Clinical evidence tables for review question: What interventions are effective in treating nausea and vomiting during pregnancy?

Mild to moderate nausea and vomiting

Table5: Clinical evidence tables for mild to moderate nausea and vomiting in pregnancy

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Basirat,Z., Moghadamnia,A.A., Kashifard,M., Sarifi-Razavi,A., The effect of ginger biscuit on nausea and vomiting in early pregnancy, Acta Medica Iranica, 47, 51-56, 2009 **Ref Id** 104406 **Country/ies where the study was carried out** Iran **Study type** Randomised controlled trial. **Aim of the study** To assess the effectiveness of ginger for the treatment of nausea and vomiting in early pregnancy.	**Sample size** N=65 (3 participants did not eat the ginger biscuit and therefore were excluded from the study) Ginger: n=35 (n=32) Placebo: n=30 **Characteristics** Women were matched in terms of age, body mass index, gestational age and parity, but no further details provided. <u>Baseline nausea score - mean ±SD</u> Ginger: 5.88 (1.83) Placebo: 4.67 (1.97) <u>Baseline vomiting episodes - mean ±SD</u> Ginger: 1.63 (1.18) Placebo: 1.3 (1.3) **Inclusion criteria** • Women aged 19 to 35 years;	**Interventions** Ginger: 0.5 g ginger power incorporated in each ginger biscuit. Placebo: Identical looking placebo biscuit. **Details** Women took 5 biscuits daily for 4 days. **Power analysis** Not stated. **Statistical analyses** Mean change in severity of nausea (post-treatment minus baseline) in treatment groups compared using Mann-Whitney *U* test. Mean change in number of vomiting episodes compared between treatment groups using Student t-test. Inter- and intra-group daily comparisons analysed using repeated measure analysis.	**Results** **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy** <u>Change in nausea score - mean ±SD</u> <u>Day 0 to day 1</u> Ginger: 2.03 (1.93) Placebo: 1.03 (0.999); p=0.021 <u>Day 0 to day 2</u> Ginger: 2.34 (2.08) Placebo: 1.43 (1.38); p=0.048 <u>Day 0 to day 3</u> Ginger: 3.06 (1.74) Placebo: 1.47 (2.25); p=0.003 <u>Day 0 to day 4</u> Ginger: 2.84 (2.09) Placebo: 1.63 (2.51); p=0.023 <u>Mean change from day 1 to day 4</u> Ginger: 3.30 (1.80) Placebo: 3.27 (1.84); p=0.99	**Limitations** **<u>Cochrane risk of bias tool V2</u>**: Randomisation process: Low risk of bias. (Random numbers table used. Allocation concealed by treatment codes kept in sequence in a sealed black envelope). Deviations from intended interventions: Low risk of bias. (Participants and personnel both blinded and unaware of treatment). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Low risk of bias. (Low amount of missing data (4%). Reasons were described, unlikely to have produced bias).

Study details	Participants	Interventions	Outcomes and Results	Comments
Study dates 2005 to 2006 **Source of funding** Research Council of Babol University of Medical Sciences.	• Weighing within 20% of normal weight; • At the beginning of pregnancy; within 7 to 17 weeks of gestation. **Exclusion criteria** • Other disease causing vomiting such as thyroid disease, history of gastroenteritis, or gastrointestinal disease, infections; • Multiple pregnancy; • Hyperemesis gravidarum; • Trophoblastic disease; • Psychological disorders; • Women receiving antiemetic agents (for example vitamin B6 or metoclopromide) or drugs enhancing the condition (for example iron tablets) during previous week.	**Interntion-to-treat (ITT) analysis** Not stated.	Mean change - day 0 minus mean day 1 to day 4 Ginger: 2.57 (1.77) Placebo: 1.39 (1.62); p=0.01 Change in vomiting episodes - mean ±SD Day 0 to day 1 Ginger: 0.84 (0.216) Placebo: 0.33 (0.175); p=0.073 Day 0 to day 2 Ginger: 0.94 (0.24) Placebo: 0.67 (0.18); p=0.384 Day 0 to day 3 Ginger: 1.09 (0.22) Placebo: 0.77 (0.28); p=0.367 Day 0 to day 4 Ginger: 0.97 (0.25) Placebo: 0.73 (0.31); p=0.556 Mean change from day 1 to day 4 Ginger: 0.66 (0.17) Placebo: 0.74 (0.21); p=0.78 Mean change - day 0 minus mean day 1 to day 4 Ginger: 0.96 (0.21) Placebo: 0.62 (0.19); p=0.243 Side-effects were considered mild and didn't require hospitalisation (Ginger: 3.12% (1 patient complained of heartburn and 1 patient experienced dizziness; Placebo: 0). No	Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Low risk of bias. (No other biases detected). Overall risk of bias: Low risk

Study details	Participants	Interventions	Outcomes and Results	Comments
			abnormal pregnancy and birth outcomes occurred.	
Full citation Belluomini, J., Litt, R. C., Lee, K. A., Katz, M., Acupressure for nausea and vomiting of pregnancy: a randomized, blinded study, Obstet GynecolObstetrics and gynecology, 84, 245-8, 1994 **Ref Id** 939282 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial. **Aim of the study** To assess the effectiveness of acupressure in the treatment of nausea and vomiting during pregnancy. **Study dates** July 1990 to October 1992. **Source of funding** Supported in part by the Loewy Fund of California Pacific Medical Centre.	**Sample size** Acupressure: N=30 Placebo: N=30 **Characteristics** <u>Maternal age (years) mean ±SD</u> Acupressure: 33.6 (4.3) Placebo: 33.4 (5.3) <u>Gestational age (weeks) - mean ±SD</u> Acupressure: 8.5 (1.4 Placebo: 8.6 (1.4) <u>Fetal number</u> Acupressure: singleton 29; twin 1 Placebo: singleton 29; twin 1 **Inclusion criteria** 1. Women complaining of nausea with or without vomiting 2. Gestational age 12 weeks or less by study completion **Exclusion criteria** 1. Hyperemesis gravidarum (5% weight loss, ketonuria, and proteinuria) 2. Diseases that produce nausea and vomiting, including molar and ectopic pregnancies 3. Current use of antiemetic medications.	**Interventions** Acupressure: pressure point Nei guan, PC-6 (located on anterior surface of the forearm, between the tendons of the flexor carpi radialis and palmaris longus muscles). Placebo: sham pressure point (located on the palmar surface of the hand, proximal to the head of the fifth metacarpal joint). **Details** Women did not receive treatment in the first 3 days, but were then instructed to being acupressure on the morning of the fourth day for 10 minutes 4 times a day for the next 7 days. Women did not receive counselling or nursing contact as part of the study. **Power analysis** Not stated. **Statistical analyses** Between group differences in pre-treatment nausea and vomiting scores and continuous data were analysed using Student *t*-test. Treatment effects over time were analysed using analysis of variance and	**Results** **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy** <u>Rhodes Index total score (range 0-32) - mean ±SD</u> <u>Days 1 to 3 and days 5 to 7</u> Acupressure: 12.64 (5.7)/8.69 (5.0); p≤0.001 Placebo: 11.47 (4.9)/10.03 (4.6); p=0.019 <u>Nausea scores (range 0 to 12) - mean ±SD</u> <u>Days 1 to 3 and days 5 to 7</u> Acupressure: 8.38 (2.2)/5.80 (2.9); p≤0.001 Placebo: 7.99 (2.5)/7.04 (2.6); p≤0.001 <u>Vomiting scores (range 0 to 12) - mean ±SD</u> <u>Days 1 to 3 and days 5 to 7</u> Acupressure: 2.09 (2.5)/1.28 (1.9); p=0.03 Placebo: 1.83 (2.7)/1.63 (2.3) Data from days 8, 9 and 10 showed no statistically significant differences between treatment groups because nausea and vomiting in both groups had improved over time.	**Limitations** **<u>Cochrane risk of bias tool V2</u>**: Randomisation process: Some concerns. (Block design randomisation; no details provided for allocation concealment). Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded and unaware of treatment allocation). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: High risk of bias. (>20% participants lost to follow up). Selection of the reported result: High risk of bias. (Retching outcome data not reported; data for nausea and vomiting not presented for all days collected). Other bias: Low risk of bias. (No other bias detected). Overall risk of bias: High risk

Study details	Participants	Interventions	Outcomes and Results	Comments
		analysis of variance for repeated measures. **Intention-to-treat (ITT) analysis** Not stated.		
Full citation Bsat, F. A., Hoffman, D. E., Seubert, D. E., Comparison of three outpatient regimens in the management of nausea and vomiting in pregnancy, J Perinatol, 23, 531-5, 2003 **Ref Id** 947460 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial **Aim of the study** To compares pyridoxine–metoclopramide combination therapy to prochlorperazine and promethazine monotherapies in the outpatient treatment of nausea and vomiting in pregnancy **Study dates**	**Sample size** N = 156 **Characteristics** No statistically significant differences among the groups. <u>Age (years) - mean (SD):</u> Pyridoxine–metoclopramide: 25.1(6.8) Prochlorperazine: 25.9 (5.6) Promethazine: 27.5 (6.4) <u>Gestational age (weeks) - mean (SD):</u> Pyridoxine–metoclopramide: 8.5 (2.0) Prochlorperazine: 7.9 (1.8) Promethazine: 8.6 (2.0) <u>Nulliparous - number (%):</u> Pyridoxine–metoclopramide: 37 (69) Prochlorperazine: 36 (72) Promethazine: 35 (67) **Inclusion criteria** 1. First trimester 2. Singleton pregnancies 3. With nausea and/or vomiting	**Interventions** Pyridoxine–metoclopramide (N=54) Prochlorperazine (N=50) Promethazine (N=52) Pyridoxine–metoclopramide: 50 mg intramuscular injection of pyridoxine, with metoclopramide 10 mg orally every 6 hours as needed Prochlorperazine: as needed, 25 mg rectal suppositories every 12 hours, or 10 mg tablets orally every 6 hours as needed Promethazine: 25 mg orally every 6 hours as needed **Details** **Power analysis** At least 46 participants were required in each arm to reach statistical significance of α=0.05 and β=0.20. **Statistical analyses** Analysis by done by χ2, analysis of variance, and the	**Results** Note: Number of participants in pyridoxine–metoclopramide group, prochlorperazine group, and promethazine for all outcomes are 54, 50 and 52, respectively. **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy** <u>Emesis episodes on the third day of treatment - mean (SD)</u> Pyridoxine–metoclopramide: 0.6 (0.8) Prochlorperazine: 1.1 (0.8) Promethazine: 0.8 (0.8) <u>Subjective patient responses to treatment (Same-Worse (score 1-3) vs Better (socre4-5)):</u> Pyridoxine–metoclopramide: 37% vs 63% Prochlorperazine: 62% vs 38% Promethazine: 59% vs 41% **<u>Important outcomes</u>**	**Limitations** **<u>Cochrane risk of bias tool V2</u>:** Randomisation process: Some concerns. (Computer-generated block randomisation sequence was used. No details provided on allocation concealment). Deviations from intended interventions: Some concerns. (It is unclear whether participants and personnel were blinded). Measurement of the outcome: Low risk of bias. (All measures were self-assessed by participants). Missing outcome data: Low risk of bias. (Very low drop-out rate, and similar reasons between the groups, and numbers add up). Selection of the reported result: Low risk of bias. (All outcomes reported).

Study details	Participants	Interventions	Outcomes and Results	Comments
January 1994 - December 1996 **Source of funding** Not reported	**Exclusion criteria** 1. With a medical condition manifesting as nausea or vomiting 2. Women necessitating hospital admission upon initial assessment 3. With hyperemesis gravidarum 4. Who lost to follow-up 5. With clinical thyroid disease, but subclinical patients with only mild dysfunction and no prior thyroid were included 6. With both abnormal thyroid stimulating hormone and abnormal free thyroxine	Kruskal-Wallis test. Statistical significance was defined as $p<0.05$. **Intention to treat analysis** Not mentioned.	**Number of days in hospital for treatment of nausea and vomiting** <u>Number of hospitalised patient - number (%)</u> Pyridoxine–metoclopramide: 3 (5.6) Prochlorperazine: 3 (6.0) Promethazine: 6 (11.5)	Other bias: Low risk of bias. (No other bias detected). Overall risk of bias: Some concerns
Full citation Galeshi, M., Ghanbarpour, A., Naeimi Rad, M., Asghari, S., A comparison of the effect of pressure on the KID21 (Youmen) and P6 (Neiguan) points on the severity of nausea and vomiting of pregnancy, Journal of Complementary and Integrative Medicine., 2020 **Ref Id** 1251296 **Country/ies where the study was carried out** Iran **Study type** Randomised single-blind clinical trial	**Sample size** N=83 (N=82 analysed) P6 acupressure: n=40 KID21 acupressure: n=43 (n=42 analysed) **Characteristics** <u>Age (years)- Mean±SD:</u> P6 acupressure: 28.86±5.94 KID21 acupressure: 26.05±5.50 <u>Gravity- Mean±SD:</u> P6 acupressure: 1.73±1.03 KID21 acupressure: 1.60±0.91 <u>Parity- Mean±SD:</u> P6 acupressure: 0.63±0.70 KID21 acupressure: 0.33±0.52 <u>Gestational age (weeks)- Mean±SD:</u> P6 acupressure: 9.58±2.45 KID21 acupressure: 9.48±1.99	**Interventions** P6 acupressure: pressure applied to the P6 point for 20 minutes, every day for 4 days. Participants were in the supine position and acupressure was given between 17.00-19.00. KID21 acupressure: pressure applied to the KID21 point for 20 minutes, every day for 4 days. Participants were in the supine position and acupressure was given between 17.00-19.00. *Both groups received 80 mg of vitamin B6 daily (two 40-mg tablets every 12 h) before the intervention.	**Results** **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy** <u>Change from baseline in nausea severity- VAS scale (0 to 10, with 10 being most severe)- Mean±SD</u> P6 acupressure: -1.25±1.39 KID21 acupressure: -0.73±1.17 <u>Change from baseline in vomiting severity- VAS scale (0 to 10, with 10 being most severe)- Mean±SD</u> P6 acupressure: -0.68±1.00 KID21 acupressure: -0.90±1.22	**Limitations** **Cochrane risk of bias tool V2:** Randomisation process: Low risk. (Allocation by block randomisation. Allocation concealment by sealed envelope method). Deviations from intended interventions (assignment): Low risk. (It was not feasible to blind participants due to study design. Researchers and study personnel blinded to intervention assignments). Missing outcome data: Low risk. (1.2% participants lost to follow-up overall). Measurement of the outcome: Some concerns. (Patient reported outcomes, subject to bias due to subjective outcome measures).

Study details	Participants	Interventions	Outcomes and Results	Comments
Aim of the study To compare the effect of pressure on KID21 and P6 on the severity of NVP **Study dates** Not reported **Source of funding** Babol University of Medical Sciences and the Clinical Research Development Unit of Rouhani Hospital	**Inclusion criteria** • 18–35 year olds; • Singleton pregnancy; • Being in the first trimester; • Moderate to severe NVP; • Planned pregnancy; • Having no diseases that could cause nausea and vomiting, such as digestive diseases; • Not smoking; • Normal electrolytes; • Lack of ketonuria; • No use of drugs affecting nausea and vomiting. **Exclusion criteria** • Unwillingness to continue participation in the study; • Loss to follow-up.	**Details** **Power analysis** The sample size was calculated as 40 per group based on a study by Ozgoli Giti. **Statistical analyses** The collected data were analysed using SPSS 22 by repeated measures ANOVA and paired sample T-Test. **Intention to treat analysis** Not mentioned.		Selection of the reported result: Some concerns. (No trial protocol reported). Other bias: Low risk. (No other biases detected). Overall risk: Some concerns
Full citation Geiger, C. J., Fahrenbach, D. M., Healey, F. J., Bendectin in the treatment of nausea and vomiting in pregnancy, Obstet GynecolObstetrics and gynecology, 14, 688-90, 1959 **Ref Id** 939288	**Sample size** N = 110 **Characteristics** Not reported **Inclusion criteria** Not reported	**Interventions** Bendectin (N=53) Placebo (N=57) Bendectin: 10 mg * 50 tablets to take 2 tablets upon retiring. Placebo: 50 tablets to take 2 tablets upon retiring. **Details**	**Results** Note: Number of participants in Bendectin group and placebo group is 53 and 57 respectively. **Critical outcomes** **Symptomatic relief during pregnancy** Patients reported complete relief from nausea and vomiting - number (%)	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Some concerns. (No details reported for randomisation process or allocation concealment).

Study details	Participants	Interventions	Outcomes and Results	Comments
Country/ies where the study was carried out US **Study type** Double- blind randomised controlled trial **Aim of the study** To examine the effect of Bendectin in the treatment of nausea and vomiting in pregnancy. **Study dates** Not reported **Source of funding** Not reported	**Exclusion criteria** Not reported	**Power analysis** Not mentioned. **Statistical analyses** Not mentioned. **Intention to treat analysis** Not mentioned.	Bendectin: 23 (44) Placebo: 13 (23) Patients reported partial relief from nausea and vomiting - number (%) Bendectin: 26 (50) Placebo: 24 (42) Patients reported no relief from nausea and vomiting - number (%) Bendectin: 3 (6) Placebo: 20 (35) **Important outcomes** **Adverse event that is not immediately due to nausea and vomiting** Serious adverse event Bendectin: 0 (0) Placebo: 0 (0)	Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded and were unaware of treatment allocation). Measurement of the outcome: Some concerns. (It is unclear how and who assessed the outcomes). Missing outcome data: Some concerns. (It is unclear whether anyone randomised to treatment withdrew from treatment or was lost to follow-up). Selection of the reported result: Some concerns. (No protocol was found). Other bias: Some concerns. (Other biases could not be determined due to insufficient reporting). Overall risk of bias: High risk
Full citation Ghule, S. B., Sureshkumar, T., Effect of Accu Tens with Accu Band on Nausea, Vomiting, Retching and Quality of Life in Early Pregnancy, Indian journal of physiotherapy & occupational therapy, 14, 233-238, 2020	**Sample size** N=107 Intervention: n=55 Control: n=52 **Characteristics** Not reported.	**Interventions** Intervention: Accu TENS (transcutaneous electrical nerve stimulation) with accu band applied to P6 point or Neiguan acupuncture point of the dominant hand Control: Placebo TENS with accu band on the dorsum of the wrist joint	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Total Rhodes Index Score-Pre-post score- Mean (SD) Intervention: 12.29 (3.07) Control: 18.61 (6.28) p<0.0001	**Limitations** **Cochrane risk of bias tool V2:** Randomisation process: Some concerns. (No details provided). Deviations from intended interventions (assignment): Some concerns. (No details provided).

Study details	Participants	Interventions	Outcomes and Results	Comments
Ref Id 1280499 **Country/ies where the study was carried out** India **Study type** Randomised controlled trial **Aim of the study** To find out the effect of effect of accu TENS with accu band on nausea, vomiting and retching in early pregnancy. **Study dates** Not reported. **Source of funding** No funding received.	**Inclusion criteria** • Morning sickness from 6 to 12 weeks of gestation; • Nausea and vomiting for a minimum of 3 days; • Estimated gestational age of between 6 and 12 weeks of gestation; • At least 18 years of age; • To have a mobile phone. **Exclusion criteria** • Participants suffering from conditions other than pregnancy associated with symptoms of nausea and vomiting; • Thyroid disease, liver disease, acquired immune deficiency syndrome, diabetes, gall bladder disease, peptic ulcer disease, malignancy treated with chemotherapy, antibiotic therapy, antidepressant medication; • Alcoholism or drug addiction; • Participants with a cardiac pacemaker;	Both groups received interventions for 5 days per week for 3 weeks. **Details** **Power analysis** Not reported. **Statistical analyses** Univariate descriptive test including mean, standard deviation , and confidence interval. Bivariate test using Paired t-test and Independent t-test. **Intention-to-treat analysis** Not reported.	**<u>Important outcomes</u>** **Women's experience and satisfaction of care during or at end of pregnancy** <u>Quality of life- Nausea Vomiting of Pregnancy Quality of Life (NVPQOL)- Mean (SD)</u> Intervention: 80.58 (21.72) Control: 115.23 (27.46) p<0.0001	Missing outcome data: Low risk of bias. (No reported loss of follow-up of participants). Measurement of the outcome: Some concerns. (Patient reported outcomes, subject to bias due to subjective outcome measures). Selection of the reported result: Some concerns. (No trial protocol reported). Other bias: Low risk. (No other biases detected). Overall risk of bias: High risk

Study details	Participants	Interventions	Outcomes and Results	Comments
	• Participants treated with acupuncture previously; Those on concomitant therapies for nausea and vomiting.			
Full citation Keating, A., Chez, R. A., Ginger syrup as an antiemetic in early pregnancy, Altern Ther Health MedAlternative therapies in health and medicine, 8, 89-91, 2002 **Ref Id** 939294 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial (double-blind). **Aim of the study** To determine if ginger syrup mixed in water is an effective remedy for the relief of nausea and vomiting in the first trimester of pregnancy. **Study dates** 1999	**Sample size** N= 26 Ginger syrup: n=14 Placebo syrup: n=12 (n=1 did not take the study drink as nausea resolved) **Characteristics** <u>Age range (years) - number</u> Ginger syrup: 24 to 37 years Placebo syrup: 24 to 37 years <u>Parity - number</u> Ginger syrup: 0.5 to 0.8 Placebo syrup: 0.5 to 0.8 <u>Gestational age (weeks) - number</u> Ginger syrup: 7 to 11 weeks Placebo syrup: 7 to 11 weeks **Inclusion criteria** • Patients in the first trimester of pregnancy; • Complaints of nausea with or without vomiting; • Not taking a prescribed or over-the-counter antiemetic.	**Interventions** Ginger syrup: 250 mg ginger, honey, water. Placebo syrup: lemon oil, honey, water. **Details** Women were asked to drink 1 tablespoon of syrup in 4-8 oz. of hot or cold water 4 times a day. Both groups received recommendations on dietary changes to decrease nausea. Women were asked to keep a daily diary for the first 2 weeks to record syrup drinks ingested and degree of vomiting/nausea. Numerical scale (1 to 10) used to assess level of nausea, number of times vomited, and self-reported daily functioning related to symptoms. **Power analysis** Not stated. **Statistical analyses** Not applied due to small sample size in each study arm.	**Results** **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy** <u>4-point improvement on nausea scale (day 9) - number (%)</u> Ginger syrup: 10 out of 13 (77%) Placebo syrup: 2 out of 10 (20%). <u>2-point or less improvement on nausea scale (day 9 and 14) - number (%)</u> Ginger syrup: 0 out of 13 (0%) Placebo syrup: 7 out of 10 (70%) <u>Vomiting stopped (day 6) - number (%)</u> Ginger syrup: 8 out of 12 (67%) Placebo syrup: 2 out of 10 (20%) <u>Other information</u> Ginger syrup: n=1 stopped study on day 5 because of taste. n=1 stopped study on day 10 because symptoms resolved. Placebo syrup: n=2 stopped study on day 7 and	**Limitations** **<u>Cochrane risk of bias tool V2</u>**: Randomisation process: Low risk of bias. (Randomisation from a computer generated random allocation list. No information on allocation concealment). Deviations from intended interventions: Some concerns. (No details provided). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: High risk of bias. (19.2% participants lost to follow up). Selection of the reported result: High risk of bias. (Data recorded daily for degree of nausea and vomiting, but only some data reported; no study protocol supplied).

Study details	Participants	Interventions	Outcomes and Results	Comments
Source of funding Not stated.	**Exclusion criteria** Not stated.	**Intention-to-treat (ITT) analysis** Not stated.	11 because of no improvement.	Other bias: Low risk of bias. (No other bias detected). Overall risk of bias: High risk **Other information** All subjects delivered viable infants at term without major complications.
Full citation Knight, B., Mudge, C., Openshaw, S., White, A., Hart, A., Effect of acupuncture on nausea of pregnancy: a randomized, controlled trial, Obstet GynecolObstetrics and gynecology, 97, 184-8, 2001 **Ref Id** 939295 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial. **Aim of the study** To compare acupuncture with sham (placebo) acupuncture for treatment of nausea of pregnancy.	**Sample size** N=55 Acupuncture: n=28 Sham acupuncture: n=27 (n=1 withdrew consent before treatment) **Characteristics** Baseline nausea scores (Day 1)- median & interquartile range Acupuncture: 85.5 (71.25-89.75) Sham acupuncture: 87.0 (73.0-90.0) Age (years) - mean (range) Acupuncture: 30.7 (22-40) Sham acupuncture: 30. 3 (22-40) Parity (Nulliparous) Acupuncture: 14 Sham acupuncture: 9 Parity (Multiparous) Acupuncture: 14 Sham acupuncture: 18 Gestational age (weeks) mean ± SD Acupuncture: 7.8 (1.0) Sham acupuncture: 8.0 (1.0)	**Interventions** Acupuncture: 40x0.25 mm needles, insertion depth 0.5-1.0 cm. Sham acupuncture: blunt cocktail stick. **Details** Both acupuncture needles and sham needles were left in position for about 15 minutes. Both were given twice in the first week, and then once a week for 2 weeks. Daily nausea measured using a visual analogue scale (0-100); where 0=no nausea and 100=nausea worst imaginable. **Power analysis** To achieve 95% and alpha of 5%, a sample size of 55 subjects were needed. **Statistical analyses**	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Nausea scores - median & interquartile range 3 days after session 1 - median & interquartile range Acupuncture: 63.0 (50.75-86.5) Sham acupuncture: 69.0 (45.0-87.0) 3 days after session 2 - median & interquartile range Acupuncture: 65.0 (36.25-79.5) Sham acupuncture: 61.0 (30.0-80.0) 3 days after session 3 - median & interquartile range Acupuncture: 44.0 (29.0-77.25)	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Low risk of bias. (Randomisation by computer-generated numbers. Allocation concealment by opaque, sequentially numbered envelopes). Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded and unaware of treatment allocation). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Low risk of bias. (Low amount of missing data (2%)).

Study details	Participants	Interventions	Outcomes and Results	Comments
Study dates Not stated. **Source of funding** Partial funding from a National Health Service Executive South West Research and Development Project grant. Acupuncture needles donated by Seirin Deutschland.	**Inclusion criteria** • Primiparous and multiparous women; • Women who were 6-10 weeks pregnant; • Complaints of nausea, with or without vomiting; • Those who were willing to consider acupuncture. **Exclusion criteria** • Women with severe symptoms necessitating hospital admission; • Women who have had acupuncture before; • Women with a fear of needles; • Women with severe bleeding disorders.	Comparison of nausea scores on the 3rd day after each scheduled treatment. Repeated measures analysis of variance, using procedure GLM in SAS. **Intention-to-treat (ITT) analysis** Stated and details available in trial protocol.	Sham acupuncture: 53.0 (25.0-80.0) 3 days after session 4 - median & interquartile range Acupuncture: 47.5 (29.25-69.5) Sham acupuncture: 48.0 (14.0-80.0) p= 0.001 Median change in nausea - median & interquartile range Acupuncture: -15 (-31 to -3) Sham acupuncture: -8 (-14.75 to 0.25) **Important outcomes** **No adverse events required hospitalisation**	Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: High risk of bias (Treatment delivered at different time intervals for participants; placebo might not have been completely inactive). Overall risk of bias: Some concerns
Full citation Koren, G., Clark, S., Hankins, G. D. V., Caritis, S. N., Miodovnik, M., Umans, J. G., Mattison, D. R., Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: A randomized placebo controlled trial, American journal of obstetrics and gynecology, 203, 571.e1-571.e7, 2010	**Sample size** Intervention: n=133 (ITT analysis n=131) Placebo: n=128 (ITT analysis n=125) **Characteristics** Age (years) - mean ±SD Intervention: 25.9 (6.0)	**Interventions** Intervention: delayed-release combination of doxylamine succinate (10 mg) and pyridoxine hydrochloride (10 mg) (Diclectin). Placebo: Similar appearing placebo tablet.	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Difference in PUQE score from baseline to day 15 - mean ±SD Intervention: -4.8 (2.7) Placebo: -3.9 (2.6); p=0.006	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Some concerns. (Randomisation and allocation concealment by interactive voice response system).

Study details	Participants	Interventions	Outcomes and Results	Comments
Ref Id 924746 **Country/ies where the study was carried out** US **Study type** Randomised, multicentre, placebo-controlled trial. **Aim of the study** To assess the effectiveness of delayed-release doxylamine and pyridoxine (Diclectin) for the treatment of nausea and vomiting during pregnancy. **Study dates** 2008 to 2009. **Source of funding** Supported by Duchesnay Inc, Canada.	Placebo: 25.0 (5.7) Body mass index (kg/m^2) - mean ±SD Intervention: 28.77 (7.60) Placebo: 29.67 (11.20) Gestational age at enrolment (weeks) - mean ±SD Intervention: 9.3 (2.0) Placebo: 9.3 (1.8) PUQE score at enrolment - mean ±SD Intervention: 9.0 (2.1) Placebo: 8.8 (2.1) Global assessment of well-being - mean ±SD Intervention: 5.0 (2.3) Placebo: 5.4 (2.2) **Inclusion criteria** • Pregnant women aged at least 18 years of age; • Gestational age ranging between 7 and 14 weeks; • Experiencing nausea and vomiting; • Pregnancy unique quantification of emesis (PUQE) score of 6 or greater; • Not responded to conservative management consisting of dietary/lifestyle advice according to the 2004 American College of	**Details** Women took 2 tablets at bedtime on day 1. If symptoms persisted on the afternoon of day 2, women were permitted to take an additional tablet the next morning on day 3. Based on clinical assessment on day 4, women were permitted to take a fourth tablet in the mid-afternoon. Women were permitted to use alternative treatments for nausea and vomiting (for example nutritional modifications, teas, aromatherapy, massage, and yoga). **Power analysis** To achieve 90% power, 140 patients per treatment group were required at enrolment to achieve 200 evaluable patients. **Statistical analyses** Outcomes analysed using ANCOVA model, with change from baseline to day 15 as response variable, baseline values as the covariate, and treatment group and study centre as fixed effects. Adverse effects occurring on or after day 1 through to day 15 were compared between treatment groups using Pearson's chi-squared test	Mean area under the curve difference in PUQE score from baseline (day-by-day) - mean ±SD Intervention: 61.5 (36.9) Placebo: 53.5 (37.5); p<0.0001 **Important outcomes** **Adverse event not immediately due to nausea and vomiting and which requires hospitalisation during treatment*** Number (%) of women with at least 1 severe treatment -emergent adverse effect Intervention: 7 (5.3) Placebo: 5 (3.9); p=0.711 The use of Diclectin was not associated with an increased rate of any adverse event compared to placebo (not stated whether adverse events required hospitalisation).	Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded and were unaware of treatment). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Low risk of bias. (Low amount of missing data (2%)). Selection of the reported result: High risk of bias. (Data recorded daily, but only changes from baseline to day 15 reported). Other bias: Some concerns. (Additional alternative therapy permitted; differences in number of Diclectin tablets taken by women in this treatment group). Overall risk of bias: High risk **Other information** *Data reported in secondary analysis publication (Koren 2015)- states use of intervention drug was not associated with an increased rate of any adverse event over placebo (when following recommended dose of 4 tablets).

Study details	Participants	Interventions	Outcomes and Results	Comments
	Obstetrics & Gynaecology (ACOG) practice bulletin. **Exclusion criteria** • Women treated with other antiemetics; • Chronic medical conditions; • Not able to communicate in English or Spanish.	or Fisher's exact test, where appropriate. **Intention-to-treat (ITT) analysis** ITT analysis.		
Full citation Koren, G., Clark, S., Hankins, G. D. V., Caritis, S. N., Umans, J. G., Miodovnik, M., Mattison, D. R., Matok, I., Maternal safety of the delayed-release doxylamine and pyridoxine combination for nausea and vomiting of pregnancy; a randomized placebo controlled trial, BMC pregnancy and childbirth, 15 (1) (no pagination), 2015 **Ref Id** 924948 **Country/ies where the study was carried out** See Koren 2010 **Study type** See Koren 2010 **Aim of the study**	**Sample size** See Koren 2010 **Characteristics** See Koren 2010 **Inclusion criteria** See Koren 2010 **Exclusion criteria** See Koren 2010	**Interventions** See Koren 2010 **Details** See Koren 2010	**Results** See Koren 2010	**Limitations** See Koren 2010 **Other information** Secondary analysis to Koren 2010.

Study details	Participants	Interventions	Outcomes and Results	Comments
See Koren 2010 **Study dates** See Koren 2010 **Source of funding** See Koren 2010				
Full citation Mobarakabadi, S. S., Shahbazzadegan, S., Ozgoli, G., The effect of P6 acupressure on nausea and vomiting of pregnancy: A randomized, single-blind, placebo-controlled trial, Advances in Integrative Medicine., 2019 **Ref Id** 1251236 **Country/ies where the study was carried out** Iran **Study type** Randomised, single-blind, placebo-controlled trial **Aim of the study** To examine the effect of Pericardium 6 (P6) acupressure with Sea-Band on the	**Sample size** N=78 pregnant women (N=75 analysed) Intervention: n=25 Placebo: n=26 (n=25 analysed) Control: n=27 (n=25 analysed) **Characteristics** Age (years)- Mean±SD: Intervention: 23.64±4.21 Placebo: 24.56±4.18 Control: 24.72±3.62 Gestational age (weeks)- Mean±SD: Intervention: 12.16±1.28 Placebo: 12.60±0.95 Control: 12.16±1.14 Number of pregnancies- Mean±SD: Intervention: 1.68±0.85 Placebo: 1.60±0.76 Control: 1.40±0.70 **Inclusion criteria**	**Interventions** Intervention: acupressure to P6 point to both wrists, for 3 days (except when in the shower) Placebo: wristband with the same method as acupressure group but without a pressure button Control: no intervention All participants were given dietary advice in written and verbal form. **Details** **Power analysis** To achieve 80% power, the minimum sample size was determined as 21 per group, and to take account of potential sample loss in the follow-up. **Statistical analyses** Chi-Square test, Fisher's exact test, the ANOVA (followed by Tukey's test)	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Change from baseline in nausea frequency (scale: 0 to 4, where 4=very severe nausea)- Mean±SD: Intervention: -4.80±4.21 Control: 0.70±1.40 Placebo: -2.31±2.51 *1 vs. 3 p=0.009, 1 vs. 2 p<0.001, 2 vs. 3 p<0.001 Change from baseline in nausea intensity- (scale: 0 to 4, where 4=very severe nausea)- Mean±SD: Intervention: -13.10±13.90 Control: 1.20±4.40 Placebo: -6.71±6.31 *1 vs. 3 p=0.69, 1 vs. 2 p<0.001, 2 vs. 3 p<0.001 Change from baseline in vomiting frequency- (scale: 0 to 4, where 4=very severe nausea)- Mean±SD: Intervention: -1.62±2.42 Control: -0.23±0.67	**Limitations** **Cochrane risk of bias tool V2:** Randomisation process: Low risk. (Allocation by computer randomisation. Allocation concealment by sealed envelope method). Deviations from intended interventions (assignment): Low risk. (It was not feasible to blind participants due to study design. Researchers and study personnel blinded to intervention assignments). Missing outcome data: Low risk. (4% participants lost to follow-up overall. No loss to follow up in intervention group, equal loss in control and placebo arms). Measurement of the outcome: Some concerns. (Patient reported outcomes, subject to bias due to subjective outcome measures).

Study details	Participants	Interventions	Outcomes and Results	Comments
severity and frequency of nausea and vomiting of pregnancy and compare it to a placebo and a control group. **Study dates** Not reported. **Source of funding** Chancellor of Ardebil University of Medical Sciences	• Mild to moderate nausea and/or vomiting (based on a Likert scale three days before the start of the intervention); • A planned and normal pregnancy; • Gestational age under 20 weeks; • Being literate. **Exclusion criteria** • Having symptoms of Hyperemesis Gravidarum, such as weight loss, and needing hydration therapy, IV drugs and/or hospitalisation for the treatment of NVP; • Molar or twin pregnancy; • Threatened abortion; • Being affected by any known medical conditions that might manifest with nausea and vomiting; • A history of recent psychologist or psychiatrist; • Having recently experienced disastrous events and traumas; • Taking medications (emetic or antiemetic); • Smoking.	and the Kruskal-Wallis test (followed by Mann-Whitney's U-test) were used to compare the baseline characteristics among the three groups. The paired t-test and Wilcoxon's test were used to determine changes in the frequency, duration and severity of nausea and the frequency of vomiting after the intervention compared to before in each group. For all the analyses, the level of statistical significance was defined as $P < 0.05$. **Intention-to-treat (ITT) analysis** Not mentioned.	Placebo: -1.24±1.82 *1 vs. 3 p=0.61, 1 vs. 2 p=0.02, 2 vs. 3 p=0.03 **Important outcomes** **Women's experience and satisfaction of care during or at end of pregnancy** Satisfaction with intervention- Yes- Number (%) Intervention: 15 (60%) Control: 3 (12%) Placebo: 6 (24%) Satisfaction with intervention- No- Number (%) Intervention: 1 (4%) Control: 16 (64%) Placebo: 0 (0%) Satisfaction with intervention- Almost- Number (%) Intervention: 9 (36%) Control: 6 (24%) Placebo: 19 (76%)	Selection of the reported result: Low risk. (Study trial protocol reported). Other bias: Some concerns. (Band used in placebo group may have stimulated P6 points. Effect of placebo can't be differentiated from the effect of acupressure). Overall risk: Some concerns

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Mohammadbeigi, R., Shahgeibi, S., Soufizadeh, N., Rezaiie, M., Farhadifar, F., Comparing the effects of ginger and metoclopramide on the treatment of pregnancy nausea, Pakistan Journal of Biological Sciences, 14, 817-820, 2011 **Ref Id** 924575 **Country/ies where the study was carried out** Iran **Study type** Randomised controlled trial. **Aim of the study** To compare the effectiveness of ginger and metoclopramide in the treatment of nausea and vomiting during pregnancy. **Study dates** Not stated. **Source of funding**	**Sample size** N=102 Metoclopramide: n=34 Ginger: n=34 Placebo: n=34 **Characteristics** <u>Age (years) - mean ±SD</u> Metoclopramide: 27.88 (3.21) Ginger: 26.94 (3.94) Placebo: 26.97 (4.22) <u>Length of pregnancy (weeks) - mean ±SD</u> Metoclopramide: 10.03 (1.99) Ginger: 9.5 (2.02) Placebo: 10.32 (2.25) **Inclusion criteria** • Women less than 20 weeks of pregnancy; • Singleton pregnancy; • Inefficiency of food regimens to control vomiting and nausea. **Exclusion criteria** • Women suffering from other diseases requiring drugs for treatment (hepatitis, gastritis, rise of	**Interventions** Metoclopramide: 10 mg capsules 3 times per day. Ginger: 200 mg capsules 3 times per day. Placebo: 200 mg flour 3 times per day. **Details** **Power analysis** To achieve 80% power, 34 women in each treatment group was required. **Statistical analyses** ANOVA used to compare data across treatment groups. Within-participant contrast tests used to assess the main effect and interactions. The sphericity assumption was assessed using Mauchly-test. **Intention-to-treat (ITT) analysis)** Not stated.	**Results** **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy** <u>Vomiting - mean ±SD</u> <u>Day 1</u> Metoclopramide: 10.56 (2.98) Ginger: 10.82 (1.98) Placebo: 10.56 (1.78) <u>Day 2</u> Metoclopramide: 9.09 (2.23) Ginger: 8.85 (1.54) Placebo: 9.68 (1.27) <u>Day 3</u> Metoclopramide: 7.29 (2.28) Ginger: 7.62 (1.99) Placebo: 8.76 (1.13) <u>Day 4</u> Metoclopramide: 8.06 (1.70) Ginger: 7.44 (1.28) Placebo: 8.12 (1.12) <u>Day 5</u> Metoclopramide: 6.53 (1.81) Ginger: 6.18 (1.25) Placebo: 7.59 (1.35) p=0.006 <u>Nausea - mean ±SD</u> <u>Day 1</u> Metoclopramide: 16.53 (4.89) Ginger: 16.59 (3.12) Placebo: 17.03 (2.53) <u>Day 2</u>	**Limitations** **<u>Cochrane risk of bias tool V2</u>**: Randomisation process: Some concerns. (Block randomisation used. No details on allocation concealment given). Deviations from intended interventions: Some concerns. (Participants blinded to treatment allocation but no details provided regarding personnel blinding). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Low risk of bias. (No reported loss to follow up). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Low risk of bias. (No other biases detected). Overall risk of bias: Some concerns

Study details	Participants	Interventions	Outcomes and Results	Comments
Support from the research deputy of Kurdistan University of Medical Sciences.	intra cranial pressure and pancreatitis); • Side-effects caused by ginger intolerance; • Metoclopramide side-effects (extra pyramidal side effects); • Pregnancy side-effects such as abortion risk, bleeding and pyelonephritis.		Metoclopramide: 16.47 (3.65) Ginger: 17.56 (2.86) Placebo: 17.68 (2.36) <u>Day 3</u> Metoclopramide: 13.06 (4.19) Ginger: 14.62 (3.24) Placebo: 16.00 (2.35) <u>Day 4</u> Metoclopramide: 22.76 (4.24) Ginger: 20.94 (3.80) Placebo: 23.68 (2.58) <u>Day 5</u> Metoclopramide: 11.21 (3.37) Ginger: 11.50 (1.81) Placebo: 14.26 (2.68) p=0.0001 <u>Rhodes index - mean ±SD</u> <u>Day 1</u> Metoclopramide: 30.00 (8.29) Ginger: 31.68 (5.32) Placebo: 30.53 (4.64) <u>Day 2</u> Metoclopramide: 25.56 (5.51) Ginger: 26.41 (4.12) Placebo: 27.35 (3.36) <u>Day 3</u> Metoclopramide: 20.35 (6.14) Ginger: 22.24 (5.02) Placebo: 24.76 (3.06) <u>Day 4</u> Metoclopramide: 22.76 (4.24) Ginger: 20.94 (3.80) Placebo: 23.68 (2.58)	

Study details	Participants	Interventions	Outcomes and Results	Comments
			Day 5 Metoclopramide: 18.53 (5.18) Ginger: 18.71 (2.81) Placebo: 23.15 (4.03) p=0.0001	
Full citation Monias, M., Evaluation of cyclizine with pyridoxine in vomiting of pregnancy, Mil MedMilitary medicine, 121, 403-4, 1957 **Ref Id** 939297 **Country/ies where the study was carried out** US **Study type** Double-blind randomised controlled trial **Aim of the study** To evaluate the benefit of cyclizine with pyridoxine hydrochloride (Maredox) for treatment of mild to moderate nausea and vomiting **Study dates** Not mentioned.	**Sample size** N= 200 Maredox: n= 100 Placebo: n= 100 **Characteristics** Not mentioned. **Inclusion criteria** • Between 6th and 20th gestational week • Complaining of nausea and/or vomiting **Exclusion criteria** Not mentioned.	**Interventions** Participants were given 20 tablets. Intervention: Instructed to take two tablets before breakfast. If there is no relief, instructed to take an additional tablet before lunch Placebo: Same regimen with placebo tablet **Details** **Power analysis** Not stated. **Statistical analyses** Not stated. **Intention-to-treat (ITT) analysis** Not stated.	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Complete relief of symptoms - Percentage Maredox: 78% Placebo: 13% Partial relief of symptoms - Percentage Maredox: 5% Placebo: 5% No relief of symtpoms - Percentage Maredox: 17% Placebo: 82%	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Some concerns. (No details provided on randomisation process. Allocation concealed by keeping tablets in coded bottles). Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded and unaware of treatment allocation). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Some concerns. (No details provided). Selection of the reported result: Some concerns. (No details provided).

Study details	Participants	Interventions	Outcomes and Results	Comments
Source of funding Not mentioned.				Other bias: High risk of bias (participants not matched for background characteristics) Overall risk of bias: Some concerns
Full citation Oliveira, L. G., Capp, S. M., You, W. B., Riffenburgh, R. H., Carstairs, S. D., Ondansetron compared with doxylamine and pyridoxine for treatment of nausea in pregnancy: A randomized controlled trial, Obstetrics and gynecology, 124, 735-742, 2014 **Ref Id** 924995 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial (double-blind). **Aim of the study** To evaluate whether ondansetron or the combination of doxylamine + pyridoxine was superior in treating nausea and vomiting of pregnancy. **Study dates** October 2012 to April 2013.	**Sample size** N=36 (n= 6 lost to follow-up) Ondansetron + placebo: n=18 (n=5 lost to follow-up) Pyridoxine + Doxylamine: n=18 (n=1 lost to follow-up) **Characteristics** The age, estimated gestational age, current medications, gravidity, and parity were recorded for each patient. <u>Gravid - median & interquartile range</u> Ondansetron: 2 (1 to 3) Pyridoxine + Doxylamine: 2 (1 to 3) <u>Parity - median & interquartile range</u> Ondansetron: 1 (0 to 1) Pyridoxine + Doxylamine: 0.5 (0 to 1) <u>Gestational age - median & interquartile range</u> Ondansetron: 8 weeks (7.1 to 8.9) Pyridoxine + Doxylamine: 8.1 weeks (7.2 to 9.9) <u>Baseline nausea score - median & interquartile range</u> Ondansetron: 73 mm (67 to 84) Pyridoxine and Doxylamine: 81 mm (68 to 93) <u>Baseline emesis score- median & interquartile range</u>	**Interventions** Baseline: used VAS scale to measure nausea & emesis experienced over previous 7 days on two separate 100mm scales, where 0 = no nausea/emesis and 100= worst nausea/emesis imaginable. Ondansetron group: 4 mg ondansetron + one placebo capsule. Pyridoxine + Doxylamine group: 25 mg pyridoxine + 12.5 mg doxylamine. Follow-up at 5-7 days after initiating drug regimen: patients asked to grade severity of nausea & emesis using VAS scale over treatment period. **Details** Women took the capsules orally, every 8 hours for 5 days. **Power analysis** 14 patients per group (28 total) provided 90% power, alpha of 0.05, to detect a 25-mm difference in the mean improvement on the VAS	**Results** **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy** <u>Change in nausea (VAS score) - Median (IQR)</u> Ondansetron: 51 (37 to 64) p=0.0.19 Pyridoxine & Doxylamine: 20 (8 to 51) <u>Change in emesis (VAS score) - Median (IQR)</u> Ondansetron: 41 (17 to 57) p=0.049 Pyridoxine & Doxylamine 17 (-4 to 38) <u>Number of women with a VAS score of 25 mm or more for change in nausea (clinically significant)</u> Ondansetron: 12 out of 13 patients; ITT analysis with imputed data 15 out of 18 Pyridoxine & Doxylamine: 7 out of 17 patients; ITT analysis with imputed data 7 out of 18 <u>Number of women with a VAS score of 25 mm or more for change in emesis (clinically significant)</u>	**Limitations** **<u>Cochrane risk of bias tool V2</u>**: Randomisation process: Low risk of bias. (Randomisation by computer-generated program. Allocation concealment by identical numbered brown bags). Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded and unaware of treatment allocation). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: High risk of bias. (17% participants lost to follow up). Selection of the reported result: Low risk of bias. (All outcomes reported).

Study details	Participants	Interventions	Outcomes and Results	Comments
Source of funding The United States government paid for all study medications. No other funding details mentioned.	Ondansetron: 53 mm (26 to 74) Pyridoxine + Doxylamine: 64 mm (26 to 89) **Inclusion criteria** • Women aged 18 years and over; • At the beginning of pregnancy; at less than 16 weeks of gestation. **Exclusion criteria** • Nausea or vomiting pre-dated the pregnancy; • Hospitalisation was required at the time of initial enrolment; • Women were already using antiemetics; • Allergies to any study medications; • Inability to return for 1 week follow-up visit; • Inability to obtain medications on the day of enrolment	between groups, with a SD of 22mm. **Statistical analysis** Demographic characteristics + the mean difference on the VAS for nausea and emesis between each group- compared using Wilcoxon rank-sum test. Difference in proportion of patients who had a clinically significant improvement (25 or more VAS units) in their nausea or emesis- assessed using the Fisher exact test. Difference in proportion of patients who experienced side effects in each group- compared using the Fisher exact test. **Intention-to-treat analysis** ITT analysis conducted. Missing data estimated by multiple imputation.	Ondansetron: 10 out of 13 patients; ITT analysis with imputed data 13 out of 18 Pyridoxine & Doxylamine: 6 out of 17 patients; ITT analysis with imputed data 6 out of 18 **Important outcomes** **Adverse events requiring no hospitalisation** Ondansetron + no hospitalisation Headache, dry mouth, pruritic, increased salivation, sedation, and constipation. Pyridoxine & Doxylamine + no hospitalisation Sedation and constipation. **At follow-up, one patient was admitted to hospital for reasons unrelated to her nausea in pregnancy. No further details given.**	Other bias: Low risk of bias. (No other bias detected). Overall risk of bias: Some concerns **Other information** No abnormal pregnancy birth outcomes reported.
Full citation Ozgoli, G., Goli, M., Simbar, M., Effects of ginger capsules on	**Sample size** N=70 (n=67 women completed study)	**Interventions** Ginger: 4 capsules daily containing 250 mg of ginger-root powder.	**Results** **Critical outcomes** **Symptomatic relief during pregnancy**	**Limitations**

Study details	Participants	Interventions	Outcomes and Results	Comments
pregnancy, nausea, and vomiting, Journal of Alternative and Complementary Medicine, 15, 243-246, 2009 **Ref Id** 924754 **Country/ies where the study was carried out** Iran **Study type** Randomised controlled trial **Aim of the study** To assess the effects of ginger in the treatment of nausea and vomiting during pregnancy. **Study dates** Women recruited between June and July 2005. **Source of funding** Support from the deputy of research of Shahid Beheshti Medical Science University.	Ginger: n=35 (3 women in this group did not complete study) Placebo: n=35 **Characteristics** Gestational age (weeks) - frequency *8 to 10 weeks* Ginger: 8 Placebo: 8 *11 to 13 weeks* Ginger: 10 Placebo: 12 *14 to 16 weeks* Ginger: 9 Placebo: 9 *17 to 19 weeks* Ginger: 5 Placebo: 6 Differences in participants age, gestational age, and parity were not statistically significant. **Inclusion criteria** • Women under 20 weeks gestational age; • No medical or surgical history; • No history of smoking or drug use; • Mild and moderate nausea with or without vomiting. **Exclusion criteria** Not stated.	Placebo: Similar appearing lactose capsule. **Details** Women did not take any other non-prescription treatments. Women took capsules morning, noon, afternoon, and at night with water for 4 days. All women advised to avoid fatty foods and to eat less food at each meal during the course of the study, but to increase the number of meals consumed each day. **Power analysis** Not stated. **Statistical analyses** Mann-Whitney test used to compared between-group differences in nausea intensity. Paired *t*-test used to compare differences in vomiting times. **Intention-to-treat (ITT) analysis** Not stated.	Improvement in nausea intensity - number (%) No improvement Ginger: 3 (9%) Placebo: 7 (21.5%) Also reports 'significant improvement' in 27 (84%) participants in ginger group and 20 (56%) in placebo group, p<0.05. However, 'significant improvement' not defined. Change in vomiting frequency Reports 50% decrease in frequency in the ginger group and 9% decrease the placebo group, p<0.05 Adverse events not due to nausea and vomiting that require hospitalisation None of the participants reported any complications during the treatment period.	**Cochrane risk of bias tool V2**: Randomisation process: High risk of bias. (Randomised continuous sampling; no details for allocation concealment provided). Deviations from intended interventions: Low risk of bias. (Only participants unaware of treatment allocation; single-blinded). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Low risk of bias. (Low amount of missing data (4%)). Selection of the reported result: High risk of bias. (Data recorded daily, but not presented; % improvement by group reported based on 2 daily assessments for 4 days per person per group). Other bias: Low risk of bias. (No other bias detected). Overall risk of bias: High risk

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Puangsricharern, A., Mahasukhon, S., Effectiveness of auricular acupressure in the treatment of nausea and vomiting in early pregnancy, Journal of the Medical Association of Thailand, 91, 1633-1638, 2008 **Ref Id** 924745 **Country/ies where the study was carried out** Bangkok **Study type** Randomised controlled trial. **Aim of the study** To assess the effectiveness of acupressure to the ear in the treatment of nausea and vomiting in early pregnancy. **Study dates** July 2004 to September 2004. **Source of funding** Not stated.	**Sample size** N=98 (n=7 lost to follow-up) Acupressure: n=45 Control: n=46 **Characteristics** <u>Age (years) - mean ±SD</u> Acupressure: 26.4 (5.6) Control: 27.0 (5.74) <u>Gestational age (weeks) - mean ±SD</u> Acupressure: 11.1 (2.1) Control: 11.2 (2.3) <u>Body mass index (BMI) - mean ±SD</u> Acupressure: 22.2 (3.9) Control: 22.6 (4.0) **Inclusion criteria** • Women less than 14 weeks gestation; • Symptoms of nausea and vomiting. **Exclusion criteria** • Women with molar pregnancy; • Multiple pregnancy; • Blighted ovum; • Hyperemesis gravidarum;	**Interventions** Acupressure: Magnet pellets placed with adhesive tape at the auricles of both ears; patients pressed magnets for 30 seconds 4 times per day (before meals and at bedtime), starting on the third day until the sixth day. Control: No treatment other than oral antiemetic treatment. **Details** Women were permitted to take 1 tablet of 50 mg dimenhydrinate every 6 hours if they could not tolerate their nausea and vomiting symptoms. **Power analysis** Assuming 13% dropout, 49 women per treatment group were required. **Statistical analyses** Outcome data analysed using Student's *t*-test, Chi-square test or Mann-Whitney *U* test depending on type of data and distribution. **Intention-to-treat (ITT) analysis** Not stated.	**Results** **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy** <u>Nausea vomiting score - mean ±SD</u> <u>Day 1</u> Acupressure: 11.1 (4.8) Control: 14.3 (7.1); p=0.074 <u>Day 2</u> Acupressure: 10.2 (4.9) Control: 12.7 (8.2); p=0.318 <u>Day 3</u> Acupressure: 9.3 (4.3) Control: 11.0 (8.7); p=0.420 <u>Day 4</u> Acupressure: 8.7 (4.3) Control: 10.6 (8.9); p=0.387 <u>Day 5</u> Acupressure: 8.0 (5.0) Control: 11.6 (9.3); p=0.274 <u>Day 6</u> Acupressure: 7.7 (4.9) Control: 11.3 (9.2); p=0.252 No patient in the treatment group experienced an adverse event. Most women (85%) were satisfied with acupressure treatment as it was convenient and effective in relieving nausea and vomiting symptoms.	**Limitations** **<u>Cochrane risk of bias tool V2</u>**: Randomisation process: Low risk of bias. (Random numbers table used for randomisation. No information provided for allocation concealment). Deviations from intended interventions: High risk of bias. (Blinding was not implemented). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Low risk of bias. (Low amount of missing data (7%)). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Some concerns. (Women permitted to take antiemetic medication; differences between treatment groups at baseline in terms of education, income and occupation)

Study details	Participants	Interventions	Outcomes and Results	Comments
	• Current use of antiemetic medications.			Overall risk of bias: Some concerns
Full citation Rad, M. N., Lamyian, M., Heshmat, R., Jaafarabadi, M. A., Yazdani, S., A randomized clinical trial of the efficacy of kid21 point (youmen) acupressure on nausea and vomiting of pregnancy, Iranian red crescent medical journal, 14, 699-703, 2012 **Ref Id** 925122 **Country/ies where the study was carried out** Iran **Study type** Randomised controlled trial. **Aim of the study** To compare the effectiveness of acupressure on KID21 point versus sham acupressure on nausea and vomiting during pregnancy. **Study dates** Not stated.	**Sample size** Acupressure: N=40 Placebo: N=40 **Characteristics** <u>Age (years) - mean ±SD</u> Acupressure: 26.03 (4.18) Placebo: 25.88 (5.58) <u>Body mass index (BMI) - mean ±SD</u> Acupressure: 24.39 (4.07) Placebo: 25.64 (5.14) <u>Gestational age (weeks) - mean ±SD</u> Acupressure: 9.55 (1.81) Placebo: 9.45 (2.02) <u>Nausea intensity - median (interquartile range; IQR)</u> Acupressure: 8 (7 to 10) Placebo: 8 (7 to 9) <u>Vomiting intensity - median (IQR)</u> Acupressure: 2 (1 to 4) Placebo: 2 (1 to 3) **Inclusion criteria** • Healthy pregnant women aged 18 to 35 years; • Singleton pregnancy (including unwanted pregnancy); • first trimester or pregnancy;	**Interventions** Acupressure: Pressure administered to KID21 points and gradually increased for 2 minutes. Followed by massage of the point for 2 minutes, then repeated for 20 minutes. Performed similarly for 4 consecutive days. Women could apply acupressure whenever they felt nausea and vomiting and were taught how to pressure on KID21 point. Placebo: Pressure similarly applied on the false point (lack of energy point) for 20 minutes daily for 4 consecutive days. **Details** Women received educational pamphlets providing advice on: increasing meals, eating smaller portions of food, giving up food before fullness, avoiding fatty and spicy foods and eating crackers or dry bread on waking, being hydrated. **Power analysis**	**Results** **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy** <u>Intensity of nausea - median (IQR)</u> <u>Day 1</u> Acupressure: 7 (6 to 8) Placebo: 7 (6 to 8); p=0.473 <u>Day 2</u> Acupressure: 6 (4 to 7.75) Placebo: 7 (6 to 8); p=0.012 <u>Day 3</u> Acupressure: 5 (3 to 5) Placebo: 7 (5 to 8); p<0.001 <u>Day 4</u> Acupressure: 4 (2 to 5) Placebo: 7 (5 to 8); p<0.001 <u>Intensity of vomiting - median (IQR)</u> <u>Day 1</u> Acupressure: 1 (0 to 2) Placebo: 1 (1-2); p=0.012 <u>Day 2</u> Acupressure: 0 (0 to 1) Placebo: 1 (0.25 to 2); p=0.003 <u>Day 3</u> Acupressure: 0 (0 to 1) Placebo: 1 (0 to 2); p=0.001	**Limitations** **<u>Cochrane risk of bias tool V2</u>**: Randomisation process: Some concerns. (Block randomisation method in a block of 6; but later states that women were matched for age, intensity of nausea and frequency of vomiting. No details provided on allocation concealment). Deviations from intended interventions: Low risk of bias. (Single blinded trial; only participants blinded). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Low risk of bias. (No reported loss to follow up). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Low risk of bias. (No other bias detected).

Study details	Participants	Interventions	Outcomes and Results	Comments
Source of funding None declared.	• Moderate to severe nausea and vomiting; • Normal electrolytes; • Lack of diseases causing nausea and vomiting such as gastrointestinal disease; • Normal blood pressure; • Lack of ketonuria; • Passive or active smokers; • Avoidance of effective drugs for nausea and vomiting. **Exclusion criteria** • Women without tendency to remain on the study.	To achieve 90% power, 40 women in each treatment group were required. **Statistical analyses** Mann-Whitney, Friedman and Sign-rank tests were used to compare intensity of nausea and frequency of vomiting. **Intention-to-treat (ITT) analysis** Not stated.	<u>Day 4</u> Acupressure: 0 (0 to 0.75) Placebo: 1 (0 to 2); p<0.001 There were no side effects.	Overall risk of bias: Low risk **Other information** All women had taken vitamin B6.
Full citation Saberi, F., Sadat, Z., Abedzadeh-Kalahroudi, M., Taebi, M., Acupressure and ginger to relieve nausea and vomiting in pregnancy: A randomized study, Iranian red crescent medical journal, 15, 854-861, 2013 **Ref Id** 924456 **Country/ies where the study was carried out**	**Sample size** N=159 (16 women lost to follow-up) Ginger: n=50 Acupressure: n=48 Control: n=45 **Characteristics** <u>Age (years) - mean ±SD</u> Acupressure: 25.68 (4.64) Ginger: 26 .64 (6.18) Control: 25.79 (3.64) <u>Gestational age (weeks) - mean ±SD</u> Acupressure: 9.32 (2.38) Ginger: 8.78 (2.32)	**Interventions** Acupressure: Trained in use of a pair of sea band (acupressure wristband) in appropriate place in both hands (pressure on the Neiguan point); only removing during bathing. Ginger: 3 x 250 mg capsules taken daily. Control: No intervention. **Details** Women were followed for 7 days; women did not receive	**Results** **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy** <u>Pre/post-intervention difference Rhodes Index Scores - mean ±SD</u> <u>Vomiting</u> Acupressure: 0.64 (2.14) Ginger: 2.66 (2.64) Control: -0.71 (2.12); p<0.001 <u>Nausea</u> Acupressure: 2.00 (2.37) Ginger: 3.94 (2.58) Control: 0.18 (1.74); p<0.001	**Limitations** **<u>Cochrane risk of bias tool V2</u>**: Randomisation process: Low risk of bias. (Table of random numbers used. No details provided for allocation concealment). Deviations from intended interventions: High risk of bias. (Blinding was not implemented).

Study details	Participants	Interventions	Outcomes and Results	Comments
Iran **Study type** Randomised controlled trial **Aim of the study** To compare the effectiveness of ginger versus acupressure in the treatment of nausea and vomiting in pregnancy. **Study dates** November 2008 to September 2009. **Source of funding** Funded and supported by the Deputy of Research, Kashan University of Medical Sciences (KaUMS).	Control: 9.11 (0.18) **Inclusion criteria** • Women with mild to moderate nausea and/or vomiting; • Less than 16 weeks' gestation; • Singleton pregnancy; • Literate and willing to participate; • No history of other diseases such as gastrointestinal disorder; • Not receiving other methods of treatment for nausea and vomiting in the past 3 weeks; • Able to eat ginger capsules or place the wristbands as prescribed in the correct placement; • Living in Kashan. **Exclusion criteria** • Women unable to return for a follow-up visit one week later; • Complications using ginger or wristbands; • Treatment method failed to relieve nausea and vomiting;	any intervention for the first 3 days, but acupressure and ginger were given in these treatment groups for the next 4 days. All women were instructed to split their meals into frequent small ones, rich in carbohydrates and low in fat; to avoid or not eat food that may make nausea worse; try eating before or as soon as feeling hungry; stop smoking; eat dry bread or cookie on waking; avoiding fried, odorous, spicy, greasy, or gas forming foods; maintain good posture; drink cold, clear, and carbonated or sour fluids. **Power analysis** To achieve 80% power and taking into account 10% loss to follow-up, 53 women per treatment group was required. **Statistical analyses** Means and standard deviations (SDs) presented. Categorical data presented as frequencies and percentages (%). ANOVA, Kruskal-Wallis, Chi-square and Fisher exact tests used for statistical analyses. Paired *t*-test used to compare mean pre- and post-intervention scores. **Intention-to-treat (ITT) analysis** ITT analysis conducted.	<u>Retching</u> Acupressure: 1.52 (1.86) Ginger: 2.01 (1.56) Control: 0.31 (1.36); p<0.001 <u>Total Score</u> Acupressure: 4.17 (5.53) Ginger: 8.61 (5.24) Control: -0.84 (3.72); p<0.001	Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Low risk of bias. (16 women (11%) lost to follow up). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Low risk of bias (no other biases detected). Overall risk of bias: Some concerns

Study details	Participants	Interventions	Outcomes and Results	Comments
	• Nausea and vomiting progressing to severe (>5 episodes per day).			
Full citation Saberi, F., Sadat, Z., Abedzadeh-Kalahroudi, M., Taebi, M., Effect of ginger on relieving nausea and vomiting in pregnancy: a randomized, placebo-controlled trial, Nursing & Midwifery StudiesNurs, 3, e11841, 2014 **Ref Id** 924707 **Country/ies where the study was carried out** Iran **Study type** Randomised controlled trial. **Aim of the study** To compare the effectiveness of ginger in the treatment of nausea and vomiting in pregnancy. **Study dates** December 2008 to July 2009.	**Sample size** N=120 (n=14 lost to follow-up) Ginger: n=37 Placebo: n=36 Control: n=33 **Characteristics** <u>Age (years) - mean ±SD</u> Ginger: 27.35 (5.93) Placebo: 26.85 (4.90) Control: 25.95 (3.46) <u>Gestational age (weeks) - mean ±SD</u> Ginger: 8.97 (0.05) Placebo: 9.85 (2.27) Control: 9.30 (2.37) **Inclusion criteria** • Women with nausea and/or mild to moderate vomiting; • Less than 16 weeks' gestation; • Singleton pregnancy; • Literate and willing to participate; • No digestive disease;	**Interventions** Ginger: 3 x 250 mg capsules taken daily. Placebo: Lactose capsules with a similar shape. Control: No intervention. **Details** Women were followed for 7 days; women did not receive any intervention for the first 3 days, then ginger or placebo were given for the next 4 days. Women were advised to seek other treatment if this treatment failed or the frequency of vomiting exceeded 5 times a day. All women were advised to increase the number of meals with less volume, reduce high fat and high carbohydrate foods, avoid foods that trigger nausea and vomiting, start eating before they felt very hungry; to avoid stop smoking; eat dry bread on waking; avoiding fried, odorous, spicy foods; maintain good posture; avoid gas forming drinks.	**Results** **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy** <u>Reduction of Rhodes Index Scores - mean ±SD</u> <u>Vomiting</u> Ginger: 2.52 (2.41) Placebo: 0.24 (2.24) Control: 0.97 (2.24); p=0.001 <u>Nausea</u> Ginger: 3.86 (2.35) Placebo: 1.26 (1.57) Control: -0.33 (1.74); p=0.001 <u>Retching</u> Ginger: 2.15 (1.62) Placebo: 0.45 (1.60) Control: -0.34 (1.26); p=0.001 <u>Total Score</u> Ginger: 8.53 (4.75) Placebo: 1.96 (4.02) Control: -1.34 (3.88); p=0.001	**Limitations** **<u>Cochrane risk of bias tool V2</u>**: Randomisation process: Some concerns. (Block randomisation. No details provided for allocation concealment). Deviations from intended interventions: Some concerns. (No details provided). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Some concerns. (12% participants lost to follow-up). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Low risk of bias. (No other bias detected).

Study details	Participants	Interventions	Outcomes and Results	Comments
Source of funding Funded and supported by the Deputy of Research, Kashan University of Medical Sciences (KaUMS).	• No history of treatment for nausea and vomiting in the past 3 weeks; • Living in Kashan. **Exclusion criteria** • Women who did not complete the forms; • Side-effects from consuming ginger; • Treatment method failed to relieve nausea and vomiting, and requiring further treatment; • Nausea and vomiting >5 episodes per day.	**Power analysis** To achieve 90% power and taking into account 10% loss to follow-up, 40 women per treatment group was required. **Statistical analyses** Difference in mean Rhodes Index scores were compared using ANOVA. ANOVA and Kruskal-Wallis tests were used for normal and non-normal data. ANCOVA was used to control for confounding variables. Post-hoc Tukey's test performed. **Intention-to-treat (ITT) analysis** ITT analysis conducted.		Overall risk of bias: Some concerns
Full citation Sahakian, V., Rouse, D., Sipes, S., Rose, N., Niebyl, J., Vitamin B6 is effective therapy for nausea and vomiting of pregnancy: a randomized, double-blind placebo-controlled study, Obstet GynecolObstetrics and gynecology, 78, 33-6, 1991 **Ref Id** 939301 **Country/ies where the study was carried out** US	**Sample size** Vitamin B6: N=31 Placebo: N=28 **Characteristics** <u>Maternal age (years) - man ±SD</u> Vitamin B6: 29.4 (5.6) Placebo: 28.1 (5.3) <u>Gestation (weeks) - mean ±SD</u> Vitamin B6: 9.3 (2.4) Placebo: 9.7 (3.0) <u>Nausea score - mean ±SE</u> Vitamin B6: 6.4 (1.8) Placebo: 6.6 (1.9) <u>Severe nausea - mean ±SE</u>	**Interventions** Vitamin B6: 9 x 25 mg tablets of pyridoxine hydrochloride, taken orally once every 8 hours for 72 hours. Placebo: identical appearing tablets taken in the same regimen. **Details** Women were advised to divide their meals into frequent small ones rich in carbohydrates and low in fat. **Power analysis**	**Results** **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy** <u>Difference in nausea (all women) - mean ±SE</u> Vitamin B6: 2.9 (2.4) Placebo: 1.9 (2.0); p=NS <u>Difference in nausea (women with severe nausea) - mean ±SE</u> Vitamin B6: 4.3 (2.1) Placebo: 1.8 (2.2); p<0.01 <u>Difference in nausea (women with mild to moderate nausea) - mean ±SE</u>	**Limitations** **<u>Cochrane risk of bias tool V2</u>**: Randomisation process: Some concerns. (Randomisation by random numbers table. No details provided for allocation concealment). Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded and unaware of

Study details	Participants	Interventions	Outcomes and Results	Comments
Study type Randomised, placebo-controlled trial. **Aim of the study** To assess the effectiveness of vitamin B6 in the treatment of nausea and vomiting during pregnancy. **Study dates** July 1989 to August 1990. **Source of funding** Not stated.	Vitamin B6 (n=12): 8.2 (0.8) Placebo (n=10): 8.7 (0.9) Mild to moderate nausea - mean ±SE Vitamin B6 (n=19): 5.2 (1.3) Placebo (n=18): 5.3 (1.6) Vomiting (all women with nausea) - number (%) Vitamin B6: 15 (48) Placebo: 10 (36) Vomiting (women with severe nausea) - number (%) Vitamin B6 (n=12): 7 (58) Placebo (n=10); 6 (60) **Inclusion criteria** • Women with nausea and vomiting during pregnancy. **Exclusion criteria** • Women with another medical condition that might be associated with nausea and vomiting or patients requiring hospitalisation.	Not stated. **Statistical analyses** Data were analysed using the Student *t*-test and chi-squared test. Stratified analysis using Mantel-Haenszel chi-squared conducted to assess the number of women with vomiting. **Intention-to-treat (ITT) analysis** Not stated.	Vitamin B6: 2.0 (2.1) Placebo: 2.2 (2.0); p=NS Difference in vomiting (all women with nausea) - number (%) Vitamin B6: 8 (26) Placebo: 15 (54); p<0.05 Difference in vomiting (women with severe nausea) - number (%) Vitamin B6 (n=12): 3 (25) Placebo (n=10); 7 (70); p<0.05	treatment allocation. Only pharmacist was aware of treatment allocation). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: High risk of bias. (High loss to follow up (>20%)). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Low risk of bias. (No other bias detected). Overall risk of bias: Some concerns
Full citation Sharifzadeh, F., Kashanian, M., Koohpayehzadeh, J., Rezaian, F., Sheikhansari, N., Eshraghi, N., A	**Sample size** N=77 Ginger: n=28 Vitamin B6: n=26 Placebo: n=23	**Interventions** Ginger capsules: 500 mg Vitamin B6 capsules: 40 mg Placebo: not specified	**Results** **Critical outcomes** **Symptomatic relief during pregnancy**	**Limitations** **Cochrane risk of bias tool V2**:

Study details	Participants	Interventions	Outcomes and Results	Comments
comparison between the effects of ginger, pyridoxine (vitamin B6) and placebo for the treatment of the first trimester nausea and vomiting of pregnancy (NVP), Journal of Maternal-Fetal and Neonatal Medicine, 31, 2509-2514, 2018 **Ref Id** 924580 **Country/ies where the study was carried out** Iran **Study type** Triple-blind randomised controlled trial. **Aim of the study** To compare the effects of ginger, vitamin B6 and placebo in the treatment of pregnant women with mild to moderate nausea and vomiting. **Study dates** September 2012 to January 2015. **Source of funding** Not stated.	**Characteristics** Maternal age (years) - mean ±SD Ginger: 28.95 (0.5) Vitamin B6: 28.03 (3.7) Placebo: 29.03 (5.2) Gestational age (weeks) - mean ±SD Ginger: 10.9 (4.6) Vitamin B6: 10.8 (4.8) Placebo: 10.9 (3.6) Frequency of nausea before treatment - mean ±SD Ginger: 3.07 (0.87) Vitamin B6: 2.5 (1.0) Placebo: 2.5 (1.0) Intensity of nausea before treatment - mean ±SD Ginger: 3.03 (1.0) Vitamin B6: 2.26 (1.0) Placebo: 2.4 (1.0) Frequency of vomiting before treatment - mean ±SD Ginger: 1.8 (1.1) Vitamin B6: 1.4 (1.0) Placebo: 1.86 (1.2) **Inclusion criteria** • Pregnant women aged 20 to 35 years; • 6 to 16 weeks gestational age (according to reliable last menstrual period and ultrasound confirmation of the first trimester);	**Details** Women took two capsules per day for 4 days. **Power analysis** To achieve 80% power, 23 participants were required to detect a difference of 50% in the Rhodes Score after treatment. **Statistical analyses** Data were compared using variance analysis, Fisher exact test, Student *t*-test, Chi-square tests, Kruskal-Wallis one-way analysis of variance, and analysis of variance (ANOVA). **Intention-to-treat (ITT) analysis** Not stated.	Intensity of nausea before and after treatment - mean ±SD Ginger: 3.03 (1.0)/1.29 (1.0) Vitamin B6: 2.26 (1.0)/1.19 (0.69) Placebo: 2.4 (1.0)/2.08 (1.0) Frequency of nausea before and after treatment - mean ±SD Ginger: 3.07 (0.87)/1.29 (0.99) Vitamin B6: 2.5 (1.0)/1.19 (0.56) Placebo: 2.5 (1.0)/1.86 (0.86) Frequency of vomiting before and after treatment - mean ±SD Ginger: 1.8 (1.1)/0.6 (0.3) Vitamin B6: 1.4 (1.0)/0.53 (0.58) Placebo: 1.86 (1.2)/1.5 (0.99) Intensity of vomiting before and after treatment - mean ±SD Ginger: 1.8 (1.2)/0.6 (0.7) Vitamin B6: 1.38 (1.13)/0.7 (0.5) Placebo: 1.9 (1.2)/1.4 (0.97) Frequency of retching before and after treatment - mean ±SD Ginger: 2.3 (1.26)/1.5 (1.0) Vitamin B6: 2.19 (1.0)/0.5 (0.6)	Randomisation process: Some concerns. (Block randomisation used. No details provided on allocation concealment). Deviations from intended interventions: Low risk of bias. (Participants, investigators and statisticians were all blinded and unaware of treatments). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: High risk of bias. (Authors stated that 77 women finished the study, but did not state how many women started the study). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Low risk of bias. (No other biases detected). Overall risk of bias: Some concerns **Other information** Rhodes Questionnaire - 8 questions with five answers for each, using Likert scale:

Study details	Participants	Interventions	Outcomes and Results	Comments
	• Mild to moderate nausea and vomiting without the need for hospitalisation; • Singleton pregnancy with a live normal fetus; • No known gastrointestinal disorder; • Literate; • No known allergy or hypersensitivity to herbal medications. **Exclusion criteria** • Severe nausea and vomiting needing hospitalisation; • No acceptance of herbal medicine • Any other symptoms showing pathological problems such as diarrhoea, known gastrointestinal or any other systemic disorder; • Any drug use except common supplementation (folic acid); • Known intolerance to herbal medicine or allergy to ginger or vitamin B6; • Any disorder which could cause nausea and vomiting.		Placebo: 2.4 (0.9)/1.9 (1.16) Total Rhodes Score before and after treatment - mean ±SD Ginger: 19.7 (5.1)/8.4 (4.4) Vitamin B6: 16.7 (3.5)/7.2 (3.8) Placebo: 18.2 (4.7)/12.7 (3.9) Total score for nausea and vomiting index before and after treatment - mean ±SD ***Nausea*** Ginger: 7.0 (3.31)/2.4 (0.8) Vitamin B6: 6.8 (3.07)/2.5 (0.88) Placebo: 6.2 (3.15)/3.07 (3.01) ***Vomiting*** Ginger: 7.1 (2.1)/3.9 (0.8) Vitamin B6: 8.1 (1.4)/4.1 (0.8) Placebo: 7.7 (2.5)/4.4 (0.1) ANOVA and Tukey method - mean difference (SE; 95% CI); p value Ginger versus placebo: 0.26 (0.26; -0.21 to 0.74) Vitamin B6 versus placebo: 0.63 (0.2; 0.15 to 1.11)	Severity of nausea (duration, number or frequency of nausea and distress due to nausea), and severity of vomiting (number or frequency of vomiting, amount of vomit each time and distress due to vomiting), and retching (number or frequency of retching and distress due to retching). The score of zero –1 -2 -3 -4 (from the best to the worst) were given to the questions (total score was 32).

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Smith, C., Crowther, C., Beilby, J., Acupuncture to treat nausea and vomiting in early pregnancy: a randomized controlled trial, BirthBirth (Berkeley, Calif.), 29, 1-9, 2002 **Ref Id** 939303 **Country/ies where the study was carried out** Australia **Study type** Single-blind randomised controlled trial. **Aim of the study** To determine whether acupuncture (traditional and p6) is better than sham acupuncture. **Study dates** January 1997 to July 1999 **Source of funding** Not stated.	**Sample size** N=593 Traditional acupuncture: n=148 Pericardium 6 group: n=148 Sham acupuncture group: n=148 No acupuncture (control) group: n=149 **Characteristics** Age (years) - mean ± SD Traditional acupuncture: 29.5 (4.7) P6 acupuncture: 30.1 (4.8) Sham acupuncture: 29.6 (4.6) No acupuncture (control): 30.0 (5.2) Gestational age (weeks) - median and range Traditional acupuncture: 8.3 (5-13) P6 acupuncture: 8.3 (4-14) Sham acupuncture: 8.0 (4-13) No acupuncture (control): 8.4 (5-14) Parity (≥20 weeks) - number and % 0 Traditional acupuncture: 59 (40) P6 acupuncture: 51 (35) Sham acupuncture: 51 (34) No acupuncture (sham): 50 (34) 1 or more Traditional acupuncture: 89 (60) P6 acupuncture: 97 (65) Sham acupuncture: 97 (66) No acupuncture (control): 99 (67) Experience of nausea (Rhodes Index) baseline - mean ± SD Traditional acupuncture: 8.3 (2.5) p6 acupuncture: 8.2 (2.6) Sham acupuncture: 8.6 (2.5) No acupuncture (control): 8.4 (2.3) Experience of dry retching (Rhodes Index) baseline - mean ± SD	**Interventions** Traditional acupuncture: treatment based on their traditional Chinese medicine diagnosis. p6 acupuncture: treatment given to single point only (anterior surface of forearm). Sham acupuncture: needles inserted into an area close to, but not on, acupuncture points. No acupuncture (control): diet information sheet + 10 min phone call to assess wellbeing. **Details** 6 x 0.2x30 mm needles inserted for 20 mins. Participation in the trial was for 4 weeks. Women in the acupunctures groups and the sham acupuncture group were treated twice in week 1 and then once every week after. Nausea, dry retching, and vomiting measured by Rhodes Index of Nausea and Vomiting Form 2 (5-point Likert scale). Women's health status measured by MOS 36 Short Form Health Survey (SF36). **Power analysis** To achieve 80% power, 114 women needed to be	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Experience of nausea (Rhodes Index) - mean ± SD Day 7 Traditional acupuncture: 5.0 (3.0) p6 acupuncture: 5.4 (3.3) Sham acupuncture: 5.7 (2.8) No acupuncture (control): 6.1 (2.9) Day 14 Traditional acupuncture: 4.6 (3.1) p6 acupuncture: 4.8 (3.6) Sham acupuncture: 5.0 (3.0) No acupuncture (control): 6.0 (3.1) Day 21 Traditional acupuncture: 3.8 (3.1) p6 acupuncture: 4.3 (3.3) Sham acupuncture: 4.4 (2.7) No acupuncture (control): 5.8 (3.1) Day 26 Traditional acupuncture: 3.4 (3.0) p6 acupuncture: 4.0 (3.3) Sham acupuncture: 3.7 (2.8) No acupuncture (control): 5.0 (3.0)	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Some concerns. (Randomisation by telephone randomisation service, block randomisation. No details provided on allocation concealment). Deviations from intended interventions: Some concerns. (Participants were blinded but no findings on this reported in the paper). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Some concerns. (10% lost to follow-up after week 1 and then 25% lost to follow-up after week 4). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Some concerns. (Previous or current use of antiemetics or comfort measures did not preclude entry into the trial- record of use measured before, during, and at end of trial)

Study details	Participants	Interventions	Outcomes and Results	Comments
	Traditional acupuncture: 2.5 (1.9) p6 acupuncture: 2.5 (2.2) Sham acupuncture: 2.4 (2.1) No acupuncture (control): 2.6 (1.8) Experience of vomiting (Rhodes Index) baseline - mean ± SD Traditional acupuncture: 2.3 (2.7) p6 acupuncture: 2.1 (2.8) Sham acupuncture: 2.4 (2.8) No acupuncture (control): 2.1 (2.7) **Inclusion criteria** • Women less than 14 weeks pregnant; • Women with symptoms of nausea and vomiting. **Exclusion criteria** • If they had clinical signs of dehydration; • If there was reason to suspect their symptoms were not due to pregnancy.	recruited, allowing for a 10% loss to follow-up. **Statistical analyses** ANOVA used for normally distributed data. Kruskal-Wallis 1-way ANOVA by ranks for data not normally distributed. Mean SF36 domain cores were explored using ANOVA for repeated measurements between treatments and control groups. Tukey mean comparisons used to adjust multiple comparisons. Chi-square test for binary variables. **Intention-to-treat (ITT) analysis** ITT analysis done.	Experience of dry retching (Rhodes Index) - mean ± SD Day 7 Traditional acupuncture: 1.3 (1.4) p6 acupuncture: 1.6 (1.7) Sham acupuncture: 1.5 (1.8) No acupuncture (control): 1.7 (1.7) Day 14 Traditional acupuncture: 0.9 (1.3) p6 acupuncture: 1.3 (1.5) Sham acupuncture: 1.3 (1.7) No acupuncture (control): 1.6 (1.7) Day 21 Traditional acupuncture: 0.9 (1.4) p6 acupuncture: 0.9 (1.3) Sham acupuncture: 0.9 (1.3) No acupuncture (control): 1.6 (1.7) Day 26 Traditional acupuncture: 0.8 (1.4) p6 acupuncture: 0.9 (1.3) Sham acupuncture: 0.9 (1.4) No acupuncture (control): 1.6 (1.7) Experience of vomiting (Rhodes Index) - mean ± SD Day 7 Traditional acupuncture: 1.4 (2.0)	Overall risk of bias: Some concerns

Study details	Participants	Interventions	Outcomes and Results	Comments
			p6 acupuncture: 1.2 (2.0) Sham acupuncture: 1.5 (2.2) No acupuncture (control): 1.5 (2.1) <u>Day 14</u> Traditional acupuncture: 1.1 (1.8) p6 acupuncture: 1.3 (2.2) Sham acupuncture: 1.4 (2.1) No acupuncture (control): 1.6 (2.2) <u>Day 21</u> Traditional acupuncture: 0.9 (1.6) p6 acupuncture: 1.2 (2.1) Sham acupuncture: 1.0 (1.7) No acupuncture (control): 1.1 (2.1) <u>Day 26</u> Traditional acupuncture: 0.9 (1.5) p6 acupuncture: 0.9 (1.8) Sham acupuncture: 1.0 (1.6) No acupuncture (control): 1.4 (2.0) **Fetal death** <u>Pregnancy loss</u> Traditional acupuncture: n=12 p6 acupuncture: n= 12 Sham acupuncture: n= 8 No acupuncture (control): n= 16	

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Vutyavanich, T., Wongtra-ngan, S., Ruangsri, R., Pyridoxine for nausea and vomiting of pregnancy: a randomized, double-blind, placebo-controlled trial, Am J Obstet GynecolAmerican journal of obstetrics and gynecology, 173, 881-4, 1995 **Ref Id** 939308 **Country/ies where the study was carried out** Thailand **Study type** Randomised placebo-controlled trial (double-blind). **Aim of the study** To determine the effectiveness of pyridoxine for nausea and vomiting of pregnancy. **Study dates** May 1993 to April 1994. **Source of funding** Research grant from the Faculty of Medicine Endowment Fund for Medical Research.	**Sample size** N= 342 (n=6 lost to follow-up) Pyridoxine group: n=173 (n=4 lost to follow-up) Placebo group: n=169 (n=2 lost to follow-up) **Characteristics** Age (years) - mean ± SD Pyridoxine group: 26.9 (5.2) Placebo group: 27.1 (5.4) Parity - number and percentage Primiparous Pyridoxine group: 80 (47.3) Placebo group: 84 (50.3) Multiparous Pyridoxine group: 89 (52.7) Placebo group: 83 (49.7) Gestational age (weeks) - mean ± SD Pyridoxine group: 10.9 (2.7) Placebo group: 10.9 (2.8) Baseline nausea scores (cm) - mean ± SD Pyridoxine group: 4.9 (2.4) Placebo group: 5.2 (5.3) **Inclusion criteria** • Pregnant women with nausea of pregnancy, with or without vomiting; • Women who first attended the clinic at gestational age ≤ 17 weeks.	**Interventions** Pyridoxine group: 20 x 10mg pyridoxine hydrochloride Placebo group: placebo tablets **Details** Tablets to be taken orally every 8 hours for 5 days. Advised to take tablets between 6-8am, 2-4pm, and 10-12pm. Nutritional advice on high carbohydrate and low fat diet given to participants. Advised to take no other medications. Severity of nausea recorded on VAS from 0 to 10, where 0=no nausea and 10=nausea as bad as it could be. Records made at baseline, and twice a day for the following 5 days. **Power analysis** Not stated. **Statistical analyses** Independent t test used to compare mean change in severity of nausea between groups. Chi square test used to compared proportions of subjects with vomiting before and after treatment. **Intention-to-treat (ITT) analysis** Not stated.	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Mean difference in nausea scores (baseline - post therapy) - mean ± SD Day 1 Pyridoxine group: 2.2 (2.1) Placebo group: 1.2 (2.4) Day 2 Pyridoxine group: 2.8 (2.3) Placebo group: 1.7 (2.8) Day 3 Pyridoxine group: 3.0 (2.4) Placebo group: 2.1 (3.0) Day 4 Pyridoxine group: 3.2 (2.6) Placebo group: 2.5 (3.2) Day 5 Pyridoxine group: 3.3 (2.7) Placebo group: 2.7 (2.9) Mean Pyridoxine group: 2.9 (2.2) Placebo group: 2.0 (2.7) Mean change in number of vomiting episodes (baseline - post therapy) - mean ± SD Day 1 Pyridoxine group: 0.67 (1.9) Placebo group: 0.07 (2.5) Day 2 Pyridoxine group: 1.17 (2.1) Placebo group: 0.32 (3.0) Day 3	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Some concerns. (Randomisation by random numbers table. No details provided for allocation concealment). Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded and unaware of treatment allocation). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Low risk of bias. (Little loss to follow up (2%)). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Low risk of bias. (No other bias detected). Overall risk of bias: Low risk

Study details	Participants	Interventions	Outcomes and Results	Comments
	Exclusion criteria • Women who had other medical disorders (for example hepatitis or GU diseases) that might manifest with nausea/vomiting; • Women who had a mental health illness, or had language/geographic barriers; • Women who had taken other medications in the past week that might aggravate or alleviate nausea or vomiting (for example, iron tablets, antiemetics, and so on); • Women who were unable to take the medication as prescribed; • Women who were unable to return for a follow-up visit within 1 week.		Pyridoxine group: 1.42 (2.1) Placebo group: 0.64 (2.9) Day 4 Pyridoxine group: 1.59 (2.2) Placebo group: 1.15 (2.3) Day 5 Pyridoxine group: 1.44 (2.6) Placebo group: 1.34 (2.3) Average Pyridoxine group: 1.22 (2.0) Placebo group: 0.65 (2.4)	
Full citation Vutyavanich, T., Kraisarin, T., Ruangsri, R., Ginger for nausea and vomiting in pregnancy: randomized, double-masked, placebo-controlled trial, Obstet GynecolObstetrics and gynecology, 97, 577-82, 2001 **Ref Id**	**Sample size** N= 70 Ginger group: n=32 Placebo group: n=38 **Characteristics** Age (years) - mean ± SD Ginger group: 28.3 (5.8)	**Interventions** Ginger group: 250mg ginger capsules Placebo group: placebo tablets **Details** One capsule, three times a day after meals, and one	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Nausea scores - mean ± SD Day 0 - day 1 Ginger group: 0.9 (2.1) Placebo group: 0.3 (1.9) p=0.078	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Some concerns. (Randomisation by random numbers table. Allocation

Study details	Participants	Interventions	Outcomes and Results	Comments
939307 **Country/ies where the study was carried out** Thailand **Study type** Randomised placebo-controlled trial (double blind). **Aim of the study** To determine the effectiveness of ginger for the treatment of nausea and vomiting of pregnancy. **Study dates** October 1998- February 1999 **Source of funding** Not stated.	Placebo group: 28.6 (5.5) Parity - number and % Nulliparous Ginger group: 13 (40.6) Placebo group: 16 (45.7) Multiparous Ginger group: 19 (59.4) Placebo group: 19 (54.3) Gestational age (week) - mean ± SD Ginger group: 10.4 (2.3) Placebo group: 10.3 (2.6) Baseline nausea scores (cm) - mean ± SD Ginger group: 5.4 (2.1) Placebo group: 4.7 (2.1) **Inclusion criteria** • Women who were before 17 weeks gestation; • Women who had nausea of pregnancy, with or without vomiting. **Exclusion criteria** • Women who had other medical disorders (for example hepatitis or GI diseases) that might manifest with nausea or vomiting; • Women with a mental health illness;	capsule before bedtime for 4 days. Nutritional advice given to have diet rich in carbohydrates and low in fat. Patients advised not to take any other medications outside the trial. A VAS was used to grade severity of nausea over the past 24 hours, 0 to 10- where 0 = no nausea and 10= nausea as bad as it could be. Recordings made twice a day, at noon and bedtime. **Power analysis** To achieve a power of 90% and an alpha of 0.05, a sample size of 31 subjects per group was required. To allow for a 10% dropout rate, a total sample size of 70 subjects was projected. **Statistical analysis** Wilcoxon rank-sum test used to compare median change in severity of nausea and change in number of vomiting episodes. Fisher exact test was used to compare change in severity of nausea. Chi squared test used to compare proportion of subjects vomiting before and after treatment. **Intention-to-treat (ITT) analysis**	Day 0 - day 2 Ginger group: 1.5 (2.1) Placebo group: 0.8 (2.7) p=0.054 Day 0 - day 3 Ginger group: 2.6 (2.5) Placebo group: 1.3 (2.4) p=0.031 Day 0 - day 4 Ginger group: 3.4 (2.5) Placebo group: 1.5 (2.9) p=0.005 Day 0 - average day 1 to 4 Ginger group: 2.1 (1.9) Placebo group: 0.9 (2.2) p=0.014 Number of vomiting episodes - mean ± SD Day 0 - day 1 Ginger group: 0.4 (1.5) Placebo group: 0.1 (1.4) p=0.153 Day 0 - day 2 Ginger group: 1.4 (1.3) Placebo group: 0.3 (1.4) p=0.001 Day 0 - day 3 Ginger group: 1.7 (1.5) Placebo group: 0.4 (1.3) p=0.001 Day 0 - day 4 Ginger group: 2.3 (1.5) Placebo group: 0.4 (1.8) p=0.001 Day 0 - average day to 4 Ginger group: 1.4 (1.3) Placebo group: 0.3 (1.1) p=0.001 Symptom rating - number and % Much worse	concealed by sealed black, opaque envelope). Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded and unaware of treatment allocation). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Some concerns. (10% participants lost to follow up. More participants lost from placebo group). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Low risk of bias. (No other bias detected). Overall risk of bias: Some concerns

Study details	Participants	Interventions	Outcomes and Results	Comments
	• Women who had language/geographic barriers; • Women who had taken other medication in the past week that might aggravate or alleviate nausea or vomiting (for example iron tablets or antiemetics); • Women who were unable to take the medication as prescribed; • Women who were unable to return for a follow-up visit within 1 week; • Women who refused to participate in the trial.	Effectiveness assessed by ITT using Wilcoxon rank-sum test.	Ginger group: 0 (0) Placebo group: 0 (0) Worse Ginger group: 0 (0) Placebo group: 9 (25.7) Same Ginger group: 4 (12.5) Placebo group: 16 (45.7) Better Ginger group: 8 (25) Placebo group: 9 (25.7) Much better Ginger group: 20 (62.5) Placebo group: 1 (2.9%) **Fetal death** Abortion - number Ginger group: n=1 Placebo group: n=3 **Important outcomes** **There were no adverse events reported**.	
Full citation Werntoft, E., Dykes, A. K., Effect of acupressure on nausea and vomiting during pregnancy. A randomized, placebo-controlled, pilot study, J Reprod MedThe Journal of reproductive medicine, 46, 835-9, 2001 **Ref Id** 939309 **Country/ies where the study was carried out**	**Sample size** N=80 (N=60 analysed) Acupressure: N=20 Placebo: N=20 Control: N=20 **Characteristics** Maternal age (years) - mean ±SD Acupressure: 31.0 (3.9) Placebo: 29.0 (5.8) Control: 30.0 (5.3) Week of pregnancy - mean ±SD Acupressure: 9.8 (1.9) Placebo: 9.6 (1.6)	**Interventions** Acupressure: instructions and wristband with button applying pressure at the P6 point. Placebo: instructions and wristband with button applying pressure at a point on the upper side of the wrist. Control: no treatment. **Details** Women were instructed to wear wristbands for 2	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Degree of nausea after day 1 - mean ±SD Acupressure: 5.2 (2.7) Placebo: 5.6 (2.5) Control: 7.6 (1.6); p=0.005 Degree of nausea after day 3 - mean ±SD Acupressure: 5.6 (2.3) Placebo: 5.5 (2.8) Control: 7.2 (1.3); p=0.038 Degree of nausea after day 6 - mean ±SD	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Some concerns. (Women drew an envelope form a box, envelopes had the same appearance but different contents. No further details provided). Deviations from intended interventions: Some concerns. (Participants opened envelopes when they got

Study details	Participants	Interventions	Outcomes and Results	Comments
Sweden **Study type** Randomised, placebo-controlled pilot study. **Aim of the study** To assess the effectiveness of acupressure (PC) in the treatment of nausea and vomiting during pregnancy. **Study dates** Not stated. **Source of funding** None stated.	Control: 10.8 (2.2) Degree of nausea before pregnancy - mean ±SD Acupressure: 1.4 (1.4) Placebo: 1.1 (0.9) Control: 1.5 (2.4) Degree of nausea before treatment - mean ±SD Acupressure: 8.4 (1.2) Placebo: 8.4 (1.4) Control: 8.0 (1.5) **Inclusion criteria** • Healthy and normal pregnancy; • Experiencing nausea and vomiting; • Signed informed consent form. **Exclusion criteria** • Ongoing use of other treatments for nausea and vomiting.	weeks, only removing on showering. **Power analysis** Not stated. **Statistical analyses** One-way ANOVA used to test for significant differences between treatment groups. General linear model repeated measure and ANOVE with post hoc Bonferoni used to compare direction of change over time. **Intention-to-treat (ITT) anlaysis** Not stated.	Acupressure: 4.9 (2.4) Placebo: 6.3 (2.4) Control: 6.9 (2.0); p=0.017 Degree of nausea after day 14 - mean ±SD Acupressure: 4.2 (2.6) Placebo: 5.9 (2.4) Control: 6.5 (2.2); p=0.011	home; not possible to blind for control (no treatment) group). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: High risk of bias. (High loss to follow up (25%). Six questionnaires from the P6 and the placebo groups were excluded due to incompleteness, four women found the wristbands too tight to use, and two women had miscarriages. Eight women did not respond, and it was unclear which group they belonged to). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Low risk of bias. (No other bias detected). Overall risk of bias: High risk
Full citation Willetts, K. E., Ekangaki, A., Eden, J. A., Effect of a ginger extract on pregnancy-induced nausea: A randomised controlled trial, Australian	**Sample size** Ginger: N=60 Placebo: N=60	**Interventions** Ginger: 125 mg ginger extract capsule taken 4 times a day. Placebo: soya bean capsule taken 4 times a day.	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** There were no significant differences between	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Some concerns. (Randomisation

Study details	Participants	Interventions	Outcomes and Results	Comments
and New Zealand Journal of Obstetrics and Gynaecology, 43, 139-144, 2003 **Ref Id** 890490 **Country/ies where the study was carried out** Australia **Study type** Randomised controlled trial. **Aim of the study** To assess the effect of ginger extract on nausea during pregnancy. **Study dates** March 1999 to November 1999. **Source of funding** Eurovita Pty Limited, Denmark.	**Characteristics** Maternal age (years) - mean (range) Ginger: 33 (22 to 43) Placebo: 31 (19 to 44) No statistically significant difference between treatment groups in terms of parity, weeks of gestation and body mass index). 68 women (58%) had nausea throughout the day with only 13 women (11%) having symptoms only in the morning. 46 women (39%) had constant nausea and 69 (58%) of women reported vomiting episodes. **Inclusion criteria** • Women <20 weeks pregnant; • Experiencing morning sickness daily for at least 1 week; • Failed to respond to dietary intervention. **Exclusion criteria** • Hospitalisation for dehydration during the current pregnancy; • Significant medical problems (for example hypertension, epilepsy or diabetes);	**Details** Women who had used ginger, vitamin B6 or prescription drugs for nausea were required to have a 3-day wash-out period prior to entering the study. **Power analysis** To achieve 80% power and assuming 20% dropout rate, 120 women were required. **Statistical analyses** Differences between treatment groups were analysed using regression models using generalised estimating equations (including treatment effect, day of effect, time effect, treatment-day interaction, and treatment-time interaction. **Intention-to-treat (ITT) analysis** Not stated.	treatment groups for any of the vomiting symptoms. For retching symptoms, the ginger extract group was reported to have statistically significant lower symptoms scores than the placebo group for the first 2 days only **Fetal death** Spontaneous abortion (number) Ginger (n=60): 3 Placebo (n=60): 1 **Important outcomes** **Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment** Adverse events (number) Ginger: 3 (n=1 hospitalisation for dehydration, n=2 heartburn/reflux) Placebo: 2 (n=1 hospitalisation for dehydration, n=1 worsening of symptoms leading to taking pharmaceutical treatment) Other adverse events were reported, but it was unclear whether they required hospitalisation.	by random blocks of 6. Allocation concealed by sealed envelopes). Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded and unaware of treatment allocation). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Low risk of bias. (<20% participants lost to follow-up). Selection of the reported result: High risk of bias. (Limited reporting on vomiting and retching; results displayed in graphs only, no raw (useable) data; only data for 4 days were analysed while women were given 2 weeks supply of capsules). Other bias: Some concerns. (Follow-up data in 81 women; women in the ginger group took ginger for 4 days and those in the placebo group took ginger for 4 days; all were given 2 weeks supply following the end of the trial). Overall risk of bias: Some concerns **Other information**

Study details	Participants	Interventions	Outcomes and Results	Comments
	• Known allergy to ginger.			Follow-up assessment was carried out in 81 women. Neonatal deaths were reported in the ginger treatment group (n=4) but not in the placebo group. There was one premature birth at 28 weeks, but it was unclear which treatment group this related to.
Full citation Zhang, R., Persaud, N., 8-way randomized controlled trial of doxylamine, pyridoxine and dicyclomine for nausea and vomiting during pregnancy: Restoration of unpublished information, Plos one, 12 (1) (no pagination), 2017 **Ref Id** 924448 **Country/ies where the study was carried out** US **Study type** Double-blind, multicentre, randomised placebo-controlled trial **Aim of the study** To assess the efficacy of doxylamine, pyridoxine, and dicyclomine and their combinations in the treatment of nausea and vomiting during pregnancy.	**Sample size** N=2,359 (n=51 excluded due to 'incomplete data'; n=132 (6%) lost to follow-up; 709 (30%) failed to meet protocol criteria); N=1,599 Doxylamine/pyridoxine: n=279 Doxylamine: n=283 Pyridoxine: n=286 Placebo: n=281 **Characteristics** Baseline nausea severity - number (%) *None* Doxylamine/pyridoxine: 0 Doxylamine: 0 Pyridoxine: 1 (0.3) Placebo: 0 *Mild* Doxylamine/pyridoxine: 50 (18) Doxylamine: 66 (23) Pyridoxine: 55 (19) Placebo: 64 (23) *Moderate* Doxylamine/pyridoxine: 147 (53) Doxylamine: 153 (54) Pyridoxine: 150 (52) Placebo: 143 (51) *Severe*	**Interventions** Doxylamine succinate (Decapryn): 10 mg Pyridoxine hydrochloride: 10 mg *Dicyclomine hydrochloride (Bentyl): 10 mg Placebo: no details provided Doxylamine succinate + pyridoxine hydrochloride: 10 mg each *Dicyclomine hydrochloride + pyridoxine hydrochloride: 10 mg each *Dicyclomine hydrochloride + doxylamine succinate: 10 mg each *Doxylamine succinate, pyridoxine hydrochloride + dicyclomine hydrochloride (Bendectin): 10 mg each Note: *data not extracted for these interventions as dicyclomine hydrochloride not intervention of interest. **Details** Each patients took 2 tablets at bedtime and, if necessary,	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Improvement in nausea - number (calculated) (%) - physician evaluations Doxylamine/pyridoxine (n=213): 166 (78) Doxylamine (n=209): 161 (77) Pyridoxine (n=191): 126 (66) Placebo (n=181): 103 (57) Absolute difference in % improved versus placebo (95% CI) - physician evaluations Doxylamine/pyridoxine: 14 (3.8 to 24) Doxylamine: 20 (1 to 29) Pyridoxine: 9 (-1.3 to 19) Improvement in nausea - reanalysis of patient diary reports - number (%); per protocol Doxylamine/pyridoxine (n=213): 136 (64) Doxylamine (n=209): 117 (56) Pyridoxine (n=191): 67 (35) Placebo (n=181): 56 (31)	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Some concerns. (No details provided for randomisation. Allocation concealment done at a centralised service inMerrell-National Laboratories). Deviations from intended interventions: Low risk of bias. (Patients, researchers and outcome assessors were not aware of treatments). Measurement of the outcome: Low risk of bias. (Mostly self-reported outcomes). Missing outcome data: High risk of bias. (High attrition-1,599 (68%) of 2,359 participants analysed).

Study details	Participants	Interventions	Outcomes and Results	Comments
Study dates **Source of funding** Original trial conducted by Merrell-National Laboratories. Subsequent authors received no project specific funding.	Doxylamine/pyridoxine: 81 (29) Doxylamine: 64 (23) Pyridoxine: 80 (28) Placebo: 74 (26) Baseline vomiting severity - number (%) *None* Doxylamine/pyridoxine: 122 (44) Doxylamine: 124 (44) Pyridoxine: 124 (43) Placebo: 104 (37) *Mild* Doxylamine/pyridoxine: 71 (25) Doxylamine: 83 (29) Pyridoxine: 67 (23) Placebo: 88 (31) *Moderate* Doxylamine/pyridoxine: 59 (21) Doxylamine: 55 (19) Pyridoxine: 66 (23) Placebo: 64 (23) *Severe* Doxylamine/pyridoxine: 26 (9) Doxylamine: 20 (7) Pyridoxine: 29 (10) Placebo: 25 (9) **Inclusion criteria** • Women in the first trimester of pregnancy (first 12 weeks of gestation); • Complaining of nausea and/or vomiting; • Assumed by the investigator to be co-	1 additional tablet in the morning and in the mid-afternoon, for 7 nights. **Power analysis** Not stated. **Statistical analyses** Not stated. Original authors presented percentages, without denominators or numerical results. Publishing authors used information available elsewhere in the trial to estimate denominators for each treatment arm and to calculate exact numbers of women with specific outcomes based on reported percentages. **Intention-to-treat (ITT) analysis** Per protocol.	Estimated relative risk (RR) of improvement versus placebo (95% CI) Doxylamine/pyridoxine: 2.1 (1.6 to 2.6) Doxylamine: 1.8 (1.4 to 2.3) Pyridoxine: 1.1 (0.85 to 1.5) Estimated absolute difference in % improvement versus placebo (95 % CI) Doxylamine/pyridoxine: 33 (23 to 42) Doxylamine: 25 (15 to 34) Pyridoxine: 4 (-6 to 14) Adverse events reported, but not clear whether they required hospitalisation (drowsiness, fatigue and headache: doxylamine/pyridoxine (n=267): 23 (9%) Doxylamine (n=273): 41 (15%) Pyridoxine (n=272): 26 (10%) Placebo (n=270): 30 (11%)	Selection of the reported result: High risk of bias. (No outcomes pre-specified in trial protocol). Other bias: High risk of bias. (Important information about the study not available. The FDA ordered that data from one investigator be excluded because of concerns about data integrity. The trial was apparently not completed. The results were never published; unclear whether statistical methods used by the publishing authors reliable/valid) Overall risk of bias: High risk **Other information** This is an unpublished 1970s trial, subsequently published according to the restoring invisible and abandoned trials (RIAT) initiative. Study includes participants who have severe nausea and/or vomiting with each arm having <33% severe forms. Note that the trial included 4 other treatment arms not eligible for inclusion as dicylomine hydrochloride is not an intervention of interest: Dicyclomine hydrochloride (Bentyl); dicyclomine

Study details	Participants	Interventions	Outcomes and Results	Comments
	operative and complete questionnaires. **Exclusion criteria** Not stated.			hydrochloride/doxylamine hydrochloride combination; dicyclomine hydrochloride/pyridoxine hydrochloride combination; dicyclomine hydrochloride/doxylamine succinate/pyridoxine hydrochloride combination.

Hyperemesis gravidarum

Table 6: Clinical evidence tables for hyperemesis gravidarum

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Abas, M. N., Tan, P. C., Azmi, N., Omar, S. Z., Ondansetron compared with metoclopramide for hyperemesis gravidarum: a randomized controlled trial, Obstetrics & GynecologyObstet Gynecol, 123, 1272-9, 2014 **Ref Id** 924996 **Country/ies where the study was carried out** Malaysia **Study type** Randomised controlled trial.	**Sample size** Ondansetron: N=60 (N=72 analysed) Metoclopramide: N=60 (N=74 analysed) **Characteristics** Age (years) - mean ±SD Ondansetron: 29.7 (4.7) Metoclopramide: 29.2 (4.5) Gestational age (weeks) - mean ±SD Ondansetron: 9.6 (2.3) Metoclopramide: 9.4 (2.5) Weight (kg) - mean ±SD Ondansetron: 57.0 (10.8) Metoclopramide: 57.0 (10.7) BMI (kg/m^2) - mean ±SD Ondansetron: 23.5 (4.3) Metoclopramide: 23.1 (3.9)	**Interventions** Ondansetron: 4 mg diluted in 100 mL normal saline. Metoclopramide: 10 mg diluted in 100 mL normal saline. **Details** Drugs infused over 10 minutes through an indwelling intravenous catheter as soon as possible after randomisation, and then every 8 hours for a course of 4 doses over the next 24 hours. Women received standard care for hyperemesis gravidarum as per hospital management.	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Vomit-free during 24-hour treatment - number (%) Ondansetron: 39 (48.8) Metoclopramide: 34 (42.5) RR: 1.3 (0.7 to 2.4); p=0.53 Nausea score - median (IQR) After 8 hours treatment Ondansetron: 4 (3 to 6) Metoclopramide: 5 (4 to 6); p=0.05 After 16 hours treatment* Ondansetron: 3 (1 to 4) Metoclopramide: 3 (2 to 4.75); p=0.28 After 24 hours treatment** Ondansetron: 1 (1 to 3)	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Low risk of bias. (Random blocks of 4 or 8 using computer-generated randomisation sequence. Allocation concealment by sealed, opaque envelopes stating drug A or B). Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded; study drug packaging identical and labelling of drugs swapped periodically to prevent inadvertent revealing of allocation).

Study details	Participants	Interventions	Outcomes and Results	Comments
Aim of the study To compare the effectiveness of ondansetron versus metoclopramide in the treatment of hyperemesis gravidarum. **Study dates** November 2011 to August 2012. **Source of funding** Supported by a University of Malaya grant.	Ketonuria - number (%) 2+ Ondansetron: 17 (21.3) Metoclopramide: 12 (15.0) 3+ Ondansetron: 13 (16.3) Metoclopramide: 11 (13.8) 4+ Ondansetron: 50 (62.5) Metoclopramide: 57 (71.3) Nausea score (10-point visual numerical rating score) - median (interquartile range; IQR) Ondansetron: 8 (7 to 9) Metoclopramide: 8 (7 to 10) **Inclusion criteria** • Women hospitalised for the first time with clinical diagnosis of hyperemesis gravidarum (presence of nausea and intractable vomiting sufficient to cause dehydration and metabolic disturbance of a severity to required hospitalisation); • Clinical dehydration and ketonuria (of 2+ or greater) on urine dipstick; • Gestation of 16 weeks or less. **Exclusion criteria**	**Power analysis** To achieve 80% power and assuming 10% dropout, 158 women were required. **Statistical analyses** Student *t*-test used to analyse normally distributed continuous data and Mann-Whitney *U* test used when data distribution not normal. Categorical data were analysed using Fisher exact test or chi-squared test. Ordinal data were analysed using Mann-Whitney *U* test. Repeated measures analysis of variance was used to analyse nausea visual numerical rating scale scores. **Intention-to-treat (ITT) analysis** ITT analysis.	Metoclopramide: 2 (1 to 3); p=0.68 **Important outcomes** **Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment** Hospital stay (days) - median (IQR) Ondansetron: 1.9 (1.5 to 2.4) Metoclopramide: 2.0 (1.7 to 2.7); p=0.10 Adverse events reported but not stated whether required hospitalisation.	Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Low risk of bias. (Low amount of missing data (9%)). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Low risk of bias. (No other bias detected). Overall risk of bias: Low risk **Other information** *n=159 (missing or incomplete data for 1 patient, but not stated in which treatment arm). **n=155 (missing or incomplete data for 5 patients, but not stated in which treatment arms).

Study details	Participants	Interventions	Outcomes and Results	Comments
	• Multiple gestation; • Established non-viable pregnancy; • Pre-existing medical condition that could be associated with nausea and vomiting; • Known allergy to metoclopramide or ondansetron.			
Full citation Adlan, A. S., Chooi, K. Y., Mat Adenan, N. A., Acupressure as adjuvant treatment for the inpatient management of nausea and vomiting in early pregnancy: A double-blind randomized controlled trial, Journal of obstetrics and gynaecology research, 43, 662-668, 2017 **Ref Id** 924458 **Country/ies where the study was carried out** Malaysia **Study type** Prospective double-blind, randomized controlled trial **Aim of the study**	**Sample size** N = 120 Acupressure: n=60 Sham acupressure: n= 60 **Characteristics** *Similar baseline demographics between the two groups* Age (years) - mean (SD) Acupressure: 29.0 (4.92) Sham acupressure:28.4 (4.34) Gestational age (weeks) - mean (SD) Acupressure: 9.7 (2.09) Sham acupressure: 9.2 (2.03) Parity - median (interquartile range) Acupressure: 1 (0-2) Sham acupressure: 1 (0-2) **Inclusion criteria** 1. Low risk, spontaneously conceived singleton pregnancies	**Interventions** Adjuvant acupressure band (N=60) Adjuvant sham acupressure band (N=60) **Details** Acupressure band with a small bead beneath it that exerted pressure onto the Neiguan point (P6) for 12 h daily for three days. Sham acupressure band without acupressure bead beneath it located at the Neiguan point (P6) for 12 h daily for three days. **Power analysis** Sample size was calculated based on previous studies. A sample size of 120 in total required. Significance was set at 0.05 with the power of 80%.	**Results** Note: Number of participants in each group for all outcomes is 60. **Critical outcomes** **Symptomatic relief during pregnancy** Severity of nausea at the end of the first treatment day using Quantification of Emesis, Retching and Nausea (PUQE) scoring system - mean (SD) Acupressure: 3.25 (1.05) Sham acupressure: 4.05 (0.79) Severity of nausea at the end of the second treatment day using PUQE - mean (SD) Acupressure: 2.27 (0.90) Sham acupressure: 3.20 (0.70) Severity of nausea at the end of the third treatment day using PUQE - mean (SD)	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Some concerns. (Block randomisation sequence used. No information provided about allocation concealment). Deviations from intended interventions: Low risk of bias. (Participants and investigator were blinded). Measurement of the outcome: Some concerns. (It is unclear who assessed the outcomes). Missing outcome data: Low risk of bias. (No reported loss to follow up and no missing data).

Study details	Participants	Interventions	Outcomes and Results	Comments
To evaluate the efficacy of acupressure at the Neiguan point (Pericardium [P]6) as adjuvant treatment during inpatient management of severe nausea and vomiting in pregnancy **Study dates** December 2012 - May 2013 **Source of funding** Not reported	2. Between 5 and 14 weeks of gestation 3. With with moderate to severe hyperemesis gravidarum requiring hospital admission **Exclusion criteria** 1. Pregnant women with multiple or molar pregnancy 2. Had prior knowledge of the acupressure band 3. Presence of infections such as urinary tract infection or gastroenteritis 4. Medical conditions such as hyperthyroidism 5. History of drug reaction toward metoclopramide	**Statistical analyses** Continuous variables assessed using the Kolmogorov–Smirnov test. The Student t test was applied in the analyses of normally distributed continuous variables, with the Mann–Whitney U test used by preference if data distribution was non-normal. Two-by two categorical datasets were analyzed by Fisher's exact test and larger than 2 × 2 datasets by the chi-square test. Ordinal variables were analyzed by Mann–Whitney U test. All tests were two-sided and $P < 0.05$ was considered significant. **Intention-to-treat analysis** Analysis was conducted by intention to treat.	Acupressure: 1.57 (0.81) Sham acupressure: 2.58 (0.93) Severity of vomiting at the end of the first treatment day using PUQE - mean (SD) Acupressure: 3.02 (0.97) Sham acupressure: 3.92 (0.79) Severity of vomiting at the end of the second treatment day using PUQE - mean (SD) Acupressure: 2.03 (0.82) Sham acupressure: 3.17 (0.64) Severity of vomiting at the end of the third treatment day using PUQE - mean (SD) Acupressure: 1.48 (0.65) Sham acupressure: 2.58 (0.62) Severity of retching at the end of the first treatment day using PUQE - mean (SD) Acupressure: 2.87 (1.19) Sham acupressure: 3.18 (1.41) Severity of retching at the end of the second treatment day using PUQE - mean (SD) Acupressure: 1.85 (0.69) Sham acupressure: 2.57 (0.83) Severity of retching at the end of the third treatment day using PUQE - mean (SD) Acupressure: 1.35 (0.52)	Selection of the reported result: Some concerns. (No trial protocol reported). Other bias: Low risk. (No significant differences between groups) Overall risk of bias: Some concerns **Other information** Both groups were administered intravenous fluid and regular intravenous metoclopramide and thiamine supplements during inpatient admission.

Study details	Participants	Interventions	Outcomes and Results	Comments
			Sham acupressure: 1.93 (0.73) Severity of nausea, vomiting, and retching at the end of the first treatment day using PUQE - mean (SD) Acupressure: 9.13 (2.02) Sham acupressure: 11.15 (1.87) Severity of nausea, vomiting, and retching at the end of the second treatment day using PUQE - mean (SD) Acupressure: 6.15 (1.93) Sham acupressure: 8.93 (1.51) Severity of nausea, vomiting, and retching at the end of the third treatment day using PUQE - mean (SD) Acupressure: 4.40 (1.63) Sham acupressure: 7.10 (1.61) **Important outcomes** **Number of days in hospital for treatment of nausea and vomiting** Days in hospital - mean (SD) Acupressure: 2.83 (0.62) Sham acupressure: 3.88 (0.87) **Women's experience and satisfaction of care during or at end of pregnancy** Women's satisfaction (Satisfied vs. Neutral) - Number (%) Acupressure: 43 vs 17 (71.7 vs 28.3)	

Study details	Participants	Interventions	Outcomes and Results	Comments
			Sham acupressure: 51 vs 9 (85 vs 15)	
Full citation Bondok, R. S., El Sharnouby, N. M., Eid, H. E., Abd Elmaksoud, A. M., Pulsed steroid therapy is an effective treatment for intractable hyperemesis gravidarum, Critical care medicine, 34, 2781-2783, 2006 **Ref Id** 925104 **Country/ies where the study was carried out** Egypt **Study type** Randomised controlled trial. **Aim of the study** To compare the effectiveness of pulsed hydrocortisone treatment versus metoclopromide for the treatment of intractable hyperemesis gravidarum. **Study dates** March 2003 to July 2005.	**Sample size** Hydrocortisone: N=20 Metoclopramide: N=20 **Characteristics** Maternal age (years) - mean ±SD Hydrocortisone: 28 (2.86) Metoclopramide: 28 (4.16) Gestational age (weeks) - mean ±SD Hydrocortisone: 10 (2.68) Metoclopramide: 11 (2.44) Loss of >5% body weight - n (%) Hydrocortisone: 8 (40) Metoclopramide: 10 (50) **Inclusion criteria** • Women with intrauterine pregnancy ≤16 weeks gestation; • Intractable hyperemesis gravidarum (defined as severe persistent vomiting, ketonuria, and weight loss >5% of pre-pregnancy weight);	**Interventions** Hydrocortisone: 300 mg intravenous hydrocorisone daily for 3 days followed by a tapering regimen of 200 mg for 2 days and then 100 mg for another 2 days. Patients received 3 syringes, each every 8 hours, 10 mL each, one containing the drug diluted in normal saline and the other two containing normal saline. Metoclopramide: 10 mg in 10 mL syringe diluted in normal saline, intravenously every 8 hours for 7 days. **Details** **Power analysis** To achieve 80% power, accounting for skewed data, 20 patients were required in each treatment group. **Statistical analyses** Data were analysed using repeated-measures general linear model analysis of variance, Friedman's test, and chi-square test, as appropriate.	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Mean number of vomiting episodes reduced by 40.9% in the hydrocortisone group on the second day, 71.6% on the third day, and 95.8% on the seventh day, compared to 16.5% in the metoclopramide group on the second day, 51.2% on the third day, and 76.6% on the seventh day (p<0.0001). **Important outcomes** **Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment** Readmission to ICU within 2 weeks after treatment Hydrocortisone: 0 Metoclopramide: 6	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Low risk of bias. (Computer generated randomisation schedule. Allocation concealment's code held, and syringes containing each drug were prepared and distributed by personnel blinded to the study). Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded and unaware of treatment allocation). Measurement of the outcome: Low risk of bias. (Self-reported outcomes; objective assessment of outcome by nurses). Missing outcome data: Some concerns. (No details provided on withdrawals or loss to follow-up). Selection of the reported result: Low risk of bias. (All outcomes reported).

Study details	Participants	Interventions	Outcomes and Results	Comments
Source of funding Not stated.	• Requiring intensive care unit (ICU) admission. **Exclusion criteria** • Molar gestation; • Twin gestation; • Placental anomalies; • Medical complications contraindicating or requiring steroid use.	**Intention-to-treat (ITT) analysis** Not stated.		Other bias: Low risk of bias. (No other bias detected). Overall risk of bias: Low risk
Full citation Habek, D., Barbir, A., Habek, J. C., Janculiak, D., Bobic-Vukovic, M., Success of acupuncture and acupressure of the Pc 6 acupoint in the treatment of hyperemesis gravidarum, Forsch Komplementarmed Klass NaturheilkdForschende Komplementarmedizin und klassische Naturheilkunde = Research in complementary and natural classical medicine, 11, 20-3, 2004 **Ref Id** 939289 **Country/ies where the study was carried out** Croatia	**Sample size** Acupuncture: N=10 Acupressure: N=11 Placebo acupuncture: N=8 Placebo acupressure: N=7 **Characteristics** Age (years) - mean ±SD Acupuncture: 20.4 (4.7) Acupressure: 21.3 (3.1) Placebo acupuncture: 20.8 (4.1) Placebo acupressure: 22.1 (3.9) Weight - mean ±SD Acupuncture: 46.9 (3.1) Acupressure: 51.3 (5.1) Placebo acupuncture: 50.4 (4.8) Placebo acupressure: 49.2 (5.1) Gestational age (weeks) - median (range) Acupuncture: 7 (6 to 9) Acupressure: 8 (6 to 10) Placebo acupuncture: 8 (7 to 12)	**Interventions** Acupuncture: insertion of needles by obstetrician to points with de-qi effect for 30 minutes a day for 7 days. Placebo acupuncture: superficial intracutaneous insertion of same type of needles by obstetrician at points without de-qui effect for 30 minutes a day over 7 days. Acupressure: pressure applied by pregnant women to PC6 point for 30 minutes when feeling nauseous. Placebo acupressure: pressure applied by pregnant women for 30 minutes 3 cm above the wrist, without acupoints.	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Efficacy of treatment - % Acupuncture: 90.0 Acupressure: 63.6 Placebo acupuncture: 12.5 Placebo acupressure: 0	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Some concerns. (No details provided on randomisation process or allocation concealment). Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded and unaware of treatment allocation). Measurement of the outcome: Low risk of bias. (Self-reported outcomes, or independent gynaecologist evaluation).

Study details	Participants	Interventions	Outcomes and Results	Comments
Study type Randomised placebo-controlled trial. **Aim of the study** To assess the effectiveness of acupuncture and acupressure of the PC6 point in the treatment of hyperemesis gravidarum. **Study dates** Not stated. **Source of funding** Not stated.	Placebo acupressure: 8 (7 to 12) **Inclusion criteria** • Pregnant women with hyperemesis gravidarum. **Exclusion criteria** Not stated.	**Details** Pregnant women with more serious hyperemesis gravidarum with electrolytic dysbalance were administered intravenous crystalloid electrolyte infusion of Ringe rlactate and 5% and 10% glucose for 3 days witih antiemetics, for example metocolopramide and promethazine. **Power analysis** Not stated. **Statistical analyses** Frequency data were analysed using independent *t*-test. **Intention-to-treat (ITT) analysis** Not stated.		Missing outcome data: Some concerns. (No details provided on loss to follow-up). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Low risk of bias. (No other bias detected). Overall risk of bias: Some concerns **Other information** **Additional treatments** Intravenous infusion during 3 days - number Acupuncture: 4 Acupressure: 7 Placebo acupuncture: 7 Placebo acupressure: 7 Metoclopramide 20 mg IV per day - number Acupuncture: 1 Acupressure: 2 Placebo acupuncture: 6 Placebo acupressure: 4 Promethazine 25 mg IM per day - number Acupuncture: NR Acupressure: 1 Placebo acupuncture: 1 Placebo acupressure: 4

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Heazell, A., Thorneycroft, J., Walton, V., Etherington, I., Acupressure for the in-patient treatment of nausea and vomiting in early pregnancy: A randomized control trial, American Journal of Obstetrics and Gynecology, 194, 815-820, 2006 **Ref Id** 787009 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial **Aim of the study** To assess the effectiveness of acupressure for the treatment of inpatients with severe nausea and vomiting in early pregnancy. **Study dates** Not stated. **Source of funding** None stated.	**Sample size** N=80 Acupressure: n=40 Placebo: n=40 **Characteristics** Age (years) - mean ±SE Acupressure: 25.4 (0.95) Placebo: 27.7 (0.89) Gestation at presentation (weeks) - mean ±SE Acupressure: 8.5 (0.32) Placebo: 9.0 (0.36) **Inclusion criteria** • Women with nausea and vomiting on their first inpatient admission; • Admitted due to at least 2 of ketonuria on urinalysis, an inability to tolerate oral fluids, and a requirement for antiemetic treatment. • Between 5 and 14 weeks of gestation. **Exclusion criteria** • Prior knowledge of or use of acupressure; • Evidence of urinary tract or gastroenterologic infection;	**Interventions** Acupressure: Seaband containing plastic bead used to apply acupressure to P6 meridian on both wrists. Placebo: Seaband containing plastic bead used to apply acupressure to the dorsal aspect of the forearm. **Power analysis** To achieve 80% power to detect a difference (α=0.05) of 1 night of inpatient hospital stay, 36 patients would be required in each group. Assuming a noncompliance rate of 10%, we planned to recruit 40 patients to each group. **Statistical analyses** Demographic data were assessed with the Student t test, because these data followed a parametric distribution. Differences between the groups were assessed with the Mann-Whitney U test and the chi-squared test. **Intention to treat analysis** Data were analysed on an intention-to-treat basis. **Details** Women wore the wristbands for 8 hours per day (9am to 5pm). Women also received 3L intravenous fluids in 24 hours	**Results** **Critical outcomes** **Fetal death** Miscarriage before 20 weeks - number Acupressure (n=29): 1 Placebo (n=28): 2; p>0.8 Termination of pregnancy - number Acupressure (n=29): 3 Placebo (n=28): 4; p>0.8 Intra-uterine fetal death after 20 weeks - number Acupressure (n=23): 1 Placebo (n=13): 1 p=0.2 Pre-term birth (before 37^{+0} weeks) Acupressure (n=23): 0 Placebo (n=13): 2; p=0.2 **Important outcomes** **Length of hospital stay in days - median (IQR)** Acupressure: 3 (2 to 4) Placebo: 3 (2 to 5)p = not stated	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Low risk of bias. (Random allocation by an independent remote researcher with no prior knowledge of the patient. Allocation concealed by ticket drawn from an opaque bag). Deviations from intended interventions: Low risk of bias. (Participants and personnel unaware of treatment assignment). Measurement of the outcome: Some concerns. (No details provided, although most outcomes were measured objectively). Missing outcome data: High risk of bias. (Overall <20% women lost to follow-up. For the outcome of 'termination of pregnancy' 44% missing data). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Some concerns. (Additional antiemetic treatments administered; underpowered to determine statistical significance of secondary outcomes)

Study details	Participants	Interventions	Outcomes and Results	Comments
	• Unable to communicate with medical team.	and parenteral antiemetic medication while unable to tolerate oral fluids and thiamine 100 mg orally once daily. Defined antiemetic protocol used cyclizine as a first-line agent, prochlorperazine as second-line agent, and metoclopramide, ondansetron, or phenothiazine as third-line agent. **Power analysis** To achieve 80% power and assuming 10% non-compliance, 40 patients were required for each treatment group. **Statistical analyses** Differences between treatment groups were assessed using Mann-Whitney *U* test and chi-squared test. **Intention-to-treat (ITT) analysis** ITT analysis.		Overall risk of bias: High risk
Full citation Kashifard, M., Basirat, Z., Kashifard, M., Golsorkhtabar-Amiri, M., Moghaddamnia, A., Ondansetrone or metoclopromide? Which is more effective in severe nausea and vomiting of pregnancy? A randomized trial double-blind study, Clinical & Experimental	**Sample size** Ondansetron: N=34 Metoclopramide: N=49 **Characteristics** <u>Age (years) - mean ±SD</u> Ondansetron: 25.3 (5.5) Metoclopramide: 25.2 (4.9)	**Interventions** Ondansetron hydrochloride: 4 mg tablets Metoclapromide: 10 mg tablets **Details**	**Results** **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy** <u>Severity of vomiting - mean ±SD</u> <u>Day 1</u> Ondansetron: 6.7 (3.1) Metoclopramide: 5.1 (4.1); p=0.06	**Limitations** **<u>Cochrane risk of bias tool V2</u>:** Randomisation process: Some concerns. (Computer generated randomisation schedule. Allocation concealment done by study co-ordinator who encoded drugs with

Study details	Participants	Interventions	Outcomes and Results	Comments
Obstetrics & GynecologyClin Exp Obstet Gynecol, 40, 127-30, 2013 **Ref Id** 925003 **Country/ies where the study was carried out** Iran **Study type** Randomised controlled trial. **Aim of the study** To compare the effectiveness of ondansetron versus metoclopramide in the treatment of hyperemesis gravidarum. **Study dates** June 2011 to March 2012. **Source of funding** Not stated.	Both treatment groups matched for weight; minimum gestational age was 5 weeks and maximum 16 weeks (mean 8.7 (SD 2.6 weeks). **Inclusion criteria** • Pregnant women aged 18 to 35 years; • Hyperemesis gravidarum; vomiting 3 times a day with weight loss more than 3 kg; • Presence of ketonuria; • Gestational age less than 16 weeks. **Exclusion criteria** • Women with thyroid and gastrointestinal disease; • Hydatidiform mole; • Multiple pregnancies.	Drugs taken 3 times daily over one week. After one week the dose was reduced and discontinued: twice daily for 3 days, once daily for 4 days within the second (final) week. **Power analysis** Not stated. **Statistical analyses** Data were analysed using t-test, ANOVA and chi-squared tests. **Intention-to-treat (ITT) analysis** Not stated.	Day 2 Ondansetron: 6.0 (3.2) Metoclopramide: 3.7 (3.8); p=0.006 Day 3 Ondansetron: 5.3 (3.0) Metoclopramide: 3.2 (3.4); p=0.006 Day 4 Ondansetron: 5.0 (3.1) Metoclopramide: 3.3 (3.0); p=0.013 Day 5 Ondansetron: 5.1 (3.0) Metoclopramide: 3.0 (3.1); p=0.011 Day 6 Ondansetron: 3.8 (2.9) Metoclopramide: 2.5 (2.6); p=0.047 Day 7 Ondansetron: 3.7 (2.8) Metoclopramide: 2.7 (3.2); p=0.01 Day 8 Ondansetron: 3.1 (4.2) Metoclopramide: 2.8 (3.4); p=0.028 Day 9 Ondansetron: 3.0 (3.7) Metoclopramide: 2.9 (3.2); p=0.06 Day 10 Ondansetron: 3.1 (3.5) Metoclopramide: 3.3 (3.3); p=0.36 Day 11 Ondansetron: 2.7 (3.2) Metoclopramide: 2.8 (2.7); p=0.09 Day 12	matching random numbers; no further details provided). Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded to treatment allocation). Measurement of the outcome: Low risk of bias. (Self-reported outcomes). Missing outcome data: Some concerns. (No details provided on withdrawal or loss to follow up). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Low risk of bias. (No other bias detected). Overall risk of bias: Some concerns

Study details	Participants	Interventions	Outcomes and Results	Comments
			Ondansetron: 6.9 (3.4) Metoclopramide: 2.9 (2.5); p=0.10 Day 13 Ondansetron: 3.2 (3.3) Metoclopramide: 2.8 (2.2); p= 0.07 Day 14 Ondansetron: 2.9 (3.1) Metoclopramide: 2.9 (2.4); p=0.10 Severity of nausea - mean ±SD Day 1 Ondansetron: 6.8 (3.2) Metoclopramide: 7.4 (2.8); p=0.39 Day 2 Ondansetron: 5.4 (3.2) Metoclopramide: 6.7 (3.0); p=0.068 Day 3 Ondansetron: 5.4 (2.9) Metoclopramide: 6.0 (2.9); p=0.024 Day 4 Ondansetron: 4.1 (2.9) Metoclopramide: 5.7 (2.8); p=0.023 Day 5 Ondansetron: 4.1 (2.8) Metoclopramide: 4.8 (2.5); p=0.32 Day 6 Ondansetron: 3.7 (2.7) Metoclopramide: 4.3 (3.0); p=0.54 Day 7 Ondansetron: 3.7 (2.7) Metoclopramide: 4.3 (2.8); p=0.25	

Study details	Participants	Interventions	Outcomes and Results	Comments
			Day 8 Ondansetron: 3.4 (2.8) Metoclopramide: 4.2 (3.1); p=0.22 Day 9 Ondansetron: 3.2 (2.9) Metoclopramide: 3.7 (3.0); p=0.52 Day 10 Ondansetron: 3.3 (3.3) Metoclopramide: 3.5 (3.1); p=0.76 Day 11 Ondansetron: 2.7 (2.8) Metoclopramide: 3.2 (2.7); p=0.53 Day 12 Ondansetron: 2.5 (2.9) Metoclopramide: 3.4 (6.9); p=0.10 Day 13 Ondansetron: 2.2 (2.8) Metoclopramide: 3.3 (3.2); p= 0.12 Day 14 Ondansetron: 2.4 (2.9) Metoclopramide: 3.1 (2.9); p=0.32 None of the patients showed any side-effects; all mothers and infants were healthy at the time of birth.	
Full citation McCarthy, F. P., Murphy, A., Khashan, A. S., McElroy, B., Spillane, N., Marchocki, Z., Sarkar, R., Higgins, J. R., Day care	**Sample size** N = 98 **Characteristics**	**Interventions** Intravenous fluids in inpatient care (N=56) Intravenous fluids in day care (N=42)	**Results** Note: Number of participants who received inpatient care and day care for all outcomes are 56 and 42, respectively.	**Limitations** **Cochrane risk of bias tool V2:** Randomisation process: Low risk of bias. (Computer-generated randomisation sequence was used.

Study details	Participants	Interventions	Outcomes and Results	Comments
compared with inpatient management of nausea and vomiting of pregnancy: A randomized controlled trial, Obstetrics and gynecology, 124, 743-748, 2014 **Ref Id** 924643 **Country/ies where the study was carried out** Ireland **Study type** Open-label, single-center, randomized controlled trial **Aim of the study** To examine day care treatment of nausea and vomiting of pregnancy compared with the traditional inpatient management of this condition **Study dates** 4 April 2009 - 5 March 2012 **Source of funding** Grant awarded by Molecular Medicine Ireland	Baseline characteristics were similar in both groups. Age (years) - mean (SD) Inpatient care: 32.7 (5.5) Day care: 31.9 (5.5) Nulliparous - number (%) Inpatient care: 20 (35.7) Day care: 23 (54.8) Current smoker (yes) - number (%) Inpatient care: 7 (13) Day care: 4 (10) Gestation at first presentation (wk) - median (interquartile range) Inpatient care: 8 (7-10) Day care: 8 (7-11) BMI (kg/m2) - mean (SD) Inpatient care: 25.4 (5) Day care: 24.1 (4.3) **Inclusion criteria** 1. Women with nausea and vomiting of pregnancy 2. Ongoing viable intrauterine pregnancy before 22 weeks of gestation 3. Persistent vomiting (more than three episodes of vomiting per 24 hours) not attributable to other causes 4. Severe nausea not attributable to other causes, 5. Dehydration diagnosed by the presence of ketonuria 6. Electrolyte imbalance not attributable to other cause	Inpatient care: 2 L of normal saline administered intravenously over 5 hours. If intravenous fluid administration did not relieve the symptoms, antiemetics were administered (10 mg i.v. metoclopramide stat, 12.5 mg prochlorperazine orally or intramuscularly, 25 mg prochlorperazine per rectum, 50 mg cyclizine orally or intramuscularly, 10 mg domperidone, 4 mg ondansetron twice a day intravenously or orally, or one ampule of multivitamin complexes with 1 L of normal saline). Day care: 1 L of normal saline administered intravenously over 3 hours, then 1 L of fluid (normal saline) intravenously every 6 hours until able to tolerate oral fluids. If intravenous fluid administration did not relieve the symptoms, antiemetics were administered (10 mg i.v. metoclopramide stat, 12.5 mg prochlorperazine orally or intramuscularly, 25 mg prochlorperazine per rectum, 50 mg cyclizine orally or intramuscularly, 10 mg domperidone, 4 mg ondansetron twice a day intravenously or orally, or one ampule of multivitamin	**Important outcomes** **Number of days in hospital for treatment of nausea and vomiting** Overnight stays - median (interquartile range) Inpatient care: 2 (1–4) Day care: 0 (0–2) p=0.001 **Women's experience and satisfaction of care during or at end of pregnancy** Women's satisfaction (Client Satisfaction Questionnaire)- median (interquartile range) Inpatient care: 67 (57–69) Day care: 63 (58–71) p= 0.7	Allocation concealed by sealed, opaque, sequentially numbered envelopes). Deviations from intended interventions: Low risk of bias. (Participants and physicians were not blinded due to the nature of the intervention). Measurement of the outcome: Some concerns. (Unclear how some outcomes were measured). Missing outcome data: Low risk of bias. (Very low drop-out rate, and similar reasons between the groups, and numbers add up). Selection of the reported result: Low risk of bias. (All outcomes reported as indicated in the protocol). Other bias: Some concerns. (Very wide range of antiemetics was administered in both groups). Overall risk of bias: Some concerns **Other information** Both groups used very various antiemetics

Study details	Participants	Interventions	Outcomes and Results	Comments
	Exclusion criteria 1. Women with a confirmed urinary tract infection 2. With molar pregnancy 3. With nonviable pregnancies were excluded 4. Who had already received treatment for nausea and vomiting of pregnancy outside of the trial 5. Not residents in the southwest of Ireland	complexes with 1 L of normal saline). **Details** **Power analysis** To have an 80% statistical power a sample size of 46 participants in each arm was required. With an anticipated drop-out of 25% the final assumption was 62 participants in each group. **Statistical analyses** If median was reported, the Mann-Whitney test was used for data analysis, whereas t test was used when the mean was reported. $\chi 2$ test was used to compare proportions. P<.05 was considered statistically significant. **Intention to treat analysis** Data were analysed on an intention-to-treat basis.		
Full citation McParlin, C., Carrick-Sen, D., Steen, I. N., Robson, S. C., Hyperemesis in Pregnancy Study: A pilot randomised controlled trial of midwife-led outpatient care, European Journal of Obstetrics Gynecology and Reproductive Biology, 200, 6-10, 2016	**Sample size** N = 53 **Characteristics** Groups were comparable at baseline <u>Age (years) - mean (SD)</u> Intervenous fluid in Maternity Assessment Unit: 24.5 (7.25)	**Interventions** Intravenous fluid in Maternity Assessment Unit (N=27) Intravenous fluid in antenatal ward (N=26) Intravenous fluid in Maternity Assessment Unit: Cyclizine, 50 mg IV, was given followed by three litres of compound sodium lactate, (Hartman's),	**Results** Note: Number of participants in the intervention and control group is 27 and 26, respectively, unless otherwise reported **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy**	**Limitations** **<u>Cochrane risk of bias tool V2:</u>** Randomisation process: Some concerns. (Computer-generated block randomisation used. No details provided on allocation concealment). Deviations from intended interventions:

Study details	Participants	Interventions	Outcomes and Results	Comments
Ref Id 924865 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial **Aim of the study** To assess the feasibility of implementing a complex intervention involving rapid intravenous rehydration and ongoing midwifery support as compared to routine in-patient care for women suffering from hyperemesis gravidarum **Study dates** 01 March 2004 - 31 December 2006 **Source of funding** The NHS Directorate of Women's Services, Newcastle upon Tyne Hospitals NHS Foundation Trust and the Institute of Cellular Medicine, Newcastle University.	Intervenous fluid in antenatal ward: 27.3 (4.8) Nulliparous - number (%) Intervenous fluid in Maternity Assessment Unit: 17 (63%) Intervenous fluid in antenatal ward: 13 (50) Gestational age (weeks) - mean (SD) Intervenous fluid in Maternity Assessment Unit: 9.3 (2.8) Intervenous fluid in antenatal ward: 10.3 (2.9) **Inclusion criteria** 1. Pregnant women less than 20 weeks gestation 2. With hyperemesis gravidarum **Exclusion criteria** 1. Had an underlying medical condition such as type 1 diabetes mellitus, renal or cardiac disease 2. Aged less than 16 years 3. Required an interpreter 4. Were planning to have a termination of pregnancy	solution over six hours. Women were then given 50 mg of oral thiamine and discharged home with a prescription for oral cyclizine, 50 mg to be taken three times daily for seven days. Then, midwife contacted all women by telephone on day three and day seven after randomisation to offer ongoing support, reassurance, advice, identify any problems and encourage compliance with anti-emetics following a standard proforma. Intravenous fluid in antenatal ward (N=26): Intravenous cyclizine was given (50 mg IV), 1 litre of Hartman's solution eight hourly until rehydrated, and a daily dose of oral thiamine (50 mg). Women were discharged home when they were tolerating diet with a prescription for oral cyclizine (as in the intervention group) All participants were given an information sheet about NVP which included simple self-help measures and advice that could be followed at home. **Details** **Power analysis** Not mentioned.	Total PUQE score - mean (SD) Intravenous fluid in Maternity Assessment Unit: 6.9 (4.1) Intravenous fluid in antenatal ward: 6.2 (2.3) **Fetal death** Spontaneous abortions - number (%) Intravenous fluid in Maternity Assessment Unit: 2 (7) Intravenous fluid in antenatal ward: 2 (8) **Important outcomes** **Number of days in hospital for treatment of nausea and vomiting** Total admission time (hours) - mean (SD) Intravenous fluid in Maternity Assessment Unit: 27.2 (50.7) Intravenous fluid in antenatal ward: 94.1 (80.2) **Women's experience and satisfaction of care during or at end of pregnancy** Women's satisfaction- mean (SD) Intravenous fluid in Maternity Assessment Unit (N=12): 29.2 (3.3) Intravenous fluid in antenatal ward (N=17): 29.8 (4.7) **Small for gestational age (SGA)** SGA infant - number (%) Intravenous fluid in Maternity Assessment Unit: 3 (13%)	Low risk of bias. (Participants and physicians were not blinded due to the nature of the intervention). Measurement of the outcome: Some concerns. (Not enough information provided about outcome assessment). Missing outcome data: Low risk of bias. (Very low drop-out rate, and similar reasons between the groups, and numbers add up). Selection of the reported result: Low risk of bias. (All outcomes reported as indicated in the protocol). Other bias: High risk (Excluding women who need an interpreter, a high percentage of declined and not approached women, and low percentage of completed questionnaires). Overall risk of bias: Some concerns

Study details	Participants	Interventions	Outcomes and Results	Comments
		Statistical analyses Independent sample *t*-test, cross tabulations, and chi-squared analysis were used to detect differences between groups. **Intention to treat analysis** Analysis was by intention to treat.	Intravenous fluid in antenatal ward: 3 (14%)	
Full citation Nelson-Piercy, C., Fayers, P., de Swiet, M., Randomised, double-blind, placebo-controlled trial of corticosteroids for the treatment of hyperemesis gravidarum, BjogBJOG : an international journal of obstetrics and gynaecology, 108, 9-15, 2001 **Ref Id** 939298 **Country/ies where the study was carried out** UK **Study type** Randomised, placebo-controlled trial. **Aim of the study** To compare the effectiveness of corticosteroids in the treatment of severe hyperemesis gravidarum in	**Sample size** Prenisolone: N=12 Placebo: N=13 **Characteristics** <u>Gestational age (weeks) - mean ±SD</u> Prednisolone: 10.6 (2.1) Placebo: 8.3 (1.9) <u>Pregnancy - number</u> Prednisolone: singleton (12); triplets (0) Placebo: singleton (11); triplets (1) <u>Weight (kg) - mean ±SD</u> Prednisolone: 68.9 (19.8) Placebo: 61.8 (15.2) <u>Vomiting ≥5 times per day - number</u> Prednisolone: 6 Placebo: 6 <u>Number requiring >1 antiemetic</u> Prednisolone: 4 Placebo: 2 <u>First admission - number</u> Prednisolone: 1 (n=1 not known) Placebo: 5 (n=1 not known)	**Interventions** Prednisolone: 20 mg (4 x 5 mg tablets) orally every 12 hours. Placebo: equivalent placebo tablets. **Details** Following 72 hours, if a woman was still vomiting or vomiting the tablets, ans was still dependent on intravenous fluid and electrolyte replacement, treatment was changed to an intravenous equivalent (hydrocortisone 100 mg every 12 hours) or normal saline as placebo. **Power analysis** To achieve 90% power, a sample size of 45 women was required. **Statistical analyses** Proportions were compared using Fisher's exact test. Other data were assessed using a non-parametric 2-	**Results** **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy** <u>Number still vomiting at 1 week</u> Prednisolone: 5 Placebo: 7 RR: 1.4 (95% CI 0.6 to 3.2) <u>Number vomiting ≥5 times per day</u> Prednisolone: 2 Placebo: 5 RR: 2.5 (95% CI 0.6 to 10.5) <u>Reduction in vomiting score - median (range)</u> Prednisolone: 2.0 (-1.0 to 4.0) Placebo: 1.5 (-3.0 to 4.0) <u>Nausea score improvement - median (range)</u> Prednisolone: 6.5 (2.0 to 10.0) Placebo: 4.0 (-5.0 to 9.0); p=0.10 <u>Length of hospital stay (days) - median (range)</u> Prednisolone: 7.0 (2.0 to 21.0)	**Limitations** **<u>Cochrane risk of bias tool V2</u>:** Randomisation process: Low risk of bias. (Randomisation by computer generated allocation schedule, stratified by centre. Allocation concealed by sequentially numbered trial packs distributed by the pharmacy department of the hospital). Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded and unaware of treatment allocation. Local pharmacists blinded to type of intravenous fluid). Measurement of the outcome: Low risk of bias. (Self-reported outcomes or objectively assessed outcomes).

Study details	Participants	Interventions	Outcomes and Results	Comments
women unresponsive to conventional care. **Study dates** April 1995 to December 1996 **Source of funding** Medical Research Council grant.	**Inclusion criteria** • Pregnant women with severe or prolonged hyperemesis gravidarum; • Onset of nausea and vomiting before 12 weeks of gestation; • Dependent on intravenous fluids for at least 1 week (first admission for hyperemesis) or 24 hours (second or subsequent admission for hyperemesis); • receiving regular treatment with at least 1 antiemetic; • Ketonuria on admission; • Mid-stream urine specimen not indicating infection; • Normal blood glucose (<6.5 mmol/l) unless known diabetic; • Vomiting at least twice a day or nausea so severe that they were unable to eat or drink; • Receiving regular treatment with oral thiamine or a single dose of parenteral thiamine. **Exclusion criteria**	sample Wilcoxon rank-sum test (adjusted for tied data). **Intention-to-treat (ITT) analysis** ITT analysis.	Placebo: 7.0 (2.0 to 26.0); p=0.84 Re-admission for hyperemsis - number Prednisolone: 5 Placebo: 8 RR: 1.6 (95% CI 0.7 to 3.5) **Fetal death** Fetal death - number Prednisolone: 1 Placebo: 3* **Important outcomes** **Pre-term birth** Pre-term birth (before 37^{+0} weeks) - number Prednisolone: 2 Placebo: 4	Missing outcome data: Low risk of bias. (Low amount of missing data (4%)). Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: High risk of bias. (The study was prematurely halted due to "a combination of different factors in different centres, including the departure of key members of staff, and the erroneous belief that steroids had had such a dramatic beneficial effect that continued randomisation of women was not justified"; number of first admissions not balanced across treatment groups) Overall risk of bias: Some concerns **Other information** *1 triplet also died at 8 weeks old

Study details	Participants	Interventions	Outcomes and Results	Comments
	• Received treatment with oral steroids in previous 2 months; • Proven peptic ulceration requiring treatment in previous 5 years; • Non-viable pregnancy.			
Full citation Safari, H. R., Fassett, M. J., Souter, I. C., Alsulyman, O. M., Goodwin, T. M., The efficacy of methylprednisolone in the treatment of hyperemesis gravidarum: a randomized, double-blind, controlled study, Am J Obstet Gynecol, 179, 921-4, 1998 **Ref Id** 947461 **Country/ies where the study was carried out** US **Study type** Randomized control trial **Aim of the study** To compare the efficacy of methylprednisolone with that of promethazine for the treatment of hyperemesis gravidarum	**Sample size** N = 40 **Characteristics** No significant differences between the groups for all characteristics except the duration of hyperemesis gravidarum before admission Maternal age (year) - mean (SD) Methylprednisolone: 27 (5.8) Promethazine: 24.8 (5.8) Gravidity - mean (SD) Methylprednisolone: 2.3 (1.1) Promethazine: 2.5 (1.5) Parity - mean (SD) Methylprednisolone: 0.9 (0.9) Promethazine: 1.0 (1.2) Gestational age at entry - mean (SD) Methylprednisolone: 9.8 (2.1) Promethazine: 9.5 (92.7) Duration of HG (days) - median (range) Methylprednisolone: 14 (6-64) Promethazine: 28 (5-75)	**Interventions** Methylprednisolone (N= 20) Promethazine (N=20) Methylprednisolone: 16 mg orally 3 times a day for 3 days, followed by a tapering regimen (halving of dose every 3 days) to none during the course of 2 weeks Promethazine: 25 mg tablets 3 times a day for a total period of 2 weeks **Details** **Power analysis** Not mentioned. **Statistical analyses** Categoric results were examined with the χ2 or Fisher exact test where appropriate. Continuous variables were examined with the Student t test. **Intention to treat analysis** Not mentioned.	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Improvement of symptoms within 2 days of starting therapy - number Methylprednisolone: 17/20 Promethazine: 18/20 **Important outcomes** **Adverse event that is not immediately due to nausea and vomiting** Adverse effects - number Methylprednisolone: 0/20 Promethazine: 0/20 **Number of days in hospital for treatment of nausea and vomiting** Readmission for hyperemesis within 2 weeks of starting the study Methylprednisolone: 0/17 Promethazine: 5/17	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Low risk of bias. (Computer-generated random table was used. Allocation concealment by envelopes containing the study assignment, which were prepared in advance and sequentially labelled by a third party not involved in the study). Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded and unaware of treatment allocation). Measurement of the outcome: Some concerns. (It is unclear how the outcomes were assessed). Missing outcome data: Low risk of bias. (Attrition and exclusions reported, similar reasons

Study details	Participants	Interventions	Outcomes and Results	Comments
Study dates July 1996 - April 1997 **Source of funding** Not reported	**Inclusion criteria** 1. With an intrauterine pregnancy of <=16 weeks' gestation 2. With the diagnosis of hyperemesis gravidarum 3. Were admitted to an outpatient triage area and given intravenous hydration **Exclusion criteria** 1. Molar gestation 2. With medical complications 3. Contraindicating or requiring steroid use 4. In whom the etiology of nausea and vomiting was unclear			between the groups, and numbers add up). Selection of the reported result: Some concerns. (No reported trial protocol found). Other bias: High risk of bias. (The duration of hyperemesis gravidarum before admission was longer in the promethazine group than in the methylprednisolone group). Overall risk of bias: High risk
Full citation Sullivan, C. A., Johnson, C. A., Roach, H., Martin, R. W., Stewart, D. K., Morrison, J. C., A pilot study of intravenous ondansetron for hyperemesis gravidarum, Am J Obstet Gynecol, 174, 1565-8, 1996 **Ref Id** 947462 **Country/ies where the study was carried out** US **Study type**	**Sample size** N = 30 **Characteristics** Patient demographics were similar between groups <u>Maternal age (years) - mean (SD)</u> Ondansetron: 20.8 (3.4) Promethazine: 23.0 (5.0) <u>Parity - number (%)</u> Ondansetron: 6 (40) Promethazine: 8 (53.3) <u>Gestational age (weeks) - mean (SD)</u> Ondansetron: 11.0 (2.7) Promethazine: 10.2 (3.8)	**Interventions** Ondansetron 10 mg intravenously Promethazine 50 mg intravenously Intravenous ondansetron infused over 30 minutes every 8 hours Intravenous promethazine infused over 30 minutes every 8 hours **Details** **Power analysis** Not mentioned. **Statistical analyses**	**Results** Note: Number of participants in each group for all outcomes is 15. **<u>Critical outcomes</u>** **Symptomatic relief during pregnancy** <u>Amount of nausea as measured by visual analog scoring (VAS-10 cm) - at the end of the first day - mean</u> Ondansetron: 2.2 Promethazine: 2.6, p-value = 0.87 <u>Amount of nausea as measured by VAS-10 cm - at the end of the second day - mean</u> Ondansetron: 2.1	**Limitations** **<u>Cochrane risk of bias tool V2</u>:** Randomisation process: Some concerns. (No details provided for randomisation process or allocation concealment). Deviations from intended interventions: Some concerns. (Although it is mentioned that the pharmacy marked the medication "hyperemesis study drug," and covered them in a plain

Study details	Participants	Interventions	Outcomes and Results	Comments
Double-blind randomised controlled trial **Aim of the study** To determine whether the antiemetic ondansetron would be more effective than promethazine in treating hyperemesis gravidarum. **Study dates** July 1993 - November 1994 **Source of funding** Not reported	**Inclusion criteria** 1. Had severe hyperemesis gravidarum during the first and early second trimesters of pregnancy 2. Had not been previously treated by intravenous medication or hospitalization **Exclusion criteria** 1. Did not have severe hyperemesis 2. Had a preexisting medical condition, eating disorder, or psychiatric disease 3. Had a multiple or molar gestation	Analysis of variance for continuous data, $\chi 2$ for nominal data, and the Kruskal-Wallis test for nonparametric data. **Intention to treat analysis** Not mentioned.	Promethazine: 3.0, p-value = 0.76 Amount of nausea as measured by VAS-10 cm - at the end of the third day - mean Ondansetron: 2.1 Promethazine: 2.4, p-value = 0.81 Amount of nausea as measured by VAS-10 cm- at the end of the fourth day - mean Ondansetron: 2.1 Promethazine: 2.2, p-value = 0.90 Amount of nausea as measured by VAS-10 cm - at the end of the fifth day - mean Ondansetron: 0.2 Promethazine: 1.4, p-value = 0.15 Treatment failure (no change in nausea or emesis after 48 hours of medication) - number (%) Ondansetron: 2 (13.3) Promethazine: 3 (20) **Important outcomes** **Adverse event that is not immediately due to nausea and vomiting** Sedation - number (%) Ondansetron: 0 (0) Promethazine: 8 (53.3) **Number of days in hospital for treatment of nausea and vomiting**	brown bag, it is not reported whether physicians and women were blinded). Measurement of the outcome: Some concerns. (Unclear how and who assessed the outcomes). Missing outcome data: Low risk of bias. (Very low drop-out rate, all exclusions and reasons for exclusions were reported, and numbers add up). Selection of the reported result: Some concerns. (No trial protocol reported). Other bias: Some concerns. (Other biases could not be determined due to insufficient reporting). Overall risk of bias: High risk

Study details	Participants	Interventions	Outcomes and Results	Comments
			Duration of hospital stay (days) - mean (SD) Ondansetron: 4.47 (2.3) Promethazine: 4.47 (1.5)	
Full citation Tan, P. C., Yow, C. M., Omar, S. Z., A placebo-controlled trial of oral pyridoxine in hyperemesis gravidarum, Gynecologic & Obstetric InvestigationGynecol Obstet Invest, 67, 151-7, 2009 **Ref Id** 925047 **Country/ies where the study was carried out** Malaysia **Study type** Randomised controlled trial. **Aim of the study** To evaluate oral pyridoxine in conjunction with standard therapy in women hospitalised for hyperemesis gravidarum (HG). **Study dates** June 2006 to March 2007. **Source of funding**	**Sample size** N= 94 (n=2 excluded after recruitment) Oral pyridoxine: n=48 (n=1 excluded due to dengue fever) Placebo: n=46 (n=1 excluded for twin pregnancy) **Characteristics** Maternal age (years) - mean ±SD Oral pyridoxine: 27.7 (4.2) Placebo: 28.5 (4.7) Parity - mean ±SD Oral pyridoxine: 0.8 (1.2) Placebo: 0.9 (1.3) Gestation age (weeks) - mean ±SD Oral pyridoxine: 10.5 (3.1) Placebo: 9.6 (2.8) Nausea score at recruitment (VAS scale)- median & interquartile range Oral pyridoxine: 7 (5) p = 0.22 Placebo: 7 (4) **Inclusion criteria** • Severe nausea and vomiting during pregnancy with clinical features warranting hospitalisation. • Gestation of less than 20 weeks. • First hospital admission.	**Interventions** Pyridoxine tablets: 10 mg Placebo tablets: tic tacs **Details** Women given intravenous metoclopramide when inpatient. Women were instructed to take 2 tablets, 3 times a day, for 2 weeks. Women also given 2 week supply of oral metoclopramide and thiamine when outpatient. 2 weeks of diary keeping for vomiting and retching. Nausea and overall wellbeing scored using a 10-point visual analogue scale. Nausea: 0 = no nausea and 10 = unbearable nausea. Overall wellbeing: 0 = feeling very unwell and 10 = feeling very well. **Power analysis** To achieve a power of 80% and taking an alpha of 0.05, 47 participants were needed in each arm of the study. **Statistical analyses** Analyses by t test for comparison of means.	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Vomiting at hospital discharge (vomiting 24 hours before discharge) - number (percentage) Oral pyridoxine: 19 (40.4) p = 0.28 Placebo: 13 (28.9) Daily mean vomiting episodes at Week 1 - mean ± SD Oral pyridoxine: 1.9 (2.4) p = 0.26 Placebo: 1.4 (1.1) Daily mean vomiting episodes at Week 2 - mean ± SD Oral pyridoxine: 1.4 (1.3) p = 0.98 Placebo: 1.4 (1.6) Nausea score at hospital discharge - median & interquartile ranges Oral pyridoxine: 2 (4) p = 0.38 Placebo: 2 (3) Nausea score at follow up Week 1 - median & interquartile ranges Oral pyridoxine: 3 (5) p = 0.78 Placebo: 3 (4)	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Low risk of bias. (Block randomisation; random generation in blocks of 10. Allocation concealment by numbered, sealed and opaque envelopes). Deviations from intended interventions: High risk of bias. (Double blinding not achieved as placebo and drug were not identical). Measurement of the outcome: Low risk of bias. (Self-reported outcomes or clinical data). Missing outcome data: High risk of bias. (26% participants lost to follow up. Equal loss across both arms). Selection of the reported result: High risk of bias. (No pre-specified outcomes). Other bias: Low risk of bias. (No other bias detected).

Study details	Participants	Interventions	Outcomes and Results	Comments
Not stated.	• Enrolment within 12 hours of admission. **Exclusion criteria** • Women with multiple pregnancies. • Prior outpatient pyridoxine use. • Other concurrent illnesses, which might exacerbate the symptoms of nausea and vomiting, or which could have delayed recovery.	Fisher's exact test for 2x2 categorical datasets Mann-Whitney U test for nausea score p > 0.05 for all analyses. **Intention-to-treat (ITT) analysis** Analysis based on ITT but no details specified.	Nausea score at follow up Week 2 - median & interquartile ranges Oral pyridoxine: 2 (3) p = 0.69 Placebo: 2.5 (4) Overall wellbeing score Week 1 (VAS)- median & interquartile ranges Oral pyridoxine: 8 (3) p = 0.81 Placebo: 8 (3) Overall wellbeing score Week 2 (VAS)- median & interquartile ranges Oral pyridoxine: 8 (1) p = 0.73 Placebo: 9 (1) **Fetal death** Fetal death Oral pyridoxine: no deaths Placebo: n=1 (miscarriage before Week 2 follow-up) **Important outcomes** Reported adverse symptoms did not require hospitalisation.	Overall risk of bias: High risk
Full citation Tan, P. C., Khine, P. P., Vallikkannu, N., Omar, S. Z., Promethazine compared with metoclopramide for hyperemesis gravidarum: A randomized controlled trial, Obstetrics and gynecology, 115, 975-981, 2010	**Sample size** N = 149 **Characteristics** Baseline characteristics were similar in both groups Age (years) - mean (SD)	**Interventions** Promethazine (N=76) Metoclopramide (N=73) **Details** 25 mg of promethazine or 10 mg of	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Vomiting episodes in the first 24 hours of treatment (N=144) - median (interquartile range) Promethazine: 2 (0–3)	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Low risk of bias. (Computer-generated random table used for randomisation. Allocation concealment by sequential

Study details	Participants	Interventions	Outcomes and Results	Comments
Ref Id 925084 **Country/ies where the study was carried out** Malaysia **Study type** Double-blind randomised controlled trial **Aim of the study** To compare the effects of promethazine with those of metoclopramide for hyperemesis gravidarum **Study dates** 25 November 2008 - 14 August 2009 **Source of funding** Funding was provided by the University of Malaya. A portion of the study drugs and packaging to effect double blinding was donated by CCM Duopharma Biotech Malaysia Berhad	Promethazine: 27.8 (4.2) Metoclopramide: 27.8 (3.5) Gestational age (week) - mean (SD) Promethazine: 9.3 (2.6) Metoclopramide: 9.2 (2.3) Gravidity - median (interquartile range) Promethazine: 1 (1–3) Metoclopramide: 1 (1–2) Parity - median (interquartile range) Promethazine: 0 (0–1) Metoclopramide: 0 (0–1) Parous - number (%) Promethazine: 29 (38.2) Metoclopramide: 33 (45.2) Body mass index - mean (SD) Promethazine: 22.5 (4.2) Metoclopramide: 23.0 (3.5) **Inclusion criteria** 1. Women hospitalized for the first time in their current pregnancies 2. With clinical hyperemesis gravidarum with dehydration and detectable ketonuria 3. At a gestation of 16 weeks or less 4. Required intravenous antiemetic therapy **Exclusion criteria** 1. Multiple gestation 2. Established nonviable pregnancy 3. Preexisting medical condition that can cause nausea and vomiting	metoclopramide administered by slow injection into an indwelling intravenous catheter over 1 to 2 minutes by providers just after randomization and 8, 16, and 24 hours later for a full course of four doses **Power analysis** Assuming a visual numerical rating scale standard deviation of 2, α=0.05, and 80% power, 64 women were required in each arm. Factoring in a non-normal distribution and 10% drop out rate, a total of 158 women were required to suitably power the study. **Statistical analyses** Normal distribution of continuous data was checked with the one sample Kolmogorov-Smirnov test. Normally distributed continuous data were analysed with the Student's t test. Two-by-two categorical data sets were analysed with the Fisher exact test and larger categorical data sets with the X2 test; ordinal data and non-normally distributed continuous data were analysed with the Mann-Whitney U test. **Intention to treat analysis** Analysis was by intention to treat after exclusions for criteria infringements.	Metoclopramide: 1 (0–5) Nausea score at 8 hours of treatment (visual numerical rating scale (VNRS)) (N=143) - median (interquartile range) Promethazine: 4 (1.75–6) Metoclopramide: 4 (1.5–5) Nausea score at 16 hours of treatment (visual numerical rating scale (VNRS)) (N=137) - median (interquartile range) Promethazine: 3 (1–5) Metoclopramide: 3 (1–5) Nausea score at 24 hours of treatment (visual numerical rating scale (VNRS)) (N=126)- median (interquartile range) Promethazine: 2 (1–4) Metoclopramide: 2 (1–5) **Important outcomes** **Number of days in hospital for treatment of nausea and vomiting** hospital stay (days) - median (interquartile range) Promethazine: 1.7 (1.5–2.4) Metoclopramide: 1.8 (1.5–2.5)	opening of numbered, sealed, opaque envelopes statinh 'Drug A' or 'Drug B'.). Deviations from intended interventions: Low risk of bias. (Participants and personnel were blinded and unaware of treatment allocation). Measurement of the outcome: Some concerns. (Most measures were self-assessed by participants, but not clear how other outcomes were assessed). Missing outcome data: Low risk of bias. (Attrition and exclusions reported, similar reasons between the groups, and numbers add up). Selection of the reported result: Low risk of bias. (Study reported all outcomes as indicated in the protocol). Other bias: Low risk of bias. (Groups similar at baseline, women asked to conceal information about their treatment during assessment, interventions carried out by 2 experienced craniosacral therapists who met to ensure consistent approach throughout study). Overall risk of bias: Low risk

Study details	Participants	Interventions	Outcomes and Results	Comments
	4. Gastrointestinal causes of vomiting 5. Medical causes of vomiting 6. known allergy to metoclopramide or promethazine			
Full citation Tan, P. C., Norazilah, M. J., Omar, S. Z., Dextrose saline compared with normal saline rehydration of hyperemesis gravidarum: a randomized controlled trial, Obstetrics & GynecologyObstet Gynecol, 121, 291-8, 2013 **Ref Id** 924657 **Country/ies where the study was carried out** Malaysia **Study type** Randomised controlled trial. **Aim of the study** To compare the effects of dextrose saline versus normal saline rehydration solution for the treatment of pregnant women hospitalised with hyperemesis gravidarum	**Sample size** N=222 Intervention: n=111 (n=102 analysed) Control: n=111 (n=101 analysed) **Characteristics** Age (years) - mean ±SD Intervention: 28.5 (4.6) Control: 29.3 (4.6) Gestation (weeks) - mean ±SD Intervention: 9.8 (2.8) Control: 9.8 (2.5) Weight (kg) - mean ±SD Intervention: 58.2 (12.2) Control: 57.3 (11.4) Body mass index (BMI) (kg/m^2) - mean ±SD Intervention: 24.0 (4.5) Control: 23.7 (4.5) Ketonuria (dipstick) - number (%) 1+ Intervention: 11 (9.9) Control: 12 (10.8) 2+ Intervention: 14 (12.5) Control: 13 (11.7) 3+ Intervention: 23 (20.7) Control: 27 (24.3) 4+	**Interventions** Intervention: 5% dextrose to 0.9% saline by intravenous infusion at a rate of 125 mL/hour over 24 hours. Control: 0.9% saline by intravenous infusion at a rate of 125 mL/hour over 24 hours. **Details** Potassium chloride was added to saline solution as required if hypokalemic, women received 10 mg oral thiamine daily, and an intravenous antiemetic (usually 10 mg metoclopramide every 8 hours). Oral intake was permitted as tolerated at a pace decided by the women. **Power analysis** To achieve 80% power and assuming 10% lost to follow-up, 223 women were required for the study. Post hoc analysis using paired t-test. Adjusting for antiemetic regimen; sensitivity analysis including	**Results** **Critical outcomes** **Symptomatic relief during pregnancy** Vomiting episodes after 24 hours - median (IQR) Intervention: 0 (0 to 2) Control: 0 (0 to 2); p=0.66 Nausea score at 8 hours** - median (IQR) Intervention: 6 (4 to 7) Control: 7 (5 to 8); p<0.01 Nausea score at 16 hours** - median (IQR) Intervention: 4 (2 to 5) Control: 5 (3 to 6); p=0.03 Nausea score at 24 hours - median (IQR) Intervention: 2 (1 to 4) Control: 2 (2 to 4); p=0.39 Hospital stay (hours) - mean ±SD Intervention: 43 (21) Control: 48 (21); p=0.14	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Low risk of bias. (Randomisation by one-to-one ratio; computer-generated. Allocation concealment by sequential opening of numbered, sealed, opaque envelopes stating 'Protocol A' or 'Protocol B'). Deviations from intended interventions: Low risk of bias. (Participants and investigators were blinded and unaware of treatments). Measurement of the outcome: Low risk of bias. (Self-reported outcomes and clinical outcomes). Missing outcome data: Low risk of bias. (Low amount of missing data (8.5%). Reasons were described, unlikely to have produced bias).

Study details	Participants	Interventions	Outcomes and Results	Comments
Study dates November 2010 to February 2012. **Source of funding** University of Malaya.	Intervention: 63 (56.8) Control: 59 (53.2) Hyponatremia (135 mmol/L or less) - number (%) Intervention: 80 (72.1) Control: 84 (75.7) Hypokalemia (3.5 mmol/L or less) - number (%) Intervention: 14 (12.6) Control: 22 (19.8) Hypochloremia (99 mmol/L or less) - number (%) Intervention: 20 (18.0) Control: 29 (26.1) Nausea score* - median (interquartile range; IQR) Intervention: 9 (7 to 10) Control: 9 (7 to 10) Antiemetic regimen - number (%) Metoclopramide Intervention: 94 (85.5) Control: 79 (72.5) Prochloperazine Intervention: 11 (10.0) Control: 18 (16.5) Ondansetron Intervention: 5 (4.5) Control: 12 (11.0) **Inclusion criteria** • Women at first hospitalisation for hyperemesis gravidarum (intractable nausea and vomiting or pregnancy with dehydration and starvation clinically judged to require hospitalisation for	only metoclopramide-exposed women. **Statistical analyses** Normality of data distribution was checked using Kolmogorov-Smirnov test. Normally distributed continuous data were analysed using Student's *t*-test. Two-by-two categorical data were analysed using Fisher's exact test and larger categorical data were analysed using the chi-squared test. Ordinal data and non-normally distributed continuous data were analysed using Mann-Whitney *U* test. A repeated-measures analysis of variance was applied to the nausea visual numerical rating scale scores and to ketonuria status. **Intention-to-treat (ITT) analysis** Data were analysed on an intention to treat basis.		Selection of the reported result: Low risk of bias. (All outcomes reported). Other bias: Low risk of bias (No other biases detected). Overall risk of bias: Low risk **Other information** *Self-scored by women using a 10-point numerical rating score, with a score of 1 to 10 as nausea increases. **Assessed using a 10-point (1 to 10) numerical rating scale: higher score signifies greater nausea.

Study details	Participants	Interventions	Outcomes and Results	Comments
	intravenous rehydration and antiemetic drugs); • Aged 18 years or older; • Ketonuria by urine dipstick of at least 1+ on admission; • Gestation 16 weeks or less; • Plasma glucose 110 mg/dL or less; • Sodium 125 mmol/L or greater on admission. **Exclusion criteria** • Women already receiving intravenous rehydration treatment; • Non-hospitalised women; • Multiple gestation; • Established non-viable pregnancy; • Pre-existing medical conditions that can cause nausea and vomiting (for example culture-proven symptomatic urinary tract infection, dengue fever); • Gastrointestinal causes of vomiting (for example gastroenteritis, gastritis, peptic ulcer); • Medical causes of vomiting (for example diabetic ketoacidosis); • Women with underlying medical problems (for			

Study details	Participants	Interventions	Outcomes and Results	Comments
	example established gestational hypertension, diabetes, heart disease, renal disease, and thyroid disorder).			
Full citation Yost, N. P., McIntire, D. D., Wians, F. H., Jr., Ramin, S. M., Balko, J. A., Leveno, K. J., A randomized, placebo-controlled trial of corticosteroids for hyperemesis due to pregnancy, Obstet GynecolObstetrics and gynecology, 102, 1250-4, 2003 **Ref Id** 939310 **Country/ies where the study was carried out** US **Study type** Randomised, placebo-controlled trial. **Aim of the study** To assess the effectiveness of corticosteroids in the treatment of women with hyperemesis gravidarum.	**Sample size** Corticosteroids: N=64 (n=56 analysed) Placebo: N=62 (n=54 analysed) **Characteristics** Maternal age (years) - mean ±SD Corticosteroids: 22.9 (4.9) Placebo: 22.3 (4.6) Singleton pregnancy - number (%) Corticosteroids: 55 (98) Placebo: 53 (98) Gestational age (weeks) at randomisation - mean ±SD Corticosteroids: 11.0 (2.7) Placebo: 10.8 (2.7) Prior pre-term birth - number (%) Corticosteroids: 2 (4) Placebo: 3 (6) Number of emergency visits - mean ±SD Corticosteroids: 1.3 (0.7) Placebo: 1.6 (1.0) Duration of hyperemesis (days) - mean ±SD Corticosteroid: 20.0 (21.7) Placebo: 19.5 (23.6) **Inclusion criteria**	**Interventions** Corticosteroids: methylprednisolone 125 mg intravenously, followed by tapering of oral prednisone (40 mg for 1 day, 20 mg for 3 days, 10 mg for 3 days, and 5 mg for 7 days) Placebo: similar placebo regimen. **Details** All women received intravenous hydration with crystalloid until ketonuria cleared. Conventional treatment also included promethazine 25 mg and metoclopramide 10 mg intravenously every 6 hours for 24 hours, followed by the same regimen administered orally as required until discharge from hospital. Women with persistent vomiting on day 2 of hospitalisation and randomised to methylprednisolone received an additional 80 mg dose,	**Results** **Critical outcomes** **Fetal death (at any stage of pregnancy, including miscarriage, still birth and termination of pregnancy)** Fetal death - number (%) Corticosteroids: 3 (5.5) Placebo: 3 (6) **Important outcomes** **Number of days in hospital for treatment of nausea and vomiting** Number of days in hospital (first admission) - mean ±SD Corticosteroids: 1.9 (0.9) Placebo: 2.2 (1.2); p=0.47 Number of days in hospital (all admissions) - mean ±SD Corticosteroids: 7.6 (18.0) Placebo: 4.3 (4.3); p=0.18 **Pre-term birth (birth before 37+0 weeks)** Pre-term birth ≤36 weeks - number (%) Corticosteroids: 7 (13)	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Some concerns. (Randomisation by computer-generate blocks of 20. No details provided for allocation concealment). Deviations from intended interventions: Low risk of bias. (Participants and personnel blinded and unaware of treatment allocation). Measurement of the outcome: Some concerns. (No details reported). Missing outcome data: Some concerns. (13% participants lost to follow up). Selection of the reported result: Low risk of bias. (All outcomes reported).

Study details	Participants	Interventions	Outcomes and Results	Comments
Study dates July 1998 to August 2001. **Source of funding** Not stated.	• Women experiencing nausea and vomiting during the first half of pregnancy (<20 weeks' gestation); • Live fetus; • Previous non-response to outpatient treatment (promethazine 25 mg every 6 hours as needed); • 3+ or 4+ dipstick urinary ketones as evidence of severe dehydration **Exclusion criteria** • Molar pregnancy.	and similarly for women in the placebo group. **Power analysis** To achieve 80% power, 70 women were required for inclusion in the study. **Statistical analyses** Data were analysed using chi-squared test, Student *t*-test, and Wilcoxon signed-rank test. **Intention-to-treat (ITT) analysis** ITT analysis.	Placebo: 4 (7); p=0.37 **Small for gestational age - number (%)** Birth weight <1,000 g Corticosteroids: 0 Placebo: 2 (4); p=0.15 Birth weight <1,500 g Corticosteroids: 1 (2) Placebo: 4 (7); p=0.16 Birth weight <2,500 g Corticosteroids: 7 (13) Placebo: 5 (9); p=0.56	Other bias: Some concerns. (Unclear influence of additional treatments on outcomes). Overall risk of bias: Some concerns
Full citation Ziaei, S., Hosseiney, F. S., Faghihzadeh, S., The efficacy low dose of prednisolone in the treatment of hyperemesis gravidarum, Acta Obstet Gynecol Scand, 83, 272-5, 2004 **Ref Id** 947463 **Country/ies where the study was carried out**	**Sample size** N = 80 **Characteristics** Baseline characteristics were similar between both groups Maternal age (year) - mean (range) Prednisolone: 25 (17–36) Promethazine: 26.5 (17–38) Gestational age (weeks) - mean (range) Prednisolone: 11 (7–14) Promethazine: 11 (7–14) Gravidity - mean (range)	**Interventions** Prednisolone (N= 40) Promethazine (N= 40) Prednisolone 5 mg/day orally in the morning for 10 days Promethazine 75 mg/day orally for 10 days **Details** **Power analysis** No details provided. **Statistical analyses** The Mann–Whitney U-test and Fisher's exact test were	**Results** Note: Number of participants in each group is 40 unless otherwise stated. **Critical outcomes** **Symptomatic relief during pregnancy** Severe nausea (between 6.1-10 using VAS) - During the first 48 hours - number (%) Prednisolone: 20 (50) Promethazine: 10 (25) Severe nausea (between 6.1-10 using VAS) -	**Limitations** **Cochrane risk of bias tool V2**: Randomisation process: Some concerns. (Ordinary tables of random numbers used for randomisation. No details provided for allocation concealment). Deviations from intended interventions: Some concerns. (The main investigator was blinded, but it is not

Study details	Participants	Interventions	Outcomes and Results	Comments
Iran **Study type** Randomized controlled trial **Aim of the study** To determine whether low dosages of prednisolone are effective in the treatment of outpatients with hyperemesis gravidarum. **Study dates** Not reported **Source of funding** No reported	Prednisolone: 1.5 (1–5) Promethazine: 2.9 (1–5) Number of vomitings/day - mean (range) Prednisolone: 3 (2–5) Promethazine: 3 (2–6) **Inclusion criteria** 1. Women at between 6- and 12-weeks' gestation 2. Vomiting more than 3 times per day during the last 72 hours or ketonuria that did not respond to dietary manipulation and caused weight loss 3. Had not to have consumed any antiemetic drugs during the last 72 h **Exclusion criteria** 1. Any situation for which prednisolone or promethazine was contraindicated or not recommended 2. Any conditions that could cause the cases to be hospitalized 3. Threatened abortion 4. Mole hydatiform 5. Ectopic pregnancy	used to compare the median data. Odds ratios and their 95% confidence intervals were also calculated. p<0.05 was considered as significant. **Intention to treat analysis** No details provided.	Between the 3rd to the 10th day - number (%) Prednisolone: 14 (35) Promethazine: 15 (37.5) Severe nausea (between 6.1-10 using VAS) - During the 17th day - number (%) Prednisolone (N=39): 22 (56.4) Promethazine (N=39): 27 (69.2) Vomiting episodes - During the first 48 hours - median (range) Prednisolone: 3 (1–7) Promethazine: 1 (0–4) Vomiting episodes - Between the 3rd to the 10th day - median (range) Prednisolone: 1.5 (1–5) Promethazine: 1 (0–5) Vomiting episodes - During the 17th day - median (range) Prednisolone (N=39): 3 (0–6) Promethazine (N=39): 3 (0–5) Sickness (became completely or partially well) - During the first 48 hours - number (%) Prednisolone: 20 (50) Promethazine: 30 (75) Sickness (became completely or partially well) - Between the 3rd to the 10th day - number (%) Prednisolone: 26 (65) Promethazine: 28 (70)	clear whether the participants were blinded). Measurement of the outcome: Some concerns. (It is not clear how and who assessed the outcomes). Missing outcome data: Low risk of bias. (Attrition and exclusions reported, similar reasons between the groups, and numbers add up). Selection of the reported result: Some concerns. No protocol was found). Other bias: Some concerns. (Other biases could not be determined due to insufficient reporting) Overall risk of bias: High risk

Study details	Participants	Interventions	Outcomes and Results	Comments
			Sickness (became completely or partially well) - During the 17th day - number (%) Prednisolone (N=39): 20 (50) Promethazine (N=39): 12 (30.7) **Important outcomes** **Adverse event that is not immediately due to nausea and vomiting** Abdominal pain - During the first 48 hours - number (%) Prednisolone: 2 (5) Promethazine: 6 (15) Abdominal pain - Between the 3rd to the 10th day - number (%) Prednisolone: 0 (0) Promethazine: 4 (10) Drowsiness - During the first 48 hours - number (%) Prednisolone: 0 (0) Promethazine: 6 (15) Drowsiness - Between the 3rd to the 10th day - number (%) Prednisolone: 0 (0) Promethazine: 6 (15)	