mean nausea and vomiting scores , day of discharge** 9.22 with acupressure at the Neiguan point (P6) applied using the thumb for 10 minutes 3 times daily for 5–7 days 14.67 with placebo (acupressure applied around the radial pulse at the wrist) for 5–7 days 13.05 with control for 5–7 days All 3 groups also received conventional IV fluid therapy See further information on studies for details of Rhodes Index score and baseline differences among patients	P <0.001 for among-group difference See further information on studies for data on placebo *v* control Weak methods (see further information on studies)		
[37] RCT **3-armed trial**	66 women diagnosed with hyperemesis gravidarum; gestational age range 5–30 weeks 23 people with acupressure 21 people with placebo	**Nausea and vomiting** with acupressure with placebo	P <0.001 Absolute values not reported Unclear which data these results are based on		Acupressure
[37] RCT **3-armed trial**	66 women diagnosed with hyperemesis gravidarum; gestational age range 5–30 weeks	**Nausea and vomiting** with acupressure with control	P = 0.002 Absolute values not reported Unclear which data these results are based on		Acupressure

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	23 people with acupressure 22 people with control				

Maternal mortality

No data from the following reference on this outcome. [37]

Hospital admission/readmission rates

No data from the following reference on this outcome. [37]

Adverse effects

No data from the following reference on this outcome. [37]

Further information on studies

[37] Nausea and vomiting were assessed using a modified form of the full Rhodes Index score (6 physical symptoms of Rhodes score: frequency of nausea and vomiting, amount of vomitus, duration of nausea, and degree of discomfort caused by nausea and vomiting measured on a scale ranging from 6 [lowest = slight nausea] to 30 [highest = severe nausea and vomiting]). The RCT reported no significant difference in mean nausea and vomiting scores among the three groups on the day of admission (mean nausea and vomiting scores: 26.26 with acupressure *v* 26.24 with placebo *v* 25.86 with control; P = 0.901 for all groups). However, the RCT found no significant difference in nausea and vomiting scores between the placebo and control groups (P = 0.802). The study also reported no significant difference in the levels of ketonuria among the three groups on discharge (P = 0.063, absolute numbers not reported); however, levels of ketonuria were controlled more quickly in the P6 acupressure group compared with placebo or control groups during hospital stay.

[37] The RCT reported that coin tossing was used to assign people to groups, but further details were not reported on how this was done for three groups. Also, each group was warded on a different floor which may have introduced bias.

Comment: Conducting high-quality trials in this area is complicated, as interventions are difficult to mask and control with credible or appropriate placebos.

OPTION ACUPUNCTURE FOR TREATING HYPEREMESIS GRAVIDARUM

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 34 .
- We don't know whether acupuncture is effective in treating hyperemesis gravidarum as we found insufficient evidence from one small RCT.

Benefits and harms

Acupuncture versus sham acupuncture:

We found one crossover RCT comparing PC6 acupuncture versus sham acupuncture. [38]

Severity of nausea and vomiting

Acupuncture compared with sham acupuncture PC6 acupuncture may be more effective at reducing nausea and vomiting in women with hyperemesis gravidarum. However, evidence was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[38] RCT **Crossover design**	40 women admitted to hospital with vomiting (all women were vomiting on the day of randomisation); gestational age range 6–16 weeks	**Time to resolution of nausea** with PC6 acupuncture (applied 5 mm beneath the skin on the lateral side of the forearm) with sham acupuncture (applied 1–2 mm beneath the skin on the lateral side of the forearm) Treatments were given 3 times daily for 30 minutes on days 1 and 2, and days 5 and 6 (after crossover) See further information on studies for data on food intake and need for IV fluids	P = 0.032 VAS estimate for nausea different between groups at baseline (P = 0.009). Hence, only speed of resolution calculated Post crossover result Results presented graphically	◌◌◌	PC6 acupuncture
Vomiting					
[38] RCT **Crossover design**	40 women admitted to hospital with vomiting (all women were vomiting on the day of randomisation); gestational age range 6–16 weeks	**Proportion of women who vomited , day 4** 7/17 (41%) with PC6 acupuncture (applied 5 mm beneath the skin on the lateral side of the forearm) 12/16 (75%) with sham acupuncture (applied 1–2 mm beneath the skin on the lateral side of the forearm) Treatments were given 3 times daily for 30 minutes on days 1 and 2, and days 5 and 6 (after crossover) See further information on studies for data on food intake and need for IV fluids	P = 0.049 Result of borderline significance 7/40 (17%) not included in analysis	◌◌◌	PC6 acupuncture

Maternal mortality

No data from the following reference on this outcome. [38]

Hospital admission/readmission rates

No data from the following reference on this outcome. [38]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[38] RCT **Crossover design**	40 women admitted to hospital with vomiting (all women were vomiting on the day of randomisation); gestational age range 6–16 weeks	**Adverse effects** with PC6 acupuncture (applied 5 mm beneath the skin on the lateral side of the forearm) with sham acupuncture (applied 1–2 mm beneath the skin on the lateral side of the forearm) The RCT found no adverse effects associated with acupuncture in any women during the study			

Further information on studies

[38] The RCT found no significant differences between groups with regard to food intake and the need for intravenous fluids (reported as not significant; significance assessments not performed).

Comment: The placebo treatment (sham acupuncture) used in the RCT was superficial acupuncture on an area away from a 'real' acupuncture point. Needles were inserted only 1–2 mm into the skin. The authors of the RCT state that this kind of stimulation minimises the specific effects of acupuncture. [38] However, it may not be an entirely inert placebo, as some sensory stimulation does occur.

OPTION CORTICOSTEROIDS FOR TREATING HYPEREMESIS GRAVIDARUM

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 34 .
- We don't know whether corticosteroids are more effective than placebo in treating hyperemesis gravidarum.
- Hydrocortisone may be more effective than metoclopramide at reducing vomiting episodes and reducing readmission to the intensive care unit in women with hyperemesis gravidarum.

Benefits and harms

Corticosteroids versus placebo:

We found two systematic reviews (search dates 1998 [21] and 2002), [12] which identified one RCT. [39] We found one subsequent RCT. [40]

Severity of nausea and vomiting

Corticosteroids compared with placebo We don't know whether corticosteroids are more effective than placebo at reducing persistent vomiting in women with hyperemesis gravidarum (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[39] RCT	25 women with severe hyperemesis, mean gestational age of 10.6 weeks for prednisolone and 8.3 weeks for placebo In review [21] [12]	**Persistent vomiting** 5/12 (42%) with oral prednisolone twice daily for 1 week 7/12 (58%) with placebo for 1 week	RR 0.71 95% CI 0.31 to 1.63 The RCT may have been too small to detect a clinically important effect	⟷	Not significant

No data from the following reference on this outcome. [40]

Hospital admission/readmission rates

Corticosteroids compared with placebo We don't know whether corticosteroids are more effective than placebo at reducing hospital readmission rates in women with persistent vomiting (low-quality evidence)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission/readmission rates					
[39] RCT	25 women with severe hyperemesis, mean gestational age of 10.6 weeks for prednisolone and 8.3 weeks for placebo In review [21] [12]	**Readmission to hospital** 5/12 (42%) with oral prednisolone twice daily for 1 week 8/12 (67%) with placebo for 1 week	RR 0.63 95% CI 0.29 to 1.36 The RCT may have been too small to detect a clinically important effect	⟷	Not significant
[40] RCT	126 women, <20 weeks' gestation	**Number of women requiring readmission to hospital for hyperemesis gravidarum** 19/56 (34%) with intravenous methylprednisolone followed by an oral prednisolone taper 19/54 (35%) with placebo (for the same regimen) All women also received promethazine and metoclopramide intravenously every 6 hours for 24 hours, followed by the same regimen given orally as needed until discharge	P = 0.89	⟷	Not significant

Maternal mortality

No data from the following reference on this outcome. [39] [40]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] Systematic review	109,602 women 8 controlled observational studies in this analysis	**Teratogenicity** with corticosteroids with control	RR 1.24 95% CI 0.97 to 1.60	⟷	Not significant
[40] RCT	126 women, <20 weeks' gestation	**Pregnancy complications** with intravenous methylprednisolone followed by an oral prednisolone taper with placebo for the same regimen All women also received promethazine and metoclopramide intravenously every 6 hours for 24 hours, followed by the same regimen given orally as needed until discharge	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [39]

Corticosteroids versus metoclopramide:

We found one RCT. [41]

Severity of nausea and vomiting

Corticosteroids compared with metoclopramide Hydrocortisone may be more effective than metoclopramide at reducing vomiting episodes in women with hyperemesis gravidarum (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[41] RCT	40 women with intractable hyperemesis gravidarum admitted to intensive care at <16 weeks' gestation	**Reduction of mean number of vomiting episodes , day 2** 41% with intravenous hydrocortisone for 1 week 17% with intravenous metoclopramide for 1 week	P <0.0001	○○○	hydrocortisone
[41] RCT	40 women with intractable hyperemesis gravidarum admitted to intensive care at <16 weeks' gestation	**Reduction of mean number of vomiting episodes , day 3** 72% with intravenous hydrocortisone for 1 week 51% with intravenous metoclopramide for 1 week	P <0.0001	○○○	hydrocortisone
[41] RCT	40 women with intractable hyperemesis gravidarum admitted to intensive care at <16 weeks' gestation	**Reduction of mean number of vomiting episodes , day 7** 96% with intravenous hydrocortisone for 1 week 77% with intravenous metoclopramide for 1 week	P <0.0001	○○○	hydrocortisone

Maternal mortality

No data from the following reference on this outcome. [41]

Hospital admission/readmission rates

Corticosteroids compared with metoclopramide Corticosteroids may be more effective than metoclopramide at reducing rates of readmission to the intensive care unit within 2 weeks of initial therapy in women with recurrent severe persistent vomiting (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission/readmission rates					
[41] RCT	40 women with intractable hyperemesis gravidarum admitted to intensive care at <16 weeks' gestation	**Proportion of women readmitted to the intensive care unit for recurrence of severe persistent vomiting , within 2 weeks of initial treatment** 0/20 (0%) with intravenous hydrocortisone for 1 week 6/20 (30%) with intravenous metoclopramide for 1 week	P <0.0001	○○○	hydrocortisone

Adverse effects

No data from the following reference on this outcome. [41]

Further information on studies

Comment: **Clinical guide:**
The rates of spontaneous resolution of symptoms in control groups were high. The possible benefit of methylprednisolone in preventing subsequent admission to hospital must be balanced against possible adverse effects of steroids given in the first trimester of pregnancy. Clinical judgement would be more important in specific situations as there are no reports of adverse effects; however, these may be rare but serious.

OPTION GINGER FOR TREATING HYPEREMESIS GRAVIDARUM

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 34 .
- We don't know whether ginger is effective in treating hyperemesis gravidarum.

Benefits and harms

Ginger versus placebo:

We found two systematic reviews (search dates 2002 [12] and 2004 [22]). Both reviews identified the same crossover RCT. [42]

Severity of nausea and vomiting

Ginger compared with placebo We don't know whether ginger is more effective than placebo at reducing hyperemesis scores at 4 days in women with hyperemesis gravidarum (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hyperemesis gravidarum					
[42] RCT **Crossover design**	30 women admitted to hospital with hyperemesis gravidarum In review [12] [22]	**Hyperemesis score (evaluates degree of nausea and vomiting, weight gain, and participant-reported symptom relief; higher score indicates fewer symptoms) , after 4 days (before crossover)** 4.1 with ginger in oral capsules taken 4 times daily 0.9 with placebo 27 women included in the analysis	P = 0.035 in RCT WMD +3.15 95% CI –0.92 to +7.22 (as calculated by review [12]) The RCT was too small to allow reliable conclusions		

Maternal mortality

No data from the following reference on this outcome. [42]

Hospital admission/readmission rates

No data from the following reference on this outcome. [42]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[42] RCT **Crossover design**	30 women admitted to hospital with hyperemesis gravidarum, 27 women included in the analysis In review [12] [22]	**Adverse effects** with ginger in oral capsules taken 4 times daily with placebo The RCT reported no adverse effects associated with ginger			

Comment: None.

OPTION METOCLOPRAMIDE FOR TREATING HYPEREMESIS GRAVIDARUM

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 34 .
- We don't know whether metoclopramide is effective in treating hyperemesis gravidarum compared with placebo, as we found no RCTs.
- Metoclopramide may be less effective than hydrocortisone at reducing vomiting episodes and reducing readmission to the intensive care unit in women with hyperemesis gravidarum.

Benefits and harms

Metoclopramide versus placebo:

We found no systematic review or RCTs.

Metoclopramide versus corticosteroids:

See option on corticosteroids, p 25 .

Metoclopramide versus ondansetron:

See option on ondansetron, p 30 .

Further information on studies

Comment: Studies of the teratogenic potential of metoclopramide are limited. One review of the safety of drugs for the treatment of nausea and vomiting reported no malformations among four first-trimester exposures to metoclopramide. [21] [35] The risk of tardive dyskinesia associated with long-term or high-dose use of metoclopramide has been highlighted by the FDA (http://www.fda.gov).

Clinical guide:
Metoclopramide is commonly used in clinical practice in some countries, but clinical trials are needed to fully evaluate its effects on nausea and vomiting in pregnancy.

OPTION ONDANSETRON FOR TREATING HYPEREMESIS GRAVIDARUM

- For GRADE evaluation of interventions for Nausea and vomiting in early pregnancy, see table, p 34 .
- We don't know whether ondansetron is effective in treating hyperemesis gravidarum.

Benefits and harms

Ondansetron versus placebo:

We found no systematic review or RCTs.

Ondansetron versus metoclopramide:

We found one RCT. [43]

Severity of nausea and vomiting

Ondansetron compared with metoclopramide We don't know whether ondansetron is more effective at reducing nausea and vomiting during treatment or post treatment in women with hyperemesis gravidarum (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[43] RCT	83 pregnant women with hyperemesis gravidarum, gestational age <16 weeks	**Mean nausea score assessed on a visual analogue scale (0 = no nausea, 10 = severe nausea) , day 1 during treatment** 6.8 with ondansetron hydrochloride, 3 times daily in week 1, stepped reduction in dose during week 2 7.4 with metoclopramide, 3 times daily in week 1, stepped reduction in dose during week 2	P = 0.39 The RCT found inconsistent results on different time points (see further information about studies)	⟷	Not significant
[43] RCT	83 pregnant women with hyperemesis gravidarum, gestational age <16 weeks	**Mean nausea score assessed on a visual analogue scale (0 = no nausea, 10 = severe nausea) , day 3 during treatment** 5.4 with ondansetron hydrochloride, 3 times daily in week 1, stepped reduction in dose during week 2 6.0 with metoclopramide, 3 times daily in week 1, stepped reduction in dose during week 2	P = 0.024 The RCT found inconsistent results on different time points (see further information about studies)		ondansetron
[43] RCT	83 pregnant women with hyperemesis gravidarum, gestational age <16 weeks	**Mean nausea score assessed on a visual analogue scale (0 = no nausea, 10 = severe nausea) , day 7 during treatment** 3.7 with ondansetron hydrochloride, 3 times daily in week 1,	P = 0.25 The RCT found inconsistent results on different time points (see further information about studies)	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		stepped reduction in dose during week 2 4.3 with metoclopramide, 3 times daily in week 1, stepped reduction in dose during week 2			
Vomiting					
[43] RCT	83 pregnant women with hyperemesis gravidarum, gestational age <16 weeks	**Mean vomiting score assessed on a visual analogue scale (0 = no nausea, 10 = severe nausea) , day 1 during treatment** 6.7 with ondansetron hydrochloride, 3 times daily in week 1, stepped reduction in dose during week 2 5.1 with metoclopramide, 3 times daily in week 1, stepped reduction in dose during week 2	P = 0.06 The RCT found inconsistent results on different time points (see further information about studies)	⟷	Not significant
[43] RCT	83 pregnant women with hyperemesis gravidarum, gestational age <16 weeks	**Mean vomiting score assessed on a visual analogue scale (0 = no nausea, 10 = severe nausea) , day 3 during treatment** 5.3 with ondansetron hydrochloride, 3 times daily in week 1, stepped reduction in dose during week 2 3.2 with metoclopramide, 3 times daily in week 1, stepped reduction in dose during week 2	P = 0.006 The RCT found inconsistent results on different time points (see further information about studies)		metoclopramide
[43] RCT	83 pregnant women with hyperemesis gravidarum, gestational age <16 weeks	**Mean vomiting score assessed on a visual analogue scale (0 = no nausea, 10 = severe nausea) , day 7 during treatment** 3.7 with ondansetron hydrochloride, 3 times daily in week 1, stepped reduction in dose during week 2 2.7 with metoclopramide, 3 times daily in week 1, stepped reduction in dose during week 2	P = 0.010 The RCT found inconsistent results on different time points (see further information about studies)		metoclopramide

Maternal mortality

No data from the following reference on this outcome. [43]

Hospital admission/readmission rates

No data from the following reference on this outcome. [43]

Further information on studies

[43] The RCT found inconclusive results. For nausea it found a significant benefit with ondansetron at 3 and 4 days, but no significant difference between ondansetron and metoclopramide at days 1, 2, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14. For vomiting it found a significant benefit with metoclopramide at days 2, 3, 4, 5, 6, 7, and 8 but no significant difference between groups at days 1, 9, 10, 11, 12, 13, 14, or 8 and 9 days post treatment cessation.

Comment: None.

GLOSSARY

Acupressure Pressure applied to a specific point of the body. It does not require needles and can be given by patients themselves. Commercial products available include an elastic band to fit around the wrist with a plastic disc to apply pressure at the P6 point.

Hydatidiform mole A condition in which there is abnormal cystic development of the placenta. The uterus is often large for the duration of pregnancy and there may be vaginal bleeding, lack of fetal movement and fetal heart sounds, and severe nausea and vomiting. Rarer, but important, complications include haemorrhage, intrauterine infection, hypertension, and persistent gestational trophoblastic disease, which may infiltrate local tissues or metastasise to distant sites.

Metabolic hypochloraemic alkalosis Excess base alkali in the body fluids caused by chloride loss.

PC6 acupuncture The needle is applied at the PC6 point located near to the wrist crease.

Wernicke's encephalopathy A severe syndrome caused by a deficiency of thiamine (vitamin B1). It is usually associated with excessive alcohol abuse and is characterised by abnormal eye movements, confusion, and loss of short term memory and muscular coordination.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Acupressure for treating nausea and vomiting in early pregnancy: New evidence added. [14] [15] [16] Categorisation unchanged (likely to be beneficial).

Acupuncture for treating nausea and vomiting in early pregnancy: One systematic review updated. [12] Categorisation unchanged (unknown effectiveness).

Ginger for treating nausea and vomiting in early pregnancy: One systematic review updated. [12] New evidence added. [23] [24] [25] Categorisation unchanged (likely to be beneficial).

Metoclopramide for treating nausea and vomiting in early pregnancy: New evidence added. [25] Categorisation unchanged (unknown effectiveness).

Ondansetron for treating hyperemesis gravidarum: New evidence added. [43] Categorisation unchanged (unknown effectiveness).

Pyridoxine (vitamin B_6) for treating nausea and vomiting in early pregnancy: One systematic review updated. [12] Categorisation unchanged (likely to be beneficial).

Acupressure for treating hyperemesis gravidarum: New evidence added. [14] [15] Categorisation changed from likely to be beneficial to unknown effectiveness.

Prochlorperazine for treating nausea and vomiting in early pregnancy: One systematic review updated. Option restructured from phenothiazines to only include prochlorperazine. Categorisation unchanged (unknown effectiveness).

Promethazine for treating nausea and vomiting in early pregnancy: Previous option on antihistamines restructured to only report promethazine. Existing evidence re-evaluated. Categorised as unknown effectiveness.

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Disclaimer

GRADE **Evaluation of interventions for Nausea and vomiting in early pregnancy.**

Important outcomes	Hospital admission/readmission rates, Maternal mortality, Severity of nausea and vomiting								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatment for nausea and vomiting in early pregnancy?									
4 (335) [16] [17] [18] [19]	Severity of nausea and vomiting	Acupressure versus placebo or control	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting or results; directness points deducted for differences in baseline in 1 RCT and use of co-interventions in 1 RCT
1 (66) [12] [20]	Severity of nausea and vomiting	Acupressure versus pyridoxine (vitamin B_6)	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for use of co-interventions in 1 RCT
6 (340) [12] [22] [24] [25] [27] [28] [29]	Severity of nausea and vomiting	Ginger versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results; directness point deducted for inconsistencies between RCTs (preparations used; outcome measures)
1 (68) [25]	Severity of nausea and vomiting	Ginger versus metoclopramide	2	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
4 (624) [12]	Severity of nausea and vomiting	Ginger versus pyridoxine (vitamin B_6)	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (949) [12] [21]	Severity of nausea and vomiting	Pyridoxine (vitamin B_6) versus placebo	4	–1	–1	–1	0	Very low	Quality point deducted for unclear randomisation; consistency point deducted for statistical heterogeneity; directness point deducted for unclear, subjective outcomes
2 (648) [12] [33] [32]	Severity of nausea and vomiting	Acupuncture compared with sham acupuncture or no treatment	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results; directness point deducted for possible placebo effect
1 (38) [25]	Severity of nausea and vomiting	Metoclopramide compared with placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and unclear randomisation
1 (102) [36]	Severity of nausea and vomiting	Prochlorperazine versus promethazine	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for no statistical analysis between groups
What are the effects of treatments for hyperemesis gravidarum?									
1 (66) [37]	Severity of nausea and vomiting	Acupressure versus placebo or control	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and weak methods
1 (40) [38]	Severity of nausea and vomiting	Acupuncture versus sham acupuncture	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and weak methods
1 (24) [39]	Severity of nausea and vomiting	Corticosteroids versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for small number of events

Important outcomes	Hospital admission/readmission rates, Maternal mortality, Severity of nausea and vomiting								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
2 (150) [39] [40]	Hospital admission/readmission rates	Corticosteroids versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of other interventions
1 (40) [41]	Severity of nausea and vomiting	Corticosteroids versus metoclopramide	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (40) [41]	Hospital admission/readmission rates	Corticosteroids versus metoclopramide	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for small number of events
1 (30) [42]	Severity of nausea and vomiting	Ginger versus placebo	4	–1	0	–2	0	Very low	Quality point deducted for sparse data; directness points deducted for composite outcome and lack of power
1 (83) [43]	Severity of nausea and vomiting	Ondansetron versus metoclopramide	4	–1	0	–1	0	Very low	Quality point deducted for sparse data; directness point deducted for multiple significance testing

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.