National Institute for Health and Care Excellence

FINAL

Antenatal care

[R] Management of nausea and vomiting in pregnancy

NICE guideline NG201

Evidence reviews underpinning recommendations 1.4.1 to 1.4.7

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Final

These evidence reviews were developed by the National Guideline Alliance, which is a part of the Royal College of Obstetricians and Gynaecologists

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Review question

What interventions are effective in treating nausea and vomiting during pregnancy?

Introduction

Nausea and vomiting of pregnancy (NVP) is common with around 50-80% of pregnant women experiencing these symptoms to a varying degree. Moderate to severe nausea and vomiting, is characterised by intractable vomiting which can be associated with electrolyte abnormalities, acid-base disturbance and weight loss, particularly the most severe form (hyperemesis gravidarum). Nausea and vomiting in pregnancy can impact on the woman's physical and mental health requiring admission to hospital for rehydration and treatment which in turn will affect her family and work life. In view of this, effective treatment for nausea and vomiting in pregnancy is essential. This review aims to find out what interventions are effective in treating nausea and vomiting in pregnancy.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Pregnant women with nausea, vomiting and/or retching of any degree (including hyperemesis gravidarum).

Intervention	**Mild and moderate nausea and vomiting**
	• Complementary therapies
	  ○ Acupressure
	  ○ Acupuncture
	• Dietary supplements
	  ○ Ginger
	• Pharmacological interventions
	  ○ Dopamine (D_2) receptor antagonists
	  – Domperidone
	  – Metoclopramide hydrochloride
	  – Prochlorperazine
	  ○ Histamine H1-receptor antagonist
	  – Cyclizine hydrochloride
	  – Doxylamine succinate
	  – Promethazine hydrochloride
	  ○ Pyridoxine hydrochloride (Vitamin B_6)
	  ○ Serotonin (5-HT) antagonists
	  – Ondansetron
	
	Severe nausea and vomiting (hyperemesis gravidarum)

	All interventions listed for mild and moderate nausea and vomiting above will be considered, plus the following:
	• Non-pharmacological interventions
	  ○ Intravenous fluids
	• Pharmacological interventions
	  ○ Any corticosteroid

Comparison	**Mild and moderate nausea and vomiting** • Complementary therapy vs placebo (placebo pill, dietary advice, sham treatment [for example sham acupuncture] or no treatment) • Dietary supplement vs placebo • Complementary therapy vs dietary supplement • Complementary therapy + dietary supplement vs complementary therapy • Complementary therapy + dietary supplement vs dietary supplement • Pharmacological intervention (including combination of listed pharmacological interventions) vs placebo • Pharmacological intervention vs another pharmacological intervention (including combination of listed pharmacological therapies) **Hyperemesis gravidarum only** Note: all comparisons for mild and moderate nausea and vomiting will be considered plus the following: • Corticosteroid vs placebo • Corticosteroid vs pharmacological intervention listed for mild and moderate nausea and vomiting • Corticosteroid + pharmacological intervention listed for mild and moderate nausea and vomiting + vs pharmacological intervention listed for mild and moderate nausea and vomiting only • Intravenous fluids vs no intravenous fluids • Intravenous fluids in one setting (for example home) vs intravenous fluids in another setting (for example hospital)
Outcome	**Critical** • Symptomatic relief during pregnancy • Fetal death (at any stage of pregnancy, including miscarriage, still birth and termination of pregnancy) • Infant death up to 4 weeks chronological age **Important** • Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment • Number of days in hospital for treatment of nausea and vomiting • Women's experience and satisfaction of care during or at end of pregnancy • Pre-term birth (birth before 37+0 weeks) • Small for gestational age (SGA)

For full details see the review protocol in appendix A

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Clinical evidence

Included studies

Forty-three articles reporting 42 randomised controlled trials (RCTs) for interventions in treating nausea and vomiting were included in this review.

Mild to moderate nausea and vomiting

Twenty-seven articles reporting 26 RCTs were included in the review of treatments for mild and moderate nausea and vomiting during pregnancy (Basirat 2009, Belluomini 1994, Bsat 2003, Galeshi 2020, Geiger 1959, Ghule 2020, Keating 2002, Knight 2001, Koren 2010, Koren 2015, Mobarakabadi 2019, Mohammadbeigi 2011, Monias 1957, Oliveira 2014, Ozgoli 2009, Puangsricharem 2008, Rad 2012, Saberi 2013, Saberi 2014, Sahakian 1991, Sharifzadeh 2018, Smith 2002, Vutyavanich 1995, Vutyavanich 2001, Werntoft 2001, Willetts 2003, Zhang 2017).

The included studies are summarised in Table 2.

Eight RCTs were multi-arm trials. Six of these were 3-arm trials, 1 of which compared ginger, pyridoxine hydrochloride and placebo (Sharifzadeh 2018); 1 RCT compared ginger, a dopamine D2 receptor antagonist (metoclopramide) and placebo (Mohammadbeigi 2011); 1 RCT compared ginger, placebo, and a control (no treatment) group (Saberi 2014); 2 RCTs compared acupressure, sham acupressure, and a control (no treatment) group (Mobarakabadi 2019, Werntoft 2001); finally, 1 RCT compared ginger, acupressure and a control (no treatment) group (Saberi 2013). One RCT was a 4-arm trial that compared traditional acupuncture, P6 acupuncture, sham acupuncture and a control (no treatment) group (Smith 2002). One RCT reported an 8-arm unpublished trial from the 1970s that aimed to evaluate the efficacy of (Zhang 2017) pyridoxine hydrochloride and doxylamine succinate. The 8 arms of the trial were pyridoxine hydrochloride, a histamine H1-receptor antagonist (doxylamine succinate), a combination of pyridoxine hydrochloride and doxylamine succinate, and a placebo. The other arms of the trial were dicyclomine, a combination of dicyclomine and pyridoxine hydrochloride, a combination of dicyclomine and doxylamine succinate, and a combination of dicyclomine, pyridoxine hydrochloride, and doxylamine succinate, all of which were not interventions of interest for this review.

Five RCTs solely compared ginger to placebo (Basirat 2009, Keating 2002, Ozgoli 2009, Vutyavanich 2001, and Willetts 2003). Two of these studies were conducted in high-income countries (Keating 2002 and Willetts 2003), whilst the remaining were conducted in middle-income countries. The mean age of participants for this comparison ranged from 19 to 37 years and the gestational age ranged from 7-19 weeks. Majority of the studies for this comparison had a treatment length of 4 days. Only one study (Keating 2002) had a duration of 14 days.

Three RCTs solely compared acupressure to placebo (sham acupressure) (Belluomini 1994, Puangsricharem 2008, Rad 2012), conducted in US, Thailand, and Iran, respectively. One

RCT compared P6 acupressure to KID21 acupressure (Galeshi 2020) and was conducted in Iran.

One RCT compared P6 acupuncture combined with transcutaneous electrical nerve stimulation to shame acupuncture combined with transcutaneous electrical nerve stimulation (Ghule 2020) and was conducted in India.

One RCT compared acupuncture to placebo (sham acupuncture) (Knight 2001) and was conducted in the UK, a high-income country.

One RCT compared a dopamine D2 receptor antagonist (metoclopramide) to a placebo, in a 3-arm trial (Mohammadbeigi 2011). This study was conducted in Iran over 5 days, where participants had an average age of 27 years and gestational age of 10 weeks.

One RCT compared a histamine H1-receptor antagonist (doxylamine succinate) to a placebo in an 8-arm trial (Zhang 2017). This study was conducted in US and the intervention was carried out over 7 days.

Two RCTs compared pyridoxine hydrochloride to placebo (Sahakian 1991, Vutyavanich 1995) of which the former was conducted in US and the latter in Thailand.

One RCT compared pyridoxine hydrochloride to a histamine H1-receptor antagonist (doxylamine succinate) in an 8-arm trial (Zhang 2017). This study was conducted in US and the intervention was carried out over 7 days.

One RCT (Bsat 2003), conducted in the US compared a combination of pyridoxine hydrochloride and a dopamine D2 receptor antagonist (metoclopramide) to a histamine H1-receptor antagonist only (promethazine).

Four studies reporting 3 RCTs, all conducted in the US, compared a combination of pyridoxine hydrochloride and a histamine H1-receptor antagonist to placebo. The histamine H1-receptor antagonist examined in two of the studies was doxylamine succinate (Geiger 1959, Koren 2010, 2015), with the other study using cyclizine hydrochloride (Monias 1957).

Finally, one RCT (Oliveira 2014) conducted in the US compared a combination of a serotonin 5-HT antagonist (ondansetron) and placebo to a combination of pyridoxine hydrochloride and a histamine H1-receptor antagonist (doxylamine succinate).

More than half of these studies were conducted in a high-income country (as defined by the World Bank). Ten studies reporting 9 RCTs were conducted in the US (Belluomini 1994, Bsat 2003, Geiger 1959, Keating 2002, Koren 2010, Koren 2015, Monias 1957, Oliveira 2014, Sahakian 1991, Zhang 2017), 2 RCTs were conducted in Australia (Smith 2002, Willetts 2003), 1 was conducted in the UK (Knight 2001), and 1 in Sweden (Werntoft 2001). The other 10 RCTs were conducted in low-income countries. Nine RCTs were carried out in Iran (Basirat 2009, Galeshi 2020, Mobarakabadi 2019, Mohammadbeigi 2011, Ozgoli 2009, Rad 2012, Saberi 2013, Saberi 2014, Sharifzadeh 2018) and 3 in Thailand (Puangsricharem 2008, Vutyavanich 1995, Vutyavanich 2001).

Within these studies, the mean age of the study participants ranged from 24 to 33 years and their gestational age ranged from 8 to 12 weeks. All studies specified that only participants in their first trimester or early second trimester were eligible.

Moderate to severe nausea and vomiting (including hyperemesis gravidarum)

Sixteen RCTs were included for the review on the treatment of moderate to severe nausea and vomiting during pregnancy (Abas 2014, Adlan 2017, Bondok 2006, Habek 2004, Heazell 2006, Kashifard 2013, McCarthy 2014, McParlin 2016, Nelson-Piercy 2001, Safari 1998,

Sullivan 1996, Tan 2009, Tan 2010, Tan 2013, Yost 2003, Ziaei 2004). Some of the included studies involved pregnant women with hyperemesis gravidarum.

The included studies are summarised in Table 3.

Two RCTs compared acupressure + standard care to placebo (sham acupressure) (Adlan 2017, Heazell 2006), which were conducted in Malaysia and the UK, respectively. Habek 2004 conducted a 4-arm trial in Croatia comparing acupressure + standard care to placebo (sham acupressure), and also compared acupuncture + standard care to placebo (sham acupuncture).

One RCT compared pyridoxine hydrochloride to placebo (Tan 2009), whilst one RCT (Tan 2010) compared a dopamine D2-receptor antagonist (metoclopramide) to a histamine H1-receptor antagonist (promethazine). Both of these studies were conducted in Malaysia, a middle-income country.

Three RCTs compared a serotonin 5-HT antagonist (ondansetron) to either a dopamine D2 receptor antagonist (metoclopramide) (Abas 2014, Kashifard 2013), or a histamine H1-receptor antagonist (promethazine) (Sullivan 1996). These studies were conducted in Malaysia, Iran, and the US, respectively.

Five RCTs compared a corticosteroid to placebo or an alternative pharmacological intervention: two RCTs compared a corticosteroid (prednisolone and a combination of methylprednisolone and prednisolone, respectively to placebo (Nelson-Piercy 2001, Yost 2003), whilst two RCTs compared a corticosteroid (methylprednisolone and prednisolone, respectively) to a histamine H1-receptor antagonist (promethazine) (Safari 1998, Ziaei 2004); finally, one study compared corticosteroids (pulsed hydrocortisone) to dopamine D2 receptor antagonist (metoclopramide) (Bondok 2006).

Finally, three RCTs examined intravenous (IV) fluids as an intervention. Two of these examined giving IV fluids in different settings, either as a day care patient or an inpatient (McCarthy 2014, conducted in Ireland), or in a maternity assessment unit or an antenatal ward (McParlin 2016, conducted in the UK). One RCT compared IV fluid of dextrose saline to an IV fluid of normal saline rehydration (Tan 2013) and was conducted in Malaysia.

Half of these RCTs were performed in a high-income country, with three studies conducted in the UK (Heazell 2006, McParlin 2016, Nelson-Piercy 2001), three in the US (Safari 1998, Sullivan 1996, Yost 2003, one in Croatia (Habek 2004) and one in Ireland (McCarthy 2014). The remaining eight studies were conducted in middle-income countries, with five conducted in Malaysia (Abas 2014, Adlan 2017, Tan 2009, Tan 2010, Tan 2013), two in Iran (Kashifard 2013, Ziaei 2004), and one in Egypt (Bondok 2006). All the trials were 2-arm trials with one exception, a 4-arm trial that compared acupressure or acupuncture to their sham equivalents (sham acupressure, sham acupuncture) (Habek 2004). Within these studies, the mean age of the study participants ranged from 21 to 32 years and their gestational age ranged from 8 to 11 weeks. Majority of the studies investigated participants in their 9th gestational week.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies excluded from the review and reasons for their exclusion are provided in appendix K.

Summary of clinical studies included in the evidence review

A summary of the studies that were included in this review is presented in Table 2 and Table 3.

Mild to moderate nausea and vomiting

Table 2: Summary of included randomised trials for mild to moderate nausea and vomiting of pregnancy

Study Country	Population	Intervention	Comparison	Outcomes
Basirat 2009 RCT Iran	N=62 Women aged 19-35 years, with a weight within 20% of normal weight, and with singleton fetuses at 7-17 gestational weeks.	• Ginger- n=32 • Treatment length: 4 days • Details: 5 ginger/placebo biscuits per day.	• Placebo- n=30	• Symptomatic relief during pregnancy – Nausea intensity (VAS score) • Symptomatic relief during pregnancy – Vomiting frequency in the last 24 hours • Adverse events requiring hospitalisation
Belluomini 1994 RCT US	N=60 Women complaining of nausea with or without vomiting, with singleton fetuses at 12 or less gestational weeks.	• Acupressure- n=30 • Treatment length: 7 days • Details: Acupressure for 10 minutes, 4 times a day, from day 4 to 7 of intervention.	• Placebo (Sham acupressure)- n=30	• Symptomatic relief during pregnancy – Overall relief (Total Rhodes Index Score) • Symptomatic relief during pregnancy – Nausea relief (Rhodes Index Score) • Symptomatic relief during pregnancy – Vomiting relief (Rhodes Index Score)
Bsat 2003 RCT US	N=106 Women with nausea and/or vomiting, with singleton fetuses at 12 or less gestational weeks.	• Pyridoxine hydrochloride + Dopamine D2 receptor antagonist (Metoclopramide)- n=54 • Treatment length: 3 days • Details: Intramuscular injection of pyridoxine (50 mg) + oral metoclopramide (10 mg) tablet or oral	• Histamine H1-receptor antagonist (Promethazine)- n=52	• Symptomatic relief during pregnancy – Vomiting frequency (Patient reported)

Study Country	Population	Intervention	Comparison	Outcomes
		promethazine (25 mg) tablet, every 6 hours.		
Galeshi 2020 RCT Iran	N=83 Women with complaints of nausea with or without vomiting, with singleton fetuses less than 12 gestational weeks.	• Acupressure- n=40 • Treatment length: 4 days • Details: acupressure to the P6 point for 20 minutes, every day for 4 days.	• Acupressure (KID21)- n=43	• Symptomatic relief during pregnancy- Change from baseline in nausea severity (VAS scale) • Symptomatic relief during pregnancy- Change from baseline in vomiting severity (VAS scale)
Geiger 1959 RCT US	N=110 No details reported.	• Pyridoxine hydrochloride + Histamine H1-receptor antagonist (Doxylamine succinate)- n=53 • Treatment length: Not mentioned • Details: 2 x 10 mg tablets every evening before sleeping. If no improvements advised to take 1 or 2 additional tablets during the morning hours.	• Placebo- n=57	• Symptomatic relief during pregnancy – Relief from nausea and vomiting • Adverse event requiring hospitalisation
Ghule 2020 RCT India	N=107 Women with nausea and vomiting, with singleton fetuses at 6 to 12 gestational weeks.	• Acupuncture and transcutaneous electrical nerve stimulation- n=55 • Treatment length: 3 weeks • Details: Intervention given 5 days per week	• Sham acupuncture and placebo transcutaneous electrical nerve stimulation- n=52	• Symptomatic relief during pregnancy – Total Rhodes Index Score • Women's experience and satisfaction of care during or at end of pregnancy
Keating 2002 RCT US	N=25 Women with complaints of nausea with or without vomiting, with singleton fetuses less than 12 gestational weeks.	• Ginger- n=14 • Treatment length: 2 weeks • Details: 1 tbsp. of ginger syrup in 4 to 8 ounces of water, 4 times a day.	• Placebo- n=11	• Symptomatic relief during pregnancy – No or little improvement on nausea intensity scale

Study Country	Population	Intervention	Comparison	Outcomes
Knight 2001 RCT UK	N=54 Women with complaints of nausea with or without vomiting, who were willing to consider acupuncture, with singleton fetuses between 6-10 gestational weeks.	• Acupuncture- n=28 • Treatment length: 3 weeks • Details: 4 treatments over treatment length	• Placebo (Sham acupuncture)- n=27	• Symptomatic relief during pregnancy – Nausea intensity (VAS score) • Adverse events requiring hospitalisation
Koren 2010 RCT US	N=261 Women aged 18 years and over, with nausea and vomiting symptoms, with singleton fetuses between 7-14 gestational weeks.	• Pyridoxine hydrochloride + Histamine H1-receptor antagonist (Doxylamine succinate)- n=133 • Treatment length: 2 weeks • Details: 2 tablets daily at bedtime, increasing when indicated, to the max dosage of 4 tablets per day. Pyridoxine (10 mg); Doxylamine (10 mg).	• Placebo- n=128	• Symptomatic relief during pregnancy – Overall relief (PUQE score)
Koren 2015 RCT US	N=261 Women aged 18 years and over, with nausea and vomiting symptoms, with singleton fetuses between 7-14 gestational weeks.	• Pyridoxine hydrochloride + Histamine H1-receptor antagonist (Doxylamine succinate)- n=133 • Treatment length: 2 weeks • Details: 2 tablets daily at bedtime, increasing when indicated, to the max dosage of 4 tablets per day. Pyridoxine (10 mg); Doxylamine (10 mg).	• Placebo- n=128	• Adverse events requiring hospitalisation
Mobarakabadi 2019 RCT US	N=78 Women with nausea and vomiting symptoms, with singleton foetuses less than 20 gestational weeks.	• Acupressure- n=25 • Treatment length: 3 days • Details: acupressure to P6 points to both wrists	• Placebo- n=26 • Details: wristband without a pressure button • Control (no treatment)- n=27	• Symptomatic relief during pregnancy – Nausea frequency (unspecified 0-4 scale) • Symptomatic relief during pregnancy – Nausea

Study Country	Population	Intervention	Comparison	Outcomes
				intensity (unspecified 0-4 scale) • Symptomatic relief during pregnancy – Vomiting frequency (unspecified 0-4 scale) • Women's experience and satisfaction of care during or at end of pregnancy
Mohammadbeigi 2011 RCT Iran	N=102 Women with nausea and vomiting symptoms, with singleton fetuses less than 20 gestational weeks.	• Ginger- n=34 • Dopamine D2 receptor antagonist (Metoclopramide)- N=34 • Treatment length: 5 days • Details: One tablet, three times a day. Ginger (200 mg); Metoclopramide (10 mg); Placebo (200 mg flour).	• Placebo- n=34	• Symptomatic relief during pregnancy – Overall relief (Total Rhodes Index score) • Symptomatic relief during pregnancy – Nausea intensity (Rhodes Index score) • Symptomatic relief during pregnancy – Vomiting intensity (Rhodes Index score)
Monias 1957 RCT US	N=200 Women complaining of nausea and/or vomiting, with singleton fetuses between 6 and 20 gestational weeks.	• Pyridoxine hydrochloride + Histamine H1 receptor antagonist (Cyclizine hydrochloride)- n=100 • Treatment length: Not mentioned. • Details: 2 tablets before breakfast[1]. For those who did not feel relief, they were instructed to take an additional tablet before lunch.	• Placebo- n=100	• Symptomatic relief during pregnancy – Relief from nausea and vomiting (Patient reported)
Oliveira 2014 RCT US	N=30 Women aged 18 years and over with symptoms of nausea and vomiting, with singleton fetuses	• Serotonin 5-HT antagonist (Ondansetron) + Placebo- n=13 • Treatment length: 5 days	• Pyridoxine hydrochloride + Histamine H1-receptor antagonist (Doxylamine succinate)- n=17	• Symptomatic relief during pregnancy – Nausea intensity (VAS score)

Study Country	Population	Intervention	Comparison	Outcomes
	at less than 16 gestational weeks.	• Details: One tablet every 8 hours. Ondansetron (4 mg); Pyridoxine (25 mg); Doxylamine (12.5 mg).		• Symptomatic relief during pregnancy – Vomiting intensity (VAS score) • Symptomatic relief during pregnancy – Number of women with clinically significant improvement • Adverse events requiring hospitalisation
Ozgoli 2009 RCT Iran	N=67 Women with mild to moderate nausea, with or without vomiting, with singleton fetuses under 20 gestational weeks.	• Ginger- n=32 • Treatment length: 4 days • Details: 4 x 250 mg tablets every day for treatment length.	• Placebo- n=35	• Symptomatic relief during pregnancy – No improvement in nausea intensity • Adverse events requiring hospitalisation
Puangsricharem 2008 RCT Thailand	N=91 Women with symptoms of nausea and vomiting, with singleton fetuses under 14 gestational weeks.	• Acupressure- n=45 • Treatment length: 6 days • Details: Intervention (press ear magnets for 30 seconds, 4 times a day (before meal times and bedtime), from day 3 to day 6..	• Control (Oral antiemetic tablet every 6 hours)- n=46	• Symptomatic relief during pregnancy – Overall relief (Total Rhodes Index score)
Rad 2012 RCT Iran	N=80 Women aged between 18-35 years, with nausea and vomiting, with singleton fetuses under 12 gestational weeks.	• Acupressure- n=40 • Treatment length: 4 days • Details: Acupressure on KID21 point applied for 2 minutes followed by massage for 2 minutes- repeated for 20 minutes.	• Placebo (Sham acupressure)- n=40	• Symptomatic relief during pregnancy – Nausea intensity (VAS score) • Symptomatic relief during pregnancy – Vomiting intensity (Patient reported)
Saberi 2013 RCT Iran	N=143 Women with mild to moderate nausea or vomiting, with singleton fetuses under 16 gestational weeks.	• Ginger- n=50 • Acupressure- n=48 • Treatment length: 4 days • Details: 3 x 250 mg tablets daily for treatment length, or	• Control (no treatment)- n=45	• Symptomatic relief during pregnancy – Overall relief (Total Rhodes Index score) • Symptomatic relief during pregnancy – Nausea relief (Rhodes Index score)

Study Country	Population	Intervention	Comparison	Outcomes
		band worn for treatment length.		• Symptomatic relief during pregnancy – Vomiting relief (Rhodes Index score) • Symptomatic relief during pregnancy – Retching relief (Rhodes Index score)
Saberi 2014 RCT Iran	N=106 Women with mild to moderate nausea or vomiting, with singleton fetuses under 16 gestational weeks.	• Ginger- n=37 • Treatment length: 4 days • Details: 3 x 250 mg tablets daily for treatment length.	• Placebo- n=36 • Control (no treatment)- n=33	• Symptomatic relief during pregnancy – Overall relief (Total Rhodes Index score) • Symptomatic relief during pregnancy – Nausea relief (Rhodes Index score) • Symptomatic relief during pregnancy – Vomiting relief (Rhodes Index score) • Symptomatic relief during pregnancy – Retching relief (Rhodes Index score)
Sahakian 1991 RCT US	N=59 Women with nausea and vomiting of pregnancy.	• Pyridoxine hydrochloride- n=31 • Treatment length: 3 days • Details: 9 x 25 mg pyridoxine tablet, every 8 hours for treatment length.	• Placebo- n=28	• Symptomatic relief during pregnancy – Nausea intensity (VAS score) • Symptomatic relief during pregnancy – Number of patients vomiting on last day of treatment
Sharifzadeh 2018 RCT Iran	N=77 Women aged 20-35 years with mild to moderate nausea and vomiting, with singleton fetuses between 6-16 gestational weeks.	• Ginger- n=28 • Pyridoxine hydrochloride- n=26 • Treatment length: 4 days • Details: 2 tablets daily for treatment length (Ginger 500 mg, Pyridoxine 40 mg).	• Placebo- n=23	• Symptomatic relief during pregnancy – Overall relief (Total Rhodes Index score) • Symptomatic relief during pregnancy – Nausea relief (Rhodes Index score) • Symptomatic relief during pregnancy – Nausea intensity (Rhodes Index score) • Symptomatic relief during pregnancy – Nausea

Study Country	Population	Intervention	Comparison	Outcomes
				frequency (Rhodes Index score) • Symptomatic relief during pregnancy – Vomiting relief (Rhodes Index score) • Symptomatic relief during pregnancy – Vomiting frequency (Rhodes Index score) • Symptomatic relief during pregnancy – Vomiting intensity (Rhodes Index score) • Symptomatic relief during pregnancy – Retching frequency (Rhodes Index score)
Smith 2002 RCT Australia	N=593 Women with symptoms of nausea and vomiting, with singleton fetuses less than 14 gestational weeks.	• Acupuncture (traditional)- n=148 • Acupuncture (P6 group)- n=148 • Treatment length: 4 weeks • Details: Two treatments on week 1, and one treatment for remaining three weeks.	• Placebo (Sham acupuncture)- n=148 • Control (No treatment)- n=149	• Symptomatic relief during pregnancy – Nausea relief (Rhodes Index score) • Symptomatic relief during pregnancy – Vomiting relief (Rhodes Index score) • Symptomatic relief during pregnancy – Retching relief (Rhodes Index score) • Fetal death
Vutyavanich 1995 RCT Thailand	N=336 Women with nausea of pregnancy, with or without vomiting, with singleton fetuses at 17 or less gestational weeks.	• Pyridoxine hydrochloride- n=169 • Treatment length: 5 days • Details: One 10 mg tablet, every 8 hours, for treatment length.	• Placebo- n=167	• Symptomatic relief during pregnancy – Nausea intensity (VAS score) • Symptomatic relief during pregnancy – Change in vomiting frequency (Patient reported)

Study Country	Population	Intervention	Comparison	Outcomes
Vutyavanich 2001 RCT Thailand	N=70 Women with nausea of pregnancy, with or without vomiting, with singleton fetuses before 17 gestational weeks.	• Ginger- n=60 • Treatment length: 4 days • Details: One 250mg tablet after every meal and one tablet before bedtime, daily.	• Placebo- n=60	• Symptomatic relief during pregnancy – Nausea intensity (VAS score) • Symptomatic relief during pregnancy – Vomiting frequency in the last 24 hours (Patient reported) • Adverse events requiring hospitalisation • Fetal death
Werntoft 2001 RCT Sweden	N=60 Women experiencing nausea and vomiting of pregnancy.	• Acupressure- n=20 • Treatment length: 14 days • Details: Wear bands for two weeks, only removing when in shower.	• Placebo (Sham acupressure)- n=20 • Control (no treatment)- n=20	• Symptomatic relief during pregnancy – Nausea intensity (VAS score)
Willetts 2003 RCT Australia	N=120 Women experiencing nausea and vomiting of pregnancy, with singleton fetuses less than 20 gestational weeks.	• Ginger- n=60 • Treatment length: 4 days • Details: 4 x 125mg capsules daily for treatment length.	• Placebo- n=60	• Adverse event requiring hospitalisation • Fetal death
Zhang 2017 RCT US	N=1599 Women experiencing nausea and vomiting of pregnancy, with singleton fetuses at 12 or less gestational weeks.	• Pyridoxine hydrochloride- n=286 • Histamine H1-receptor antagonist (Doxylamine succinate)- n=283 • Pyridoxine hydrochloride + Histamine H1-receptor antagonist (Doxylamine succinate)- n=279 • Treatment length: 7 days • Details: 2 x 10mg tablets at bedtime and one additional tablet in the afternoon or morning, if needed.	• Placebo- n=281 • Pyridoxine hydrochloride • Histamine H1-receptor antagonist (Doxylamine succinate) • Pyridoxine hydrochloride + Histamine H1-receptor antagonist (Doxylamine succinate)	• Symptomatic relief during pregnancy – Number of women with improvement sin symptoms – physician evaluations

Notes: [1]Dosage not mentioned. Abbreviations: PUQE- Pregnancy unique quantification of emesis and nausea; VAS- Visual analogue scale

See appendix D for full evidence tables

Moderate to severe nausea and vomiting (including hyperemesis gravidarum)

Table 3: Summary of included randomised trials for moderate to severe nausea and vomiting (including hyperemesis gravidarum)

Study Country	Population	Intervention	Comparison	Outcomes
Abas 2014 RCT Malaysia	N=120 Women hospitalised for the first time with clinical diagnosis of hyperemesis gravidarum (HG) with singleton fetuses at 16 or less completed gestational weeks.	• Serotonin 5-HT antagonist (Ondansetron)- n=60 • Treatment length: 1 day • Details: 4mg Ondansetron diluted in 100ml normal saline, 10mg metoclopramide diluted in 100ml normal saline. Drug given over 10 minutes as soon as randomised, and then every 8 hours for a course of four doses over the next 24 hours.	Dopamine D2 receptor antagonist (Metoclopramide)- n=60	• Symptomatic relief during pregnancy – Number of women vomit free during 24 hour treatment • Symptomatic relief during pregnancy – Patient wellbeing (VNRS score) • Symptomatic relief during pregnancy – Nausea severity (VNRS score) Number of days in hospital for treatment of nausea and vomiting
Adlan 2017 RCT Malaysia	N=120 Women with moderate to severe HG requiring hospital admission with singleton fetuses at 5-14 completed gestational weeks.	• Acupressure- n=60 • Treatment length: 3 days • Details: Band worn 12 hours daily from time of admission to day 3 of intervention. • Standard care: both groups were administered intravenous fluid and regular intravenous metoclopramide and thiamine supplements during inpatient admission	Placebo (Sham acupressure)- n=60	• Symptomatic relief during pregnancy – Overall relief (PUQE score) • Symptomatic relief during pregnancy – Nausea severity (PUQE score) • Symptomatic relief during pregnancy – Vomiting severity (PUQE score) • Symptomatic relief during pregnancy – Retching severity (PUQE score) • Number of days in hospital for treatment of nausea and vomiting

Study Country	Population	Intervention	Comparison	Outcomes
				Women's experience and satisfaction of care during or at end of pregnancy
Bondok 2006 RCT Egypt	N=40 Women with HG requiring intensive care unit (ICU) admission, with singleton fetuses at 16 or less gestational weeks.	• Corticosteroid (Pulsed hydrocortisone treatment)- n=20 • Treatment length: 7 days • Details: Daily dose of 300mg IV hydrocortisone- dose tapered during the course of treatment. Daily dose of 10mg IV metoclopramide, 3 times daily- dose stayed the same over treatment.	Dopamine D2 receptor antagonist (Metoclopramide)- n=20	• Symptomatic relief during pregnancy – Vomiting frequency (Patient reported) • Number of days in hospital for treatment of nausea and vomiting
Habek 2004 RCT Croatia	N=36 Women who are pregnant and have HG.	• Acupressure- n=11 • Acupuncture- n=10 • Treatment length: 7 days • Details: Acupressure/acupuncture applied for 30 minutes a day for treatment length. • Standard care: intravenous crystalloid electrolyte infusion of Ringer lactate and 5% and 10% glucose (500–1,500 ml) for 3 days with antiemetics	• Placebo (Sham acupressure)- n=7 • Placebo (Sham acupuncture)- n=8	• Symptomatic relief during pregnancy – Number of women with disappearance of symptoms
Heazell 2006 RCT UK	N=80 Women with nausea and vomiting on their first inpatient admission, with singleton fetuses between 5-14 gestational weeks.	• Acupressure- n=40 • Treatment length: Not mentioned • Details: Acupressure bands worn for 8 hours daily for treatment length. • Standard care: 3L of intravenous fluid in 24 hours and parenteral antiemetic	• Placebo (Sham acupressure)- n=40	• Pre-term birth (before 37 weeks) • Fetal Death • Number of days in hospital for treatment of nausea and vomiting

Study Country	Population	Intervention	Comparison	Outcomes
		medication while the patient was unable to tolerate oral fluids and thiamine 100 mg that was taken orally once daily		
Kashifard 2013 RCT Iran	N=83 Women aged 18-35 years, with HG and the presence of ketonuria, with singleton fetuses less than 16 gestational weeks.	• Serotonin 5-HT antagonist (Ondansetron)- n=34 • Treatment length: 2 weeks • Details: Week 1 (drugs taken 3 times, daily); Week 2 (drugs taken twice for 3 days and once for 4 days). Ondansetron (4 mg) and Metoclopramide (10 mg).	• Dopamine D2 receptor antagonist (Metoclopramide)- n=49	• Symptomatic relief during pregnancy – Nausea severity (VAS score) • Symptomatic relief during pregnancy – Vomiting severity (VAS score)
McCarthy 2014 RCT Ireland	N=98 Women with severe nausea and vomiting of pregnancy, with singleton fetuses under 22 gestational weeks.	• Intravenous fluids in day care- n=42 • Treatment length: until women reached 22 weeks of gestation • Details: IV fluids in day care from 8am-4pm, Monday to Friday: 2L of IV fluid over 5 hours. Inpatient: 1L of fluid (normal saline) administered over 3 hours. The patient then received 1 L of fluid (normal saline) intravenously every 6 hours until able to tolerate oral fluids.	• Intravenous fluids in inpatient care- n=56	• Number of days in hospital for treatment of nausea and vomiting • Women's experience or satisfaction of care during or at end of pregnancy
McParlin 2016 RCT United Kingdom	N=53 Women with HG, with singleton fetuses under 20 gestational weeks.	• Intravenous fluids in Maternity Assessment Unit- n=27 • Treatment length: 7 days • Intervention group (standard treatment): Maternity Assessment Unit- 50 mg IV	• Intravenous fluids in Antenatal ward- n=26	• Symptomatic relief during pregnancy – Overall relief (PUQE score) • Women's experience or satisfaction of care during or at end of pregnancy • Fetal death

Study Country	Population	Intervention	Comparison	Outcomes
		cyclizine + 3L of Hartman's solution over 6 hours + 50mg oral thiamine daily. Control group (standard treatment): Antenatal ward- 50mg IV cyclizine + 1L of Hartman's solution every 8 hours until rehydrated + 50mg oral thiamine daily.		• Small for gestational age
Nelson-Piercy 2001 RCT UK	N=25 Women with severe HG, with singleton fetuses before 12 gestational weeks.	• Corticosteroid (Prednisolone)- n=12 • Treatment length: 7 days • Details: 4 x 5 mg prednisolone tablets, every 12 hours.	• Placebo- n=13	• Symptomatic relief during pregnancy – Improvement in nausea intensity • Symptomatic relief during pregnancy – Vomiting frequency (Patient reported) • Symptomatic relief during pregnancy – Reduction in vomiting intensity • Number of days in hospital for treatment of nausea and vomiting • Fetal death • Pre-term birth (before 37 weeks)
Safari 1998 RCT US	N=40 Women with a HG diagnosis, with singleton fetuses less than or at 16 gestational weeks.	• Corticosteroid (Methylprednisolone)- n=20 • Treatment length: 2 weeks • Details: 16 mg oral methylprednisolone 3 times a day for 3 days followed by halving of dose every 3 days until to nothing (at the end of 2 weeks). 25 mg promethazine tablets, 3 times a day.	• Histamine H1-receptor antagonist (Promethazine)- n=20	• Symptomatic relief during pregnancy – Number of women with improvement of symptoms • Adverse event requiring hospitalisation • Number of days in hospital for treatment of nausea and vomiting

Study Country	Population	Intervention	Comparison	Outcomes
Sullivan 1996 RCT US	N=30 Women with severe HG in the first and early second trimester of pregnancy.	• Serotonin 5-HT antagonist (Ondansetron)- n=15 • Treatment length: 5 days • Details: 10 mg Ondansetron infused intravenously over 30 minutes every 8 hours. 50 mg promethazine infused intravenously over 30 minutes every 8 hours.	• Histamine H1-receptor antagonist (Promethazine)- n=15	• Adverse event requiring hospitalisation • Number of days in hospital for treatment of nausea and vomiting
Tan 2009 RCT Malaysia	N=92 Women with severe HG warranting hospitalisation, with singleton fetuses at less than 20 gestational weeks.	• Pyridoxine hydrochloride- n=47 • Treatment length: 2 weeks • Details: 2 x 10mg pyridoxine, thrice a day. Placebo: tic tacs.	• Placebo- n=45	• Symptomatic relief during pregnancy – Overall wellbeing score (VAS score) • Symptomatic relief during pregnancy – Nausea intensity (VAS score) • Symptomatic relief during pregnancy – Daily mean vomiting episodes (Patient reported) • Symptomatic relief during pregnancy – Number of women vomiting in the last 24 hours before discharge • Adverse event requiring hospitalisation • Fetal death
Tan 2010 RCT Malaysia	N=149 Women with severe HG warranting hospitalisation, with singleton fetuses at 16 or less gestational weeks.	• Histamine H1-receptor antagonist (Promethazine)- n=76 • Treatment length: 1 day • Details: 25 mg of promethazine or 10 mg of metoclopramide administered by slow injection into an indwelling intravenous catheter over 1 to 2 minutes by providers just after	• Dopamine D2 receptor antagonist (Metoclopramide)- n=73	• Symptomatic relief during pregnancy – Nausea severity (VNRS score) • Symptomatic relief during pregnancy – Vomiting frequency (Patient reported) • Number of days in hospital for treatment of nausea and vomiting

Study Country	Population	Intervention	Comparison	Outcomes
		randomization and 8, 16, and 24 hours later for a full course of four doses		• Women's experience and satisfaction of care during or at end of pregnancy – Patient wellbeing (VNRS score)
Tan 2013 RCT Malaysia	N=203 Women aged 18 years or older, with severe HG requiring hospitalisation, with singleton fetuses at 16 or less gestational weeks.	• Intravenous saline (Dextrose saline)- n=102 • Treatment length: 1 day • Details: 5% dextrose-0.9% saline by IV infusion at a rate 125mL/h over 24 hours. 0.9% saline by IV infusion at a rate 125mL/h over 24 hours.	• Intravenous saline (normal saline rehydration)- n=101	• Symptomatic relief during pregnancy – Nausea intensity (VNRS score) • Symptomatic relief during pregnancy – Vomiting frequency (Patient reported) • Women's experience and satisfaction of care during or at end of pregnancy
Yost 2003 RCT US	N=110 Women with HG requiring hospitalisation, with singleton fetuses less than 20 gestational weeks.	• Corticosteroid (Methylprednisolone and oral prednisolone)- n=56 • Treatment length: 14 days • Details: 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- n=54	• Number of days in hospital for treatment of nausea and vomiting • Fetal death • Pre-term birth (before 37 weeks)
Ziaei 2004 RCT Iran	N=80 Women with HG requiring hospitalisation, with singleton fetuses between 6-12 gestational weeks.	• Corticosteroid (Prednisolone)- n=40 • Treatment length: 10 days • Details: Prednisolone 5 mg/day orally in the morning. Promethazine 75 mg/day orally.	• Histamine H1-receptor antagonist (Promethazine)- n=40	• Symptomatic relief during pregnancy – Number of women with severe nausea • Symptomatic relief during pregnancy – Vomiting frequency (Patient reported) • Symptomatic relief during pregnancy – Number of patients with complete or partial relief • Adverse event requiring hospitalisation

Abbreviations: IV: intravenous; PUQE- Pregnancy unique quantification of emesis and nausea; VAS- Visual analogue scale; VNRS: Visual numerical rating scale

See appendix D for full evidence tables.

Quality assessment of clinical outcomes included in the evidence review

See the evidence profiles in appendix F.

Economic evidence

Included studies

One relevant study was identified in a literature review of published cost-effectiveness analyses on this topic; Murphy 2015 (see appendix H and appendix I for summary and full evidence tables). The economic evaluation, attached to the RCT in the clinical review (McCarthy 2014), considered the cost-effectiveness of day care over inpatient management of nausea and vomiting in pregnancy (NVP). The analysis conducted was a cost-utility analysis measuring effectiveness in terms of quality adjusted life years (QALYs). Studies excluded from the review and reasons for their exclusion are provided in appendix K.

Excluded studies

There was no economic evidence identified for this review question and therefore there is no excluded studies list in appendix K.

Summary of studies included in the economic evidence review

Murphy (2014) adopt a combined health care payer and patient perspective in Ireland. However, in this review only the costs concerned from a healthcare payer perspective are included, as according to the NICE guidelines manual. The resource use estimates are based on the RCT, though, the source of the unit costs are unclear. The primary outcome for the study was total number of inpatient nights related to nausea and committing of pregnancy.

The economic analysis employs a Markov model which consists of three health states: Healthy Discharged, Moderate NVP and Severe NVP, with a time horizon over 52 days. This period was divided into a series of discrete time periods referred to as cycles, which represent each episode of care for NVP.

Utilities were assigned to each state in the Markov model to generate QALYs. Trial data was used to inform quality of life for patients in the Severe NVP state. For both Moderate and Healthy states, Non-preference based data was obtained indirectly from published literature of SF-36 results and then mapped into EQ-5D estimates.

In the deterministic analysis, the mean cost per patient in day care management was €609 (95% CI: 453-860). With regards to inpatient management, the average cost per patient was €2135 (95% CI: 2124-8466). In terms of QALYs, patients receiving day care management experienced 9.49 QALYs (95% CI: 4.32-12.39) whilst patients randomised to inpatient management experienced 9.42 QALYs (95% CI: 4.19-12.25). Thus, day care management dominates inpatient management as it is both less costly and more effective. The study includes a cost effectiveness acceptability curve which, at a threshold of €45,000/per QALY, the probability that day care management is cost effective is 73% while the probability that inpatient management is cost effective is 23%.

This study is deemed as directly applicable for the following reasons: the study population is in accordance with that specified in the protocol; the interventions are appropriate to the review question; the study was conducted in a system sufficiently similar to the UK (Ireland; a healthcare payer's perspective was undertaken for costs and the study utilises QALYs as a measure of effectiveness.

The overall methodological quality of the study can be classified as having minor limitations. Despite using an RCT as a vehicle for an economic evaluation, it is not clear from where the unit cost data is derived from. there is no reported deterministic sensitivity analysis on key model parameters.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Clinical evidence statements

Mild to moderate nausea and vomiting

Comparison 1. Ginger versus placebo

Critical outcomes

Symptomatic relief during pregnancy

Overall relief

- Moderate quality evidence from 4 RCTs (N=287) showed that there is a clinically important difference favouring ginger tablets over placebo on overall symptomatic relief as assessed by the Total Rhodes Index score up to 7 days after treatment in women who experience pregnancy-related nausea and vomiting: MD -6.33 (95% CI -8.64 to -4.02).

Nausea relief

- Very low quality evidence from 3 RCTs (N=219) showed that there is a clinically important difference favouring ginger tablets over placebo on relief from nausea as assessed by the Rhodes Index up to 7 days after treatment in women who experience pregnancy-related nausea and vomiting: MD -2.52 (95% CI -4.22 to -0.83).

Nausea intensity

- Moderate quality evidence from 2 RCTs (N=119) showed that there is no clinically important difference favouring ginger tablets over placebo on nausea intensity as assessed by the Rhodes Index after treatment in women who experience pregnancy-related nausea and vomiting: MD -1.72 (95% CI -3.64 to 0.21).
- Moderate quality evidence from 2 RCTs (N=132) showed that there is a clinically important difference favouring ginger biscuit or tablet over placebo on nausea intensity from baseline as assessed by a visual analogue scale after treatment in women who experience pregnancy-related nausea and vomiting: MD -1.52 (95% CI -2.38 to -0.67).

Nausea frequency

- Low quality evidence from 1 RCT (N=51) showed that there is a clinically important difference favouring ginger tablet over placebo on nausea frequency as assessed by the Rhodes Index after treatment in women who experience pregnancy-related nausea and vomiting: MD -0.57 (95% CI -1.08 to -0.06).

Vomiting relief

- Very low quality evidence from 3 RCTs (N=219) showed that there is a clinically important difference favouring ginger tablets over placebo on relief from vomiting as assessed by the Rhodes Index up to 7 days after treatment in women who experience pregnancy-related nausea and vomiting: MD -1.74 (95% CI -3.35 to -0.14).

Vomiting intensity

- Low quality evidence from 2 RCTs (N=119) showed that there is no clinically important difference between ginger tablet and placebo on vomiting intensity as assessed by the Rhodes Index after treatment in women who experience pregnancy-related nausea and vomiting: MD -1.07 (95% CI -1.67 to -0.48).

Vomiting frequency

- Low quality evidence from 1 RCT (N=51) showed that there is a clinically important difference favouring ginger tablet over placebo on vomiting frequency as assessed by the Rhodes Index after treatment in women who experience pregnancy-related nausea and vomiting: MD -0.9 (95% CI -1.32 to -0.48).
- Very low quality evidence from 2 RCTs (N=132) showed that there is no clinically important difference between ginger biscuit or capsule and placebo on vomiting frequency as assessed by patient report in the last 24 hours up to 7 days after treatment in women who experience pregnancy-related nausea and vomiting: MD -1.02 (95% CI -2.65 to 0.60).

Retching relief

- Moderate quality evidence from 2 RCTs (N=168) showed that there is a clinically important difference favouring ginger tablets over placebo on relief from retching as assessed by the Rhodes Index after treatment in women who experience pregnancy-related nausea and vomiting: MD -2.18 (95% CI -2.74 to -1.63).

Retching frequency

- Low quality evidence from 1 RCT (N=51) showed that there is no clinically important difference between ginger tablet and placebo on retching frequency as assessed by the Rhodes Index after treatment in women who experience pregnancy-related nausea and vomiting: MD -0.40 (95% CI -1.00 to 0.20).

Improvement in nausea intensity

Very low quality evidence from 1 RCT (N=67) showed that there is no clinically important difference between ginger tablet and placebo on the number of women who experience pregnancy-related nausea and vomiting whose nausea intensity does not improve as assessed by a visual analogue scale score: RR 0.47 (95% CI 0.13 to 1.66).

- Low quality evidence from 1 RCT (N=23) showed that there is a clinically important difference favouring ginger syrup over placebo on the number of women who experience pregnancy-related nausea and vomiting whose nausea intensity either does not improve or only improves a little as assessed by a numerical scale: Peto OR 0.04 (95% CI 0.01 to 0.24).

Fetal death

Abortion

- Very low quality evidence from 2 RCTs (N=190) showed that there is no statistically significant difference between ginger capsules and placebo on abortion, up to 7 days after treatment in women who experience pregnancy-related nausea and vomiting: RR 1.09 (95% CI 0.27 to 4.39) p=0.90.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

- Very low quality evidence from 4 RCTs (N=319) showed that there is no clinically important difference between ginger capsule, biscuit, or tablet, and placebo on adverse events requiring hospitalisation up to 7 days after treatment in women who experience pregnancy-related nausea and vomiting: Peto OR 1.51 (95% CI 0.25 to 9.00).
  - Very low quality evidence from 1 RCT (N=120) showed that there is no clinically important difference between ginger capsules and placebo on adverse events requiring hospitalisation in high-income countries, up to 7 days after treatment in women who experience pregnancy-related nausea and vomiting: RR 1.50 (95% CI 0.26 to 8.66).
  - Very low quality evidence from 3 RCTs (N=199) showed that there is no clinically important difference between ginger biscuit, tablet or capsule, and placebo on adverse events requiring hospitalisation in middle-income countries, up to 7 days after treatment in women who experience pregnancy-related nausea and vomiting: RD 0.00 (95% CI -0.03 to 0.03).

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 2. Acupressure versus acupressure

Critical outcomes

Symptomatic relief during pregnancy

Nausea severity

- Low quality evidence from 1 RCT (N=82) showed that there is no clinically important difference between P6 acupressure and KID21 acupressure on nausea severity on change score from baseline, as assessed by the visual analogue scale in women who experience pregnancy-related nausea and vomiting: MD -0.52 (95% CI -1.08 to 0.04).

Vomiting severity

- Moderate quality evidence from 1 RCT (N=82) showed that there is no clinically important difference between P6 acupressure and KID21 acupressure on vomiting severity on change score from baseline, as assessed by the visual analogue scale in women who experience pregnancy-related nausea and vomiting: MD 0.22 (95% CI -0.26 to 0.70).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 3. Acupressure versus placebo

Critical outcomes

Symptomatic relief during pregnancy

Overall relief

- Moderate quality evidence from 2 RCTs (N=151) showed that there is no clinically important difference between acupressure and placebo on overall relief up to 7 days after treatment, as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -2.23 (95% CI -4.12 to -0.34).
    - Low quality evidence from 1 RCT (N=60) showed that there is no clinically important difference between acupressure and placebo on overall relief in high-income countries after treatment, as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -1.34 (95% CI -3.77 to 1.09).
    - Low quality evidence from 1 RCT (N=91) showed that there is no clinically important difference between acupressure and placebo on overall relief in low-income countries 7 days after treatment, as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -3.60 (95% CI -6.62 to -0.58).

Nausea relief

- Low quality evidence from 1 RCT (N=60) showed that there is no clinically important difference between acupressure and placebo on relief from nausea up to 7 days after treatment, as assessed by the Rhodes Index, in women who experience pregnancy-related nausea and vomiting: MD -1.24 (95% CI -2.63 to 0.15).

Nausea frequency

- Low quality evidence from 1 RCT (N=50) showed that there is no clinically important difference between acupressure and placebo on nausea frequency up to 4 days after treatment, as assessed by an unspecified scale from 0 to 4, in women who experience pregnancy-related nausea and vomiting: MD -2.49 (95% CI -4.41 to -0.57).

Nausea intensity

- Very low quality evidence from 1 RCT (N=40) showed that there is a clinically important difference favouring acupressure over placebo on nausea intensity after treatment as

assessed by a visual analogue scale in women who experience pregnancy-related nausea and vomiting: MD -1.70 (95% CI -3.25 to -0.15).

- Low quality evidence from 1 RCT (N=80) showed that there is a statistically significant difference favouring acupressure over placebo on nausea intensity after treatment as assessed by a visual analogue scale in women who experience pregnancy-related nausea and vomiting: difference between medians 3, p=0.001.
- Low quality evidence from 1 RCT (N=50) showed that there is no clinically important difference between acupressure and placebo on nausea intensity up to 4 days after treatment, as assessed by an unspecified scale from 0 to 4, in women who experience pregnancy-related nausea and vomiting: MD -6.39 (95% CI -12.37 to -0.41).

Vomiting relief

- Moderate quality evidence from 1 RCT (N=60) showed that there is no clinically important difference between acupressure and placebo on relief from vomiting up to 7 days after treatment, as assessed by the Rhodes Index, in women who experience pregnancy-related nausea and vomiting: MD -0.35 (95% CI -1.42 to 0.72).

Vomiting frequency

- Low quality evidence from 1 RCT (N=80) showed that there is a statistically significant difference favouring acupressure over placebo on vomiting intensity as assessed by patient report in women who experience pregnancy-related nausea and vomiting: difference between medians 1, p=0.001.
- Moderate quality evidence from 1 RCT (N=50) showed that there is no clinically important difference between acupressure and placebo on vomiting frequency up to 4 days after treatment, as assessed by an unspecified scale from 0 to 4, in women who experience pregnancy-related nausea and vomiting: MD -0.38 (95% CI -1.57 to 0.81).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

- Low quality evidence from 1 RCT (N=50) showed that there is a clinically important difference favouring acupressure over placebo on women's experience and satisfaction of care during or at end of pregnancy for those reporting satisfaction with the intervention in women who experience pregnancy-related nausea and vomiting: RR 2.50 (95% CI 1.16 to 5.39).
- Very low quality evidence from 1 RCT (N=50) showed that there is no clinically important difference between acupressure and placebo on women's experience and satisfaction of care during or at end of pregnancy for those reporting no satisfaction with the intervention

in women who experience pregnancy-related nausea and vomiting: Peto OR 7.39 (95% CI 0.15 to 372.38).

- Low quality evidence from 1 RCT (N=50) showed that there is a clinically important difference favouring placebo over acupressure on women's experience and satisfaction of care during or at end of pregnancy for those reporting they were almost satisfied with the intervention in women who experience pregnancy-related nausea and vomiting: RR 0.47 (95% CI 0.27 to 0.84).

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 4. Acupressure versus control (no treatment)

Critical outcomes

Symptomatic relief during pregnancy

Overall relief

- Low quality evidence from 1 RCT (N=93) showed that there is no clinically important difference between acupressure and control (no treatment) on overall relief up to 7 days after treatment, as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -2.67 (95% CI -5.84 to 0.50).

Nausea relief

- Low quality evidence from 1 RCT (N=93) showed that there is no clinically important difference between acupressure and control (no treatment) on relief from nausea up to 7 days after treatment, as assessed by the Rhodes Index, in women who experience pregnancy-related nausea and vomiting: MD 0.95 (95% CI -0.51 to 2.41).

Nausea frequency

- Moderate quality evidence from 1 RCT (N=50) showed that there is a clinically important difference favouring P6 acupressure over control (no treatment) on change score from baseline for nausea frequency, as assessed by an unspecified scale from 0 to 4, in women who experience pregnancy-related nausea and vomiting: MD -5.50 (95% CI -7.24 to -3.76).

Nausea intensity

- Very low quality evidence from 1 RCT (N=40) showed that there is a clinically important difference favouring acupressure over control (no treatment) on nausea intensity after treatment as assessed by a visual analogue scale in women who experience pregnancy-related nausea and vomiting: MD -2.30 (95% CI -3.79 to -0.81).
- Moderate quality evidence from 1 RCT (N=50) showed that there is a clinically important difference favouring P6 acupressure over control (no treatment) on change score from baseline for nausea intensity, as assessed by an unspecified scale from 0 to 4, in women who experience pregnancy-related nausea and vomiting: MD -14.30 (95% CI -20.02 to -8.58).

Vomiting relief

- Low quality evidence from 1 RCT (N=93) showed that there is no clinically important difference between acupressure and control (no treatment) on relief from vomiting up to 7 days after treatment, as assessed by the Rhodes Index, in women who experience pregnancy-related nausea and vomiting: MD -1.41 (95% CI -2.73 to -0.09).

Vomiting frequency

- Low quality evidence from 1 RCT (N=50) showed that there is a clinically important difference favouring P6 acupressure over control (no treatment) on change score from baseline for vomiting frequency, as assessed by an unspecified scale from 0 to 4, in women who experience pregnancy-related nausea and vomiting: MD -1.39 (95% CI -2.37 to -0.41).

Retching relief

- Low quality evidence from 1 RCT (N=93) showed that there is no clinically important difference between acupressure and control (no treatment) on relief from retching 7 days after treatment, as assessed by the Rhodes Index, in women who experience pregnancy-related nausea and vomiting: MD -0.82 (95% CI -1.78 to 0.14).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

- Moderate quality evidence from 1 RCT (N=50) showed that there is a clinically important difference favouring acupressure over control (no treatment) on women's experience and satisfaction of care during or at end of pregnancy for those reporting satisfaction with the intervention in women who experience pregnancy-related nausea and vomiting: RR 5.00 (95% CI 1.65 to 15.15).
- Moderate quality evidence from 1 RCT (N=50) showed that there is a clinically important difference favouring acupressure over control (no treatment) on women's experience and satisfaction of care during or at end of pregnancy for those reporting no satisfaction with the intervention in women who experience pregnancy-related nausea and vomiting: RR 0.06 (95% CI 0.01 to 0.44).
- Very low quality evidence from 1 RCT (N=50) showed that there is no clinically important difference between acupressure and control (no treatment) on women's experience and satisfaction of care during or at end of pregnancy for those reporting they were almost satisfied with the intervention in women who experience pregnancy-related nausea and vomiting: RR 1.50 (95% CI 0.63 to 3.59).

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 5. Acupressure versus ginger

Critical outcomes

Symptomatic relief during pregnancy

Overall relief

- Moderate quality evidence from 1 RCT (N=98) showed that there is a clinically important difference favouring ginger over acupressure on overall relief 7 days after treatment, as assessed by the Rhodes Index, in women who experience pregnancy-related nausea and vomiting: MD 6.24 (95% CI 3.03 to 9.45).

Nausea relief

- Moderate quality evidence from 1 RCT (N=98) showed that there is a clinically important difference favouring ginger over acupressure on relief from nausea 7 days after treatment, as assessed by the Rhodes Index, in women who experience pregnancy-related nausea and vomiting: MD 4.41 (95% CI 2.96 to 5.86).

Vomiting relief

- Low quality evidence from 1 RCT (N=98) showed that there is a clinically important difference favouring ginger over acupressure on relief from vomiting 7 days after treatment, as assessed by the Rhodes Index, in women who experience pregnancy-related nausea and vomiting: MD 1.67 (95% CI 0.37 to 2.97).

Retching relief

- Low quality evidence from 1 RCT (N=98) showed that there is a clinically important difference favouring ginger over acupressure on relief from retching 7 days after treatment, as assessed by the Rhodes Index, in women who experience pregnancy-related nausea and vomiting: MD 1.54 (95% CI 0.60 to 2.48).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 6. Acupuncture versus placebo

Critical outcomes

Symptomatic relief during pregnancy

Nausea relief

- Moderate quality evidence from 1 RCT (N=445) showed that there is no clinically important difference favouring placebo over P6 acupuncture on relief from nausea after treatment as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -0.35 (95% CI -0.98 to 0.28).
- Low quality evidence from 1 RCT (N=445) showed that there is no clinically important difference between traditional acupuncture and placebo on relief from nausea after treatment as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -0.95 (95% CI -1.54 to -0.36).

Nausea intensity

- Low quality evidence from 1 RCT (N= 55) showed that there was no statistically significant difference favouring traditional acupuncture over placebo on nausea intensity after treatment as assessed by a visual analogue scale in women who experience pregnancy-related nausea and vomiting: difference between medians 0.5, p=0.9.

Vomiting relief

- Moderate quality evidence from 1 RCT (N=445) showed that there is no clinically important difference between P6 acupuncture and placebo on relief from vomiting after treatment as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -0.30 (95% CI -0.66 to 0.06).
- Moderate quality evidence from 1 RCT (N=445) showed that there is no clinically important difference between traditional acupuncture and placebo on relief from vomiting after treatment as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -0.30 (95% CI -0.62 to 0.02).

Retching relief

- Moderate quality evidence from 1 RCT (N=445) showed that there is no clinically important difference between P6 acupuncture and placebo on relief from retching after treatment as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -0.35 (95% CI -0.63 to -0.07).
- Moderate quality evidence from 1 RCT (N=445) showed that there is no clinically important difference between traditional acupuncture and placebo on relief from retching after treatment as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -0.45 (95% CI -0.74 to -0.16).

Fetal death

- Low quality evidence from 1 RCT (N=445) showed that there is no statistically significant difference between P6 acupuncture and placebo on fetal death after treatment in women

who experience pregnancy-related nausea and vomiting: RR 0.50 (95% CI 0.21 to 1.20) p=0.12.

- Low quality evidence from 1 RCT (N=445) showed that there is no statistically significant difference between traditional acupuncture and placebo on fetal death after treatment in women who experience pregnancy-related nausea and vomiting: RR 0.50 (95% CI 0.21 to 1.20) p=0.12.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

- Low quality evidence from 1 RCT (N=55) showed that there was no clinically important difference between traditional acupuncture and placebo for adverse events requiring hospitalisation in women who experience pregnancy-related nausea and vomiting: RD 0.00 (95% CI -0.07 to 0.07).

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 7. Acupuncture + component versus sham acupuncture + placebo component

Critical outcomes

Symptomatic relief during pregnancy

Overall relief

- Low quality evidence from 1 RCT (N=107) showed that there is a clinically important difference favouring P6 acupuncture and transcutaneous electrical nerve stimulation over sham acupuncture and placebo transcutaneous electrical nerve stimulation on overall relief as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -6.32 (95% CI -8.21 to -4.43).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

- Low quality evidence from 1 RCT (N=107) showed that there was a clinically important difference favouring P6 acupuncture and transcutaneous electrical nerve stimulation over sham acupuncture and placebo transcutaneous electrical nerve stimulation on quality of life as assessed by the Nausea Vomiting of Pregnancy Quality of Life questionnaire in women who experience pregnancy-related nausea and vomiting: MD -34.65 (95% CI -40.64 to -28.66).

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 8. Dopamine D2-receptor antagonist versus placebo

Critical outcomes

Symptomatic relief during pregnancy

Overall relief

- High quality evidence from 1 RCT (N=68) showed that there is a clinically important difference favouring dopamine D2-receptor antagonist (metoclopramide hydrochloride) over placebo on overall relief after treatment as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -4.62 (95% CI -6.83 to -2.41).

Nausea intensity

- High quality evidence from 1 RCT (N=68) showed that there is a clinically important difference favouring dopamine D2-receptor antagonist (metoclopramide hydrochloride) over placebo on overall relief after treatment as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -3.05 (95% CI -4.50 to -1.60).

Vomiting intensity

- Moderate quality evidence from 1 RCT (N=68) showed that there is a clinically important difference favouring dopamine D2-receptor antagonist (metoclopramide hydrochloride) over placebo on overall relief after treatment as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -1.06 (95% CI -1.82 to -0.30).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 9. Histamine H1-receptor antagonist versus placebo

Critical outcomes

Symptomatic relief during pregnancy

Improvement on symptoms

- Very low quality evidence from 1 RCT (N=390) showed that there is a clinically important difference favouring histamine H1-receptor antagonist (doxylamine succinate) over placebo on number of women with improvement in nausea after treatment as assessed by physician evaluations in women who experience pregnancy-related nausea and vomiting: RR 1.33 (95% CI 1.12 to 1.57).
- Very low quality evidence from 1 RCT (N=390) showed that there is no clinically important difference between histamine H1-receptor antagonist (doxylamine succinate) and placebo on number of women with improvement in vomiting after treatment as assessed by physician evaluations in women who experience pregnancy-related nausea and vomiting: RR 1.19 (95% CI 1.04 to 1.35).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 10. Pyridoxine hydrochloride versus placebo

Critical outcomes

Symptomatic relief during pregnancy

Overall relief

- Moderate quality evidence from 1 RCT (N=49) showed that there is a clinically important difference favouring pyridoxine hydrochloride over placebo on overall relief after treatment as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -5.50 (95% CI -7.66 to -3.34).

Nausea intensity

- Low quality evidence from 1 RCT (N=49) showed that there is a clinically important difference favouring pyridoxine hydrochloride over placebo on nausea intensity after treatment as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -0.89 (95% CI -1.38 to -0.4).
- Moderate quality evidence from 2 RCTs (N=401) showed that there is no clinically important difference between pyridoxine hydrochloride and placebo on nausea intensity after treatment as assessed by a visual analogue scale: MD -0.60 (95% CI -1.2 to -0.01).

Nausea frequency

- Low quality evidence from 1 RCT (N=49) showed that there is a clinically important difference favouring pyridoxine hydrochloride over placebo on nausea frequency after treatment as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -0.67 (95% CI -1.08 to -0.26).

Vomiting intensity

- Low quality evidence from 1 RCT (N=49) showed that there is a clinically important difference favouring pyridoxine hydrochloride over placebo on vomiting intensity after treatment as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -0.7 (95% CI -1.14 to -0.26).

Vomiting frequency

- Low quality evidence from 1 RCT (N=49) showed that there is a clinically important difference favouring pyridoxine hydrochloride over placebo on vomiting frequency after treatment as assessed by the Rhodes Index in women who experience pregnancy-related nausea and vomiting: MD -0.97 (95% CI -1.43 to -0.51).

Change in vomiting frequency

- High quality evidence from 1 RCT (N=342) showed that there no clinically important difference between pyridoxine hydrochloride and placebo on change in vomiting frequency after treatment as assessed by patient report in women who experience pregnancy-related nausea and vomiting: MD -0.1 (95% CI -0.62 to 0.42).

Number of patients vomiting on last day of treatment

- Low quality evidence from 1 RCT (N=59) showed that there is a clinically important difference favouring pyridoxine hydrochloride over placebo on the number of patients vomiting on last day of treatment in women who experience pregnancy-related nausea and vomiting: RR 0.48 (95% CI 0.24 to 0.96).

Improvement on symptoms

- Very low quality evidence from 1 RCT (N=372) showed that there is a clinically important difference favouring pyridoxine hydrochloride over placebo on the number of women with improvement in nausea after treatment as assessed by physician evaluation in women who experience pregnancy-related nausea and vomiting: RR 1.31 (95% CI 1.11 to 1.55).
- Low quality evidence from 1 RCT (N=372) showed that there is no clinically important difference favouring pyridoxine hydrochloride over placebo on the number of women with improvement in vomiting after treatment as assessed by physician evaluation in women who experience pregnancy-related nausea and vomiting: RR 1.00 (95% CI 0.87 to 1.16).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 11. Pyridoxine hydrochloride versus histamine H1-receptor antagonist

Critical outcomes

Symptomatic relief during pregnancy

Improvement on symptoms

- Low quality evidence from 1 RCT (N=400) showed that there is no clinically important difference between pyridoxine hydrochloride and histamine H1-receptor antagonist (doxylamine succinate) on the number of women with improvement in nausea after treatment as assessed by physician evaluation in women who experience pregnancy-related nausea and vomiting: RR 0.99 (95% CI 0.86 to 1.13).
- Very low quality evidence from 1 RCT (N=400) showed that there is no clinically important difference between pyridoxine hydrochloride and histamine H1-receptor antagonist (doxylamine succinate) on the number of women with improvement in vomiting after treatment as assessed by physician evaluation in women who experience pregnancy-related nausea and vomiting: RR 0.85 (95% CI 0.75 to 0.96).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 12. Pyridoxine hydrochloride + dopamine D2-receptor antagonist versus histamine H1-receptor antagonist

Critical outcomes

Symptomatic relief during pregnancy

Vomiting frequency

- Moderate quality evidence from 1 RCT (N=106) showed that there is no clinically important difference between pyridoxine hydrochloride + dopamine D2-receptor antagonist (metoclopramide hydrochloride) and histamine H1-receptor antagonist (promethazine hydrochloride) on vomiting frequency after treatment as assessed by patient report in

women who experience pregnancy-related nausea or vomiting: MD -0.20 (95% CI -0.5 to 0.1).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 13. Pyridoxine hydrochloride + histamine H1-receptor antagonist versus placebo

Critical outcomes

Symptomatic relief during pregnancy

Overall relief

- Moderate quality evidence from 1 RCT (N=256) showed that there is no clinically important difference between pyridoxine hydrochloride + histamine H1-receptor antagonist (doxylamine succinate) and placebo on overall relief at 15 days after treatment as assessed by change scores on the PUQE (pregnancy unique quantification of emesis and nausea) index in women who experience pregnancy-related nausea and vomiting: MD -0.90 (95% CI -1.55 to -0.25).

Relief from nausea and vomiting

- Low quality evidence from 2 RCTs (N=310) showed that there is a clinically important difference favouring pyridoxine hydrochloride and histamine H1-receptor antagonist (doxylamine succinate or cyclizine hydrochloride) over placebo on relief from nausea and vomiting after treatment as assessed by patient report in women who experience pregnancy-related nausea and vomiting: RR 3.40 (1.08 to 10.70).

Improvement on symptoms

- Very low quality evidence from 1 RCT (N=394) showed that there is a clinically important difference favouring pyridoxine hydrochloride + histamine H1-receptor antagonist (doxylamine succinate) over placebo on the number of women with improvements in nausea after treatment as assessed by physician evaluation in women who experience pregnancy-related nausea and vomiting: RR 1.45 (95% CI 1.23 to 1.70).
- Very low quality evidence from 1 RCT (N=394) showed that there is no clinically important difference between pyridoxine hydrochloride + histamine H1-receptor antagonist (doxylamine succinate) and placebo on the number of women with improvements in vomiting after treatment as assessed by physician evaluation in women who experience pregnancy-related nausea and vomiting: RR 1.11 (95% CI 0.97 to 1.26).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

- Low quality evidence from 2 RCTs (N=368) showed that there is no clinically important difference between pyridoxine hydrochloride + histamine H1-receptor antagonist (doxylamine succinate and cyclizine hydrochloride) and placebo on adverse events requiring hospitalisation after treatment in women who experience pregnancy-related nausea and vomiting: RD 0.00 (95% CI -0.02 to 0.02).

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 14. Pyridoxine hydrochloride + histamine H1-receptor antagonist versus pyridoxine hydrochloride

Critical outcomes

Symptomatic relief during pregnancy

Number of women with improvements in symptoms

- Very low quality evidence from 1 RCT (N=404) showed that there is no clinically important difference between pyridoxine hydrochloride + histamine H1-receptor antagonist (doxylamine succinate) and pyridoxine hydrochloride on the number of women with improvement in nausea after treatment as assessed by physician evaluation in women who experience pregnancy-related nausea and vomiting: RR 1.10 (95% CI 0.97 to 1.25).
- Very low quality evidence from 1 RCT (N=404) showed that there is no clinically important difference between pyridoxine hydrochloride + histamine H1-receptor antagonist (doxylamine succinate) and pyridoxine hydrochloride on the number of women with improvement in vomiting after treatment as assessed by physician evaluation in women who experience pregnancy-related nausea and vomiting: RR 1.10 (95% CI 0.97 to 1.26).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 15. Pyridoxine hydrochloride + histamine H1-receptor antagonist versus histamine H1-receptor antagonist

Critical outcomes

Symptomatic relief during pregnancy

Number of women with improvements in symptoms

- Low quality evidence from 1 RCT (N=422) showed that there is no clinically important difference between pyridoxine hydrochloride + histamine H1-receptor antagonist (doxylamine succinate) and histamine H1-receptor antagonist (doxylamine succinate) on

the number of women with improvement in nausea after treatment as assessed by physician evaluation in women who experience pregnancy-related nausea and vomiting: RR 1.09 (95% CI 0.97 to 1.23).

- Low quality evidence from 1 RCT (N=422) showed that there is no clinically important difference between pyridoxine hydrochloride + histamine H1-receptor antagonist (doxylamine succinate) and histamine H1-receptor antagonist (doxylamine succinate) on the number of women with improvement in vomiting after treatment as assessed by physician evaluation in women who experience pregnancy-related nausea and vomiting: RR 0.93 (95% CI 0.84 to 1.04).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 16. Serotonin 5-HT antagonist + placebo versus pyridoxine hydrochloride + histamine H1-receptor antagonist

Critical outcomes

Symptomatic relief during pregnancy

Nausea intensity

- Low quality evidence from 1 RCT (N=30) showed that there is a statistically significant favouring serotonin 5-HT antagonist (ondansetron) + placebo over pyridoxine hydrochloride + histamine H1-receptor antagonist (doxylamine succinate) on nausea intensity 7 days after treatment as assessed by change scores on a visual analogue scale in women who experience pregnancy-related nausea and vomiting: difference between medians 31, p=0.019.

Vomiting intensity

- Low quality evidence from 1 RCT (N=30) showed that there is a statistically significant difference favouring serotonin 5-HT antagonist (ondansetron) + placebo over pyridoxine hydrochloride + histamine H1-receptor antagonist (doxylamine succinate) on vomiting

intensity 7 days after treatment as assessed by change scores on a visual analogue scale in women who experience pregnancy-related nausea and vomiting: difference between medians 24, p=0.049.

Number of women with improvement in symptoms (score on VAS ≥25 mm, considered clinically important in study)

- Moderate quality evidence from 1 RCT (N=30) showed that there is a clinically important difference favouring serotonin 5-HT antagonist (ondansetron) + placebo over pyridoxine hydrochloride + histamine H1-receptor antagonist (doxylamine succinate) on the number of women with a clinically significant improvement in nausea symptoms 7 days after treatment as assessed by a visual analogue scale in women who experience pregnancy-related nausea and vomiting: RR 2.24 (95% CI 1.24 to 4.04).
- Moderate quality evidence from 1 RCT (N=30) showed that there is a clinically important difference favouring serotonin 5-HT antagonist (ondansetron) + placebo over pyridoxine hydrochloride + histamine H1-receptor antagonist (doxylamine succinate) on the number of women with a clinically significant improvement in vomiting symptoms 7 days after treatment as assessed by a visual analogue scale in women who experience pregnancy-related nausea and vomiting: RR 2.18 (95% CI 1.07 to 4.43).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

- Low quality evidence from 1 RCT (N=30) showed that there is no clinically important difference between serotonin 5-HT antagonist (ondansetron) + placebo and pyridoxine hydrochloride + histamine H1-receptor antagonist (doxylamine succinate) on adverse events requiring hospitalisation after treatment in women who experience pregnancy-related nausea and vomiting: RD 0.00 (95% CI -0.12 to 0.12).

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Moderate to severe nausea and vomiting (including hyperemesis gravidarum)

Comparison 1. Acupressure vs placebo

Critical outcomes

Symptomatic relief during pregnancy

Overall relief

- Moderate quality evidence from 1 RCT (N=120) showed that there is a clinically important difference favouring P6 acupressure combined with standard care over placebo on overall relief after treatment as assessed by the PUQE (pregnancy unique quantification of emesis and nausea) index in women who experience pregnancy-related nausea and vomiting: MD -2.70 (95% CI -3.28 to -2.12).

Nausea severity

- Moderate quality evidence from 1 RCT (N=120) showed that there is a clinically important difference favouring P6 acupressure combined with standard care over placebo on nausea severity after treatment as assessed by the PUQE (pregnancy unique quantification of emesis and nausea) index in women who experience pregnancy-related nausea and vomiting: MD -1.01 (95% CI -1.32 to -0.70).

Vomiting severity

- Moderate quality evidence from 1 RCT (N=120) showed that there is a clinically important difference favouring P6 acupressure combined with standard care over placebo on vomiting severity after treatment as assessed by the PUQE (pregnancy unique quantification of emesis and nausea) index in women who experience pregnancy-related nausea and vomiting: MD -1.10 (95% CI -1.33 to -0.87).

Retching severity

- Low quality evidence from 1 RCT (N=120) showed that there is no clinically important difference between P6 acupressure combined with standard care and placebo on retching severity after treatment as assessed by the PUQE (pregnancy unique quantification of emesis and nausea) index in women who experience pregnancy-related nausea and vomiting: MD -0.58 (95% CI -0.81 to -0.35).

Number of women with disappearance of symptoms

- Moderate quality evidence from 1 RCT (N=18) showed that there is a clinically important difference favouring P6 acupressure over placebo on the number of women with disappearance of symptoms 2 weeks after treatment in women who experience pregnancy-related nausea and vomiting: Peto OR 12.54 (95% CI 1.90 to 82.93).

Fetal death

Miscarriage before 20 weeks

- Very low quality evidence from 1 RCT (N=57) showed that there was no statistically significant difference between P6 acupressure and placebo on fetal death after treatment in women who experience pregnancy-related nausea and vomiting: RR 0.48 (95% CI 0.05 to 5.03) p=0.54.

Termination of pregnancy

- Very low quality evidence from 1 RCT (N=57) showed that there was no statistically significant difference between P6 acupressure and placebo on fetal death after treatment in women who experience pregnancy-related nausea and vomiting: RR 0.72 (95% CI 0.18 to 2.95) p=0.65.

Intra-uterine fetal death after 20 weeks

- Very low quality evidence from 1 RCT (N=36) showed that there was no statistically significant difference between P6 acupressure and placebo on fetal death after treatment in women who experience pregnancy-related nausea and vomiting: RR 0.57 (95% CI 0.04 to 8.30) p=0.68.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

- Moderate quality evidence from 1 RCT (N=120) showed that there is a clinically important difference between P6 acupressure combined with standard care and placebo on number of days in hospital after treatment in women who experience pregnancy-related nausea and vomiting: MD -1.05 (95% CI -1.32 to -0.78).
- Very low quality evidence from 1 RCT (N=80) showed that there was no statistically significant difference favouring P6 acupressure over placebo on number of days in hospital after treatment in women who experience pregnancy-related nausea and vomiting: difference between medians 0, p= not stated.

Women's experience and satisfaction of care during or at end of pregnancy

- Low quality evidence from 1 RCT (N=120) showed that there was no clinically important difference between P6 acupressure combined with standard care and placebo on women's experience and satisfaction after treatment in women who experience pregnancy-related nausea and vomiting: RR 0.84 (95% CI 0.70 to 1.02).

Preterm birth

- Moderate quality evidence from 1 RCT (N=36) showed that there was no clinically important difference between P6 acupressure and placebo on preterm birth after treatment in women who experience pregnancy-related nausea and vomiting: Peto OR 0.06 (95% CI 0.00 to 1.08) p=0.06.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 2. Acupuncture vs placebo

Critical outcomes

Symptomatic relief during pregnancy

Number of women with relief from symptoms

- Low quality evidence from 1 RCT (N=18) showed that there is a clinically important difference favouring P6 acupuncture over placebo on the number of women with disappearance of symptoms 2 weeks after treatment in women who experience pregnancy-related nausea and vomiting: RR 7.2 (95% CI 1.14 to 45.56).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 3. Pyridoxine hydrochloride vs placebo

Critical outcomes

Symptomatic relief during pregnancy

Nausea intensity

- Very low quality evidence from 1 RCT (N=52) showed that there is no statistical significance between pyridoxine hydrochloride and placebo on nausea intensity 2 weeks after treatment as assessed by a visual analogue scale in women who experience pregnancy-related nausea and vomiting: difference between medians 0.5, p=0.69.

Daily mean vomiting episodes

- Very low quality evidence from 1 RCT (N=52) showed that there is no clinically important difference between pyridoxine hydrochloride and placebo on daily mean vomiting episodes 2 weeks after treatment as assessed by patient report in women who experience pregnancy-related nausea and vomiting: MD 0 (95% CI -0.79 to 0.79).

Number of women vomiting in the last 24 hours

- Very low quality evidence from 1 RCT (N=92) showed that there is no clinically important difference favouring pyridoxine hydrochloride over placebo on the number of women vomiting in the last 24 hours before discharge 2 weeks after treatment in women who experience pregnancy-related nausea and vomiting: RR 1.4 (95% CI 0.79 to 2.49).

Fetal death

- Very low quality evidence from 1 RCT (N=68) showed that there is no statistically significant difference between pyridoxine hydrochloride and placebo on fetal death 2 weeks after

treatment in women who experience pregnancy-related nausea and vomiting: Peto OR 0.15 (95% CI 0.00 to 7.67) p=0.35.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

- Very low quality evidence from 1 RCT (N=52) showed that there is no clinically important difference between pyridoxine hydrochloride and placebo on adverse events requiring hospitalisation 2 weeks after treatment in women who experience pregnancy-related nausea and vomiting: RD 0.00 (95% CI -0.07 to 0.07).

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

Overall wellbeing score

- Very low quality evidence from 1 RCT (N=52) showed that there is no statistically significant difference between pyridoxine hydrochloride and placebo on overall wellbeing score 2 weeks after treatment as assessed by a visual analogue scale in women who experience pregnancy-related nausea and vomiting: difference between medians 1, p=0.73.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 4. Dopamine D2 receptor antagonist vs Histamine H1-receptor antagonist

Critical outcomes

Symptomatic relief during pregnancy

Nausea severity

- Low quality evidence from 1 RCT (N=149) showed that there is no statistically significant difference between dopamine D2 receptor antagonist (metoclopramide hydrochloride) and histamine H1-receptor antagonist (promethazine hydrochloride) on nausea severity after treatment as assessed by a visual numerical rating scale in women who experience pregnancy-related nausea and vomiting: difference between medians 0, p=0.99.

Vomiting frequency

- Low quality evidence from 1 RCT (N=149) showed that there is no statistically significant difference between dopamine D2 receptor antagonist (metoclopramide hydrochloride) and histamine H1-receptor antagonist (promethazine hydrochloride) on vomiting frequency after treatment as assessed by patient report in women who experience pregnancy-related nausea and vomiting: difference between medians 1, p=0.81.

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

- Low quality evidence from 1 RCT (N=149) showed that there is no statistically significant difference between dopamine D2 receptor antagonist (metoclopramide hydrochloride) and histamine H1-receptor antagonist (promethazine hydrochloride) on number of days in hospital after treatment in women who experience pregnancy-related nausea and vomiting: difference between medians 0.1, p=0.71.

Women's experience and satisfaction of care during or at end of pregnancy

Patient wellbeing

- Moderate quality evidence from 1 RCT (N=149) showed that there is no clinically important difference between dopamine D2 receptor antagonist (metoclopramide hydrochloride) and histamine H1-receptor antagonist (promethazine hydrochloride) on patient wellbeing after treatment as assessed by a visual numerical rating scale in women who experience pregnancy-related nausea and vomiting: MD 0.5 (95% CI -0.22 to 1.22).

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 5. Serotonin 5-HT antagonist vs Dopamine D2 receptor antagonist

Critical outcomes

Symptomatic relief during pregnancy

Nausea severity

- High quality evidence from 1 RCT (N=83) showed that there is no clinically important difference between serotonin 5-HT antagonist (ondansetron) and dopamine D2 receptor antagonist (metoclopramide hydrochloride) on nausea severity 7 days after treatment as assessed by a visual analogue scale in women who experience pregnancy-related nausea and vomiting: MD -0.70 (95% CI -1.97 to 0.57).
- Low quality evidence from 1 RCT (N=120) showed that there is no statistically significant difference between serotonin 5-HT antagonist (ondansetron) and dopamine D2 receptor antagonist (metoclopramide hydrochloride) on nausea severity after treatment as assessed by a visual numerical rating scale in women who experience pregnancy-related nausea and vomiting: difference between medians 1, p=0.68.

Vomiting severity

- High quality evidence from 1 RCT (N=83) showed that there is no clinically important difference between serotonin 5-HT antagonist (ondansetron) and dopamine D2 receptor antagonist (metoclopramide hydrochloride) on vomiting severity 7 days after treatment as assessed by a visual analogue scale in women who experience pregnancy-related nausea and vomiting: MD 0 (95% CI -1.24 to 1.24).

Number of women vomit free during 24 hours

- Moderate quality evidence from 1 RCT (N=120) showed that there is no clinically important difference between serotonin 5-HT antagonist (ondansetron) and dopamine D2 receptor antagonist (metoclopramide hydrochloride) on the number of women vomit free during 24 hours after treatment in women who experience pregnancy-related nausea and vomiting: RR 1.15 (95% CI 0.86 to 1.53).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

- Low quality evidence from 1 RCT (N=120) showed that there is no statistically significant difference between serotonin 5-HT antagonist (ondansetron) and dopamine D2 receptor antagonist (metoclopramide hydrochloride) after treatment in women who experience pregnancy-related nausea and vomiting: difference between medians 0.1, p=0.10.

Women's experience and satisfaction of care during or at end of pregnancy

Patient wellbeing

- Moderate quality evidence from 1 RCT (N=160) showed that there is no clinically important difference between serotonin 5-HT antagonist (ondansetron) and dopamine D2 receptor antagonist (metoclopramide hydrochloride) on patient wellbeing after treatment as assessed by a visual numerical rating scale in women who experience pregnancy-related nausea and vomiting: MD 0.4 (95% CI -0.03 to 0.83).

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 5. Serotonin 5-HT antagonist vs Histamine H1-receptor antagonist

Critical outcomes

Symptomatic relief during pregnancy

No evidence was identified to inform this outcome.

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

Sedation

- Low quality evidence from 1 RCT (N=30) showed that there is a clinically important difference favouring serotonin 5-HT antagonist (ondansetron) over histamine H1-receptor antagonist (promethazine hydrochloride) on sedation after treatment in women who experience pregnancy-related nausea and vomiting: Peto OR 0.07 (95% CI 0.01 to 0.35).

Number of days in hospital for treatment of nausea and vomiting

- Very low quality evidence from 1 RCT (N=30) showed that there is no clinically important difference between serotonin 5-HT antagonist (ondansetron) and histamine H1-receptor antagonist (promethazine hydrochloride) on number of days in hospital in women who experience pregnancy-related nausea and vomiting: MD 0 (95% CI -1.39 to 1.39).

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 6. Corticosteroid vs Placebo

Critical outcomes

Symptomatic relief during pregnancy

Improvement in nausea intensity

- Low quality evidence from 1 RCT (N=24) showed that there is no statistically significant difference between corticosteroids (prednisolone) and placebo on improvement in nausea intensity 7 days after treatment as assessed by a numerical scale in women who experience pregnancy-related nausea and vomiting: difference between medians 2.5, p=0.10.

Reduction in vomiting intensity

- Low quality evidence from 1 RCT (N=24) showed that there is no statistically significant difference between corticosteroids (prednisolone) and placebo on reduction in vomiting

intensity 7 days after treatment as assessed by a numerical scale in women who experience pregnancy-related nausea and vomiting: difference between medians 0.5, p=0.26.

Vomiting frequency

- Low quality evidence from 1 RCT (N=24) showed that there is no clinically important difference between corticosteroids (prednisolone) and placebo on vomiting frequency 7 days after treatment as assessed by patient report in women who experience pregnancy-related nausea and vomiting: RR 0.4 (95% CI 0.1 to 1.67).

Fetal death

- Very low quality evidence from 2 RCTs (N=134) showed that there is no statistically significant difference between corticosteroids (prednisolone and methylprednisolone + oral prednisolone) and placebo on fetal death up to 7 days after treatment in women with pregnancy-related nausea and vomiting: RR 0.65 (95% CI 0.19 to 2.19) p=0.49.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

- Low quality evidence from 1 RCT (N=24) showed that there is no statistically significant difference between corticosteroids (prednisolone) and placebo on number of days in hospital 7 days after treatment in women who experience pregnancy-related nausea and vomiting: difference between medians 0, p=0.84
- Low quality evidence from 1 RCT (N=110) showed that there is no clinically important difference between corticosteroids (methylprednisolone + oral prednisolone) and placebo on number of days in hospital after treatment in women who experience pregnancy-related nausea and vomiting: MD 3.3 (95% CI -1.55 to 8.15).

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

- Moderate quality evidence from 2 RCTs (N=134) showed that there is no clinically important difference between corticosteroids (prednisolone and methylprednisolone + oral prednisolone) and placebo on preterm birth up to 7 days after treatment in women with pregnancy-related nausea and vomiting: RR 1.1 (95% CI 0.45 to 2.67).

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 7. Corticosteroid vs Dopamine D2 receptor antagonist

Critical outcomes

Symptomatic relief during pregnancy

Reduction in mean number of vomiting episodes

- Moderate quality evidence from 1 RCT (N=40) showed that there is a clinically significant difference favouring corticosteroid (hydrocortisone) over dopamine D2 receptor antagonist (metoclopramide hydrochloride) on reduction in mean number of vomiting episodes 2 weeks after treatment as assessed by patient report in women who experience pregnancy-related nausea and vomiting: SMD -1.37 (95% CI -2.06 to -0.68).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 8. Corticosteroid vs Histamine H1-receptor antagonist

Critical outcomes

Symptomatic relief during pregnancy

Number of women with severe nausea

- Low quality evidence from 1 RCT (N=78) showed that there is no clinically important difference between corticosteroid (prednisolone) and histamine H1-receptor antagonist (promethazine hydrochloride) on number of women with severe nausea 7 days after treatment in women who experience pregnancy-related nausea and vomiting: RR 0.81 (95% CI 0.58 to 1.15).

Vomiting frequency

- Very low quality evidence from 1 RCT (N=78) showed that there is no statistically significant difference between corticosteroid (prednisolone) and histamine H1-receptor antagonist (promethazine hydrochloride) on vomiting frequency 7 days after treatment as assessed by

patient report in women who experience pregnancy-related nausea and vomiting: difference between medians 0, p=1.00.

Number of patients with complete or partial relief

- Low quality evidence from 1 RCT (N=80) showed that there is no clinically important difference between corticosteroid (prednisolone) and histamine H1-receptor antagonist (promethazine hydrochloride) on number of patients with complete or partial relief 7 days after treatment in women who experience pregnancy-related nausea and vomiting: RR 1.67 (95% CI 0.95 to 2.92).

Number of women with improvement of symptoms

- Low quality evidence from 1 RCT (N=40) showed that there is no clinically important difference between corticosteroid (methylprednisolone) and histamine H1-receptor antagonist (promethazine hydrochloride) on number of women with improvement of symptoms 2 weeks after treatment in women who experience pregnancy-related nausea and vomiting: RR 0.94 (95% CI 0.75 to 1.19).

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

- Very low quality evidence from 1 RCT (N=40) showed that there is no clinically important difference between corticosteroid (methylprednisolone) and histamine H1-receptor antagonist (promethazine hydrochloride) on adverse events requiring hospitalisation 2 weeks after treatment in women who experience pregnancy-related nausea and vomiting: RD 0.00 (95% CI -0.09 to 0.09).

Abdominal pain

- Low quality evidence from 1 RCT (N=80) showed that there is a clinically important difference between corticosteroid (prednisolone) and histamine H1-receptor antagonist (promethazine hydrochloride) on abdominal pain 7 days after treatment in women who experience pregnancy-related nausea and vomiting: Peto OR 0.13 (95% CI 0.02 to 0.92).

Drowsiness

- Moderate quality evidence from 1 RCT (N=80) showed that there is a clinically important difference between corticosteroid (prednisolone) and histamine H1-receptor antagonist (promethazine hydrochloride) on drowsiness 7 days after treatment in women who experience pregnancy-related nausea and vomiting: Peto OR 0.12 (95% CI 0.02 to 0.62).

Number of days in hospital for treatment of nausea and vomiting

- Moderate quality evidence from 1 RCT (N=34) showed that there is a clinically important difference between corticosteroid (methylprednisolone) and histamine H1-receptor antagonist (promethazine hydrochloride) on number of days in hospital 2 weeks after treatment in women who experience pregnancy-related nausea and vomiting: Peto OR 0.10 (95% CI 0.02 to 0.67).

Women's experience and satisfaction of care during or at end of pregnancy

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 9. Intravenous fluids vs Intravenous fluids

Critical outcomes

Symptomatic relief during pregnancy

Nausea intensity

- Moderate quality evidence from 1 RCT (N=203) showed that there is no statistically significant difference between dextrose saline and normal saline on nausea intensity after treatment as assessed by a visual numerical rating scale in women who experience pregnancy-related nausea and vomiting: difference between medians 0, p=0.39.

Vomiting frequency

- Moderate quality evidence from 1 RCT (N=203) showed that there is no statistically significant difference between dextrose saline and normal saline on vomiting frequency after treatment as assessed by patient report in women who experience pregnancy-related nausea and vomiting: difference between medians 0, p=0.66.

Fetal death

No evidence was identified to inform this outcome.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or at end of pregnancy

- High quality evidence from 1 RCT (N=203) showed that there is no clinically important difference between dextrose saline and normal saline on women's experience and satisfaction after treatment as assessed by a visual numerical rating scale in women who experience pregnancy-related nausea and vomiting: MD 0.1 (95% CI -0.33 to 0.53).

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 10. Intravenous fluids in one setting vs Intravenous fluids in another setting

Critical outcomes

Symptomatic relief during pregnancy

Overall relief

- Very low quality of evidence from 1 RCT (N=31) showed that there is no clinically important difference between IV fluids in the maternity assessment unit and IV fluids in the antenatal ward on overall relief after treatment as assessed by the PUQE (pregnancy unique quantification of emesis and nausea) index in women who experience pregnancy-related nausea and vomiting: MD 0.7 (95% CI -1.77 to 3.17).

Fetal death

Spontaneous abortions

- Very low quality evidence from 1 RCT (N=53) showed that there is no statistically significant difference between IV fluids in the maternity assessment unit and IV fluids in the antenatal ward on spontaneous abortions after treatment in women who experience pregnancy-related nausea and vomiting: RR 0.96 (95% CI 0.15 to 6.34) p=0.97).

Termination of pregnancy

- Very low quality evidence from 1 RCT (N=53) showed that there is no statistically significant difference between IV fluids in the maternity assessment unit and IV fluids in the antenatal ward on termination of pregnancy after treatment in women who experience pregnancy-related nausea and vomiting: Peto OR 7.12 (95% CI 0.14 to 359.1) p=0.33.

Infant death up to 4 weeks chronological age

No evidence was identified to inform this outcome.

Important outcomes

Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment

No evidence was identified to inform this outcome.

Number of days in hospital for treatment of nausea and vomiting

- Low quality evidence from 1 RCT (N=98) showed that there is a statistically significant difference favouring IV fluids in day care over IV fluids in inpatient care on number of days in hospital after treatment in women who experience pregnancy-related nausea and vomiting: difference between medians 2, p=0.001.

Women's experience and satisfaction of care during or at end of pregnancy

- Low quality evidence from 1 RCT (N=98) showed that there is no statistically significant difference between IV fluids in inpatient care and IV fluids in day care on women's experience and satisfaction after treatment as assessed by the client satisfaction questionnaire in women who experience pregnancy-related nausea and vomiting: difference between medians 67, p=0.70.

- Low quality evidence from 1 RCT (N=29) showed that there is no clinically important difference between IV fluids in the maternity assessment unit and IV fluids in the antenatal ward on women's experience and satisfaction after treatment as assessed by the short satisfaction survey in women who experience pregnancy-related nausea and vomiting: MD -0.60 (95% CI -3.51 to 2.31).

Preterm birth

No evidence was identified to inform this outcome.

Small for gestational age

- Very low quality of evidence from 1 RCT (N=53) showed that there is no clinically important difference favouring IV fluids in the maternity assessment unit over IV fluids in the antenatal ward on small for gestational age after treatment for women who experience pregnancy-related nausea and vomiting: RR 0.96 (95% CI 0.21 to 4.35).

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that symptomatic relief during pregnancy was a critical outcome for the woman, and fetal death and infant death up to 4 weeks chronological age were critical outcomes for the baby. Important outcomes were adverse events requiring hospitalisation; number of days in hospital; and women's experience and satisfaction of care; preterm birth and small for gestational age.

The quality of the evidence

The quality of evidence for outcomes in this review ranged from high to very low quality and was generally moderate to low quality.

Outcomes were typically downgraded due to imprecision around the effect estimate in a few outcomes; the presence of serious heterogeneity in some outcomes, which was unresolved by subgroup analysis; and risk of bias, most often arising due to selection and attrition bias.

The evidence for pyridoxine hydrochloride as a treatment for mild to moderate NVP was of a mixed quality and showed variation in clinical effectiveness. Larger studies showed no effect whilst smaller studies showed clinically important benefits over placebo. Although publication bias was not formally detected through the GRADE process, the committee suspected some bias was present.

One RCT conducted an 8-arm trial in the US in the 1970s, which was published in 2017 under the 'restoring invisible and abandoned trials' (RIAT) initiative. This study, known as the "'8-way' Bendectin Study", examined the efficacy of doxylamine, pyridoxine hydrochloride, and dicyclomine in tablet form, separately and in combination, compared to each other and placebo. The study reported high risk of bias in the results given the high attrition rate in the 7 day trial, the absence of prespecified outcomes or analyses, and the exclusion of some data because of questionable data integrity. The committee agreed that this evidence should be included on the basis that it was downgraded to very low evidence. The committee agreed they would not consider this evidence when making recommendations due to data integrity concerns.

Evidence was found for all interventions noted in the protocol. Studies mostly reported on symptoms relating to nausea & vomiting, including relief and vomiting intensity. There was very

little evidence for the critical outcomes on maternal or fetal deaths. There was no evidence identified for the outcome of infant death up to 4 weeks chronological age.

Benefits and harms

The committee discussed that mild to moderate nausea and vomiting are common in early pregnancy and can significantly affect the day-to-day life and quality of life for some pregnant women. The committee discussed that it is important to reassure women that in most cases it is likely to resolve before 16 to 20 weeks and so a recommendation was made to reflect this.

The committee discussed that many women may consider nausea and vomiting to be a normal part of pregnancy and endure even guite significant nausea and vomiting before seeking help. Some women may also try self-help interventions at home to alleviate their nausea and vomiting before consulting a healthcare professional. The committee discussed that in this case it is important for healthcare professionals to recognise that these pregnant women consider their symptoms severe enough to seek medical help. The committee agreed that it was important for healthcare providers to acknowledge this and give advice about interventions accordingly.

Non-pharmacological treatments for women with mild to moderate nausea and vomiting in pregnancy

Evidence from 5 RCTs showed that ginger had a clinically important benefit compared to placebo or acupressure in terms of a variety of nausea and vomiting symptom related outcomes (for example overall symptomatic relief and nausea relief). Ginger tablets were the most common form of ginger product used in the evidence, although the committee were aware from their own experience that ginger biscuits are often suggested to women. Although there were some outcomes for which no clinically important difference was observed (for example vomiting intensity) the committee agreed that those were generally less impactful outcomes as far as the woman's own experience. There was no evidence of harms from the use of ginger. The committee also noted that ginger is generally readily accessible to women with NVP and does not need to be prescribed.

The committee recognised that some women prefer a non-pharmacological treatment. Based on the evidence, the committee recommended that ginger could be used as a non-pharmacological treatment for mild to moderate nausea and vomiting in pregnancy (NVP) because there was evidence that ginger is effective in providing symptomatic relief during pregnancy - overall and for nausea, vomiting and retching - and that there are no substantial harms associated with its use compared to either placebo or acupressure.

There was no evidence showing a clinically important benefit of acupuncture in this population and very little evidence of benefit from acupressure. Acupressure was shown to be less effective than ginger in this group in terms of symptomatic relief and for most outcomes it had no benefit compared to placebo (for example overall relief) and any benefits were generally in comparisons likely to be less impactful for women (for example vomiting intensity).

Pharmacological treatments for women with mild to moderate nausea and vomiting in pregnancy

There was high quality evidence supporting metoclopramide hydrochloride, a dopamine D2-receptor antagonist, as a treatment for mild to moderate NVP when compared to placebo. One RCT of 68 women with mild to moderate NVP showed that there is a clinically important benefit favouring 10mg of metoclopramide three times a day for 5 days on providing overall symptomatic relief, and alleviating nausea intensity and vomiting intensity, compared to placebo. This trial did not report any adverse effects or other harms.

There was moderate quality evidence supporting ondansetron, a serotonin 5-HT antagonist as treatment for mild to moderate NVP. The evidence showed that women who received ondansetron combined with a placebo tablet are more likely to show an improvement on nausea symptoms and on vomiting symptoms, respectively, compared to those who received a combination of pyridoxine hydrochloride and doxylamine succinate. This study also found a statistically significant difference favouring ondansetron on reducing nausea intensity and reducing vomiting intensity, compared to pyridoxine hydrochloride and doxylamine succinate. Finally, the trial reported that there were no adverse events in any of the participants.

The committee agreed that the evidence for metoclopramide hydrochloride and ondansetron was consistent with their clinical experience. The committee discussed that it was important to highlight and discuss the advantages and disadvantages of pharmacological treatments with the woman.

The evidence for histamine H1 receptor antagonists as a treatment for mild to moderate NVP was of very low quality and the one identified study was at high risk of bias. Evidence for the use of doxylamine succinate, a histamine H1 receptor antagonist, for the treatment of mild to moderate NVP was gleaned from one RCT conducted in the US in the 1970s but not published until 2017 under the 'restoring invisible and abandoned trials' (RIAT) initiative. This 8-arm study, known as the "'8-way' Bendectin Study", examined the efficacy of doxylamine, pyridoxine hydrochloride, and dicyclomine in tablet form, separately and in combination, compared to each other and placebo. Women randomised to each arm were instructed to take 2 tablets before going to sleep for 7 nights and could take an additional 2 tablets (one in the morning and one in the mid-afternoon) as needed. The authors of the article (who were not involved in the original trial itself) raise several serious issues with the quality of the data and provenance of the trial.

The evidence for pyridoxine hydrochloride as a treatment for mild to moderate NVP showed mixed results, where larger studies showed no effect whilst smaller studies did show clinically important benefits of the drug over placebo in terms of symptom related outcomes. Although publication bias was not formally detected through the GRADE process, this is challenging when few published studies are available and the committee suspected some bias was present. The committee discussed that pyridoxine hydrochloride was commonly used as first line treatment in current practice.

The committee discussed that pyridoxine hydrochloride was commonly used as a combination treatment with a histamine H1 receptor antagonist like doxylamine succinate. Some evidence of low quality was identified that suggested a clinically important benefit of pyridoxine hydrochloride combined with doxylamine succinate vs placebo on the outcome of relief from nausea and vomiting. However, the committee noted that this evidence was published in the 1950s and as such might not be relevant to the population today and a more recent trial found no important benefit of the combination for overall relief. One RCT from the US, conducted in 1975 and reported in 2017 under the RIAT initiative, compared combined pyridoxine hydrochloride and doxylamine succinate against a placebo, pyridoxine hydrochloride alone, and doxylamine succinate alone. The evidence was of a very low quality and showed no clinically important benefit on any symptomatic outcomes. The committee also noted that this combination treatment is more expensive compared to other treatments. Overall, despite the fact that doxylamine succinate/pyridoxine hydrochloride is the only drug licensed for use in pregnancy for nausea & vomiting, the committee agreed the evidence did not justify specifically recommending its use.

There was no evidence assessing the efficacy of cyclizine as a monotherapy for treatment of mild to moderate NVP. The committee noted that this is commonly used in the UK as a first line pharmacological treatment, however the only evidence identified on cyclizine was in combination with pyridoxine hydrochloride, a combination that is not available in the UK.

The committee agreed that there are various pharmacological treatments used in current practice, all with different levels of evidence and varying advantages and disadvantages in terms of effectiveness, safety and practical aspects. The drugs may have side effects and safety profiles (not covered by this review). The committee used information available from the British National Formulary (BNF), the UK teratology information service monographs and patient information leaflets, and the manufacturers' summaries of product characteristics to inform about the potential side effects and potential effects on the baby. The committee recognised that women are concerned about the effects of medicines on the baby and how, in the unfortunate event of an adverse pregnancy outcome, women might associate it with medicine use, even when there is no evidence of harm. The committee discussed how it is important to discuss with women that there is always a background risk of congenital malformations, miscarriage and stillbirths irrespective of whether any medicines are taken during pregnancy. In order to support shared decision making about what pharmacological treatment to choose, a table listing the different pharmacological treatment option and their advantages and disadvantages were listed (see Table 1 in the guideline). The committee agreed that the shared decision making should take into consideration the woman's preferences, her experience with medicines in previous pregnancies, any co-morbidities, and any current medications.

Moderate to severe nausea and vomiting

The committee discussed that nausea and vomiting in pregnancy is a continuum with most cases presenting as mild to moderate and some as more severe. At the extreme severe end of the spectrum is hyperemesis gravidarum which is a rare and significant condition with potentially serious consequences, including decision to terminate the pregnancy. The committee agreed that the management of hyperemesis gravidarum does not only require consideration about the treatment of the nausea and vomiting itself but also the consequences of it, for example nutritional interventions and psychological management. The focus of this review was on interventions to treat nausea and vomiting in pregnancy and the committee considered the comprehensive management of hyperemesis gravidarum to be outside the scope of this guideline which covers routine antenatal care.

Generally, the committee concluded that for pregnant women with more severe nausea and vomiting, the same antiemetics should be offered as to those women with nausea and vomiting in the mild to moderate end of the continuum. The committee discussed that there is no clearly defined point at which severe nausea and vomiting becomes hyperemesis gravidarum and so the way the population is defined in studies can be unclear. For example, some studies investigating treatments for hyperemesis gravidarum clearly focus on hyperemesis gravidarum while others include a population with moderate to severe nausea and vomiting of pregnancy.

Outpatient care

The committee recommended that intravenous (IV) fluids should be considered as part of treatment for women with moderate to severe nausea and vomiting, ideally in outpatient care. One RCT from Ireland (2014) reported that pregnant women with severe nausea and vomiting who had received IV fluids in day care, spent fewer days in hospital for the treatment of nausea and vomiting than those women who had received IV fluids in inpatient care and that there were no clinically important differences for overall relief of symptoms or experience and satisfaction of care.

The committee decided to recommend offering IV fluids as outpatient care because there was no evidence showing inpatient care was superior for any outcomes and the economic data suggested no difference between the two outcomes in terms of QALYs.

The committee agreed that for this comparison, a woman's preferences in terms of setting of treatment was particularly important and that the decision should be made taking into account

the woman's preferences. The committee discussed that if vomiting is severe and cannot be managed without inpatient care, this should be considered.

Acupressure

The committee recommended that acupressure should be considered as an adjunct treatment of moderate to severe nausea and vomiting in pregnant women because there was evidence that acupressure in addition to standard care is effective in aiding symptomatic relief during pregnancy, compared to placebo.

One RCT from Malaysia (2017) reported that pregnant women with severe nausea and vomiting, who had received P6 acupressure in addition to standard care (IV fluids, IV metoclopramide and thiamine supplements) showed a clinically important difference on overall relief, nausea severity, and vomiting severity than those who had taken the placebo.

Two RCTs, one from Malaysia (2017) and one from the UK (2006) found that there was a clinically important and statistically significant difference, respectively, on number of days in hospital for women treated with P6 acupressure than those who had taken a placebo. The results show that women spend fewer days in hospital when given acupressure in addition to standard treatment than a placebo and standard treatment.

There was no evidence of a difference between the interventions on the outcomes of retching severity (PUQE score); number of women with disappearance of symptoms; women's experience and satisfaction of care; fetal death; and preterm birth.

Other interventions

Acupuncture

One RCT from Croatia (2004) reported a clinically important difference favouring P6 acupuncture over placebo for pregnant women on the number of women with relief from symptoms. However, since this was the only evidence found for this intervention and it was of a low quality, the committee did not recommend acupuncture for severe nausea and vomiting in pregnancy.

Pyridoxine hydrochloride

One RCT from Malaysia (2009) was found for this intervention, but no evidence of a difference between the interventions was found on overall wellbeing score; nausea intensity; daily mean vomiting episodes; number of women vomiting in the last 24 hours; adverse events; and fetal death. Since the evidence showed no benefits or no harms, the committee could not make a recommendation.

Dopamine D2 receptor antagonist

One RCT from Malaysia (2010) was found for this intervention, but no evidence of a difference between the interventions was found on nausea severity; vomiting frequency; number of days in hospital; and women's experience and satisfaction of care. Since the evidence showed no benefits or no harms, the committee could not make a recommendation.

Histamine H1 receptor antagonist

One RCT from US (1996) reported a clinically important difference on the adverse event sedation for women in the serotonin 5-HT antagonist arm over the women in the promethazine hydrochloride arm. The committee discussed that this was not an unusual adverse event of this pharmacological agent. Since there was no evidence of a difference between the interventions on the outcome of number of days in hospital, the committee concluded that there was no difference between promethazine hydrochloride and ondansetron and did not make a

recommendation. No recommendation was made on the use of promethazine hydrochloride as a treatment for severe nausea and vomiting in pregnant women.

Serotonin 5-HT receptor antagonist

Although two RCTs were found for this intervention among women with hyperemesis gravidarum from Iran (2013) and Malaysia (2014), there was no evidence of a difference between the interventions on the outcomes of number of women vomit free during 24 hours; vomiting severity; nausea severity; number of days in hospital; and women's experience and satisfaction of care.

Corticosteroids

Two RCTs comparing corticosteroids to a placebo were found for this intervention from the UK (2001) and US (2003). However, there was no evidence of a difference between the interventions on the outcomes of improvement in nausea intensity; vomiting frequency; reduction in vomiting intensity; number of days in hospital; fetal death; and preterm birth.

One RCT from Egypt (2006) comparing corticosteroids to a dopamine D2 receptor antagonist (metoclopramide hydrochloride) reported a clinically important difference favouring hydrocortisone over metoclopramide hydrochloride on the reduction in mean number of vomiting episodes. Though the evidence shows that hydrocortisone reduced the frequency of vomiting, these results come from a small study that is of low quality. Therefore, the committee could not make a recommendation based on this evidence.

One RCT from Iran (2004) comparing prednisolone to a histamine H1 receptor antagonist (promethazine hydrochloride) found that there was no clinically important difference between the number of patients with complete and partial relief although the result bordered on statistical significance. There was an important difference favouring corticosteroids in terms of abdominal pain, drowsiness and number of days in hospital however this evidence was of low to moderate quality principally due to the very low event rates. Within this comparison, there was no evidence of a difference between the interventions on the outcomes of number of women with severe nausea; vomiting frequency; number of women with improvement of symptoms.

Overall, there was not enough evidence of benefit of steroids when compared to a placebo, a histamine H1 receptor antagonist, or a dopamine D2 receptor antagonist for the committee to make a recommendation. The committee suggested a research recommendation was appropriate in this case. Although not found in the evidence, the committee discussed that steroids have well known harms and side effects that should be highlighted when used in the treatment of severe nausea and vomiting in pregnancy. The committee also pointed out that corticosteroids are commonly prescribed to women in cases of very severe nausea and vomiting in pregnancy.

Type of intravenous fluid

No recommendation was made on the type of intravenous fluid used for pregnant women with severe nausea and vomiting needing IV fluids.

Although one RCT was found for this intervention from Malaysia (2013), there was no evidence of a difference between the interventions on the outcomes of vomiting frequency; nausea intensity; and women's experience and satisfaction of care. Since the evidence showed no benefits or no harms, the committee could not make a recommendation.

Cost effectiveness and resource use

The recommendation made by the committee to recommend ginger as a non-pharmacological treatment reflects current practice. The committee refrained from specifying a dose or form of

ginger, but indicated from their professional experience that it would usually be suggested as a dietary supplement. Therefore, this would not lead to any additional costs to the NHS and, due to evidence of a lack of adverse effects, would be unlikely to have associated downstream treatment costs.

The committee considered evidence presented in the accompanying clinical review and recommended metoclopramide hydrochloride as a potential option following discussion as a pharmacological treatment for women. Current practice, according to the Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum Green-top guideline (Royal College of Obstetricians and Gynaecologists, 2016) is that cyclizine is usually administered as a treatment in tablet form. This was also current practice from the committee's own experience. There may be some additional costs owing to the increase in staff time where metoclopramide is administered as an injection. However, these additional costs are minimal and, owing to the increase in effectiveness, as presented in the clinical review, may be a cost effective use of resources. The committee recommended Ondansetron as a treatment, noting the one included study demonstrating its effectiveness. The committee were also mindful that administering Ondansetron can be costlier than other pharmacological interventions, though this would be dependent on the mode of birth. According to the BNF (2019), Ondansetron is only costlier when it is administered in the form of a solution for injection. Owing to the short duration of nausea and vomiting and that the majority of women would choose alternative recommended pharmacological treatments following discussion, it is unlikely that this recommendation would lead to a great increase in costs.

The recommendation to consider acupressure as a complementary therapy represents current practice and is usually administered as a self-administered therapy.

The committee also considered evidence presented in the clinical review of an Irish study that compared day care over inpatient management of nausea and vomiting during pregnancy (Murphy 2015). It was acknowledged that day care management was a cost effective option as it resulted in lower costs and a slight increase in QALYs. The committee acknowledged that the driver of cost effectiveness was the lower costs associated with day care management. Day care was associated a higher QALY gain although with uncertainty between the two interventions. At a cost per additional QALY threshold of €45,000 day care was 73% likely to be cost effective. Day care had a higher probability of cost effectiveness as the threshold decreased, thus furthering its relevance to the NICE decision making context.

Other factors the committee took into account.

The long term effects of treatments for nausea and vomiting in pregnancy and hyperemesis gravidarum on the child was an outcome the committee considered to be important, however, this outcome was outside the scope of the guideline and for information on the safety of any pharmacological interventions BNF/MHRA should be consulted.

References

Abas 2014

Abas, M. N., Tan, P. C., Azmi, N., Omar, S. Z., Ondansetron compared with metoclopramide for hyperemesis gravidarum: a randomized controlled trial, Obstetrics & Gynecology, 123, 1272-9, 2014

Adlan 2017

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

Basirat 2009

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

Belluomini 1994

Belluomini, J., Litt, R. C., Lee, K. A., Katz, M., Acupressure for nausea and vomiting of pregnancy: a randomized, blinded study, Obstetrics and gynecology, 84, 245-8, 1994

Bondok 2006

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

Bsat 2003

Bsat, F. A., Hoffman, D. E., Seubert, D. E., Comparison of three outpatient regimens in the management of nausea and vomiting in pregnancy, Journal of Perinatology, 23, 531-5, 2003

Galeshi 2020

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

Geiger 1959

Geiger, C. J., Fahrenbach, D. M., Healey, F. J., Bendectin in the treatment of nausea and vomiting in pregnancy, Obstetrics and gynecology, 14, 688-90, 1959

Ghlue 2020

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

Habek 2004

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, Research in complementary and natural classical medicine, 11, 20-3, 2004

Heazell 2006

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

Kashifard 2013

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 Obstetrics & Gynecology, 40, 127-30, 2013

Keating 2002

Keating, A., Chez, R. A., Ginger syrup as an antiemetic in early pregnancy, Alternative therapies in health and medicine, 8, 89-91, 2002

Knight 2001

Knight, B., Mudge, C., Openshaw, S., White, A., Hart, A., Effect of acupuncture on nausea of pregnancy: a randomized, controlled trial, Obstetrics and gynecology, 97, 184-8, 2001

Koren 2010

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

Koren 2015

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

McCarthy 2014

McCarthy, F. P., Murphy, A., Khashan, A. S., McElroy, B., Spillane, N., Marchocki, Z., Sarkar, R., Higgins, J. R., Day care compared with inpatient management of nausea and vomiting of pregnancy: A randomized controlled trial, Obstetrics and gynecology, 124, 743-748, 2014

McParlin 2016

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

Mobarakabadi 2019

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

Mohammadbeigi 2011

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

Monias 1957

Monias, M., Evaluation of cyclizine with pyridoxine in vomiting of pregnancy, Military medicine, 121, 403-4, 1957

Nelson-Piercy 2001

Nelson-Piercy, C., Fayers, P., de Swiet, M., Randomised, double-blind, placebo-controlled trial of corticosteroids for the treatment of hyperemesis gravidarum, BJOG: an international journal of obstetrics and gynaecology, 108, 9-15, 2001

Oliveira 2014

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

Ozgoli 2009

Ozgoli, G., Goli, M., Simbar, M., Effects of ginger capsules on pregnancy, nausea, and vomiting, Journal of Alternative and Complementary Medicine, 15, 243-246, 2009

Puangsricharern 2008

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

Rad 2012

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

Saberi 2013

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

Saberi 2014

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 Studies, 3, e11841, 2014

Safari 1998

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, American Journal of Obstetrics and Gynecology, 179, 921-4, 1998

Sahakian 1991

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, Obstetrics and gynecology, 78, 33-6, 1991

Sharifzadeh 2018

Sharifzadeh, F., Kashanian, M., Koohpayehzadeh, J., Rezaian, F., Sheikhansari, N., Eshraghi, N., A 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

Smith 2002

Smith, C., Crowther, C., Beilby, J., Acupuncture to treat nausea and vomiting in early pregnancy: a randomized controlled trial, Birth (Berkeley, California), 29, 1-9, 2002

Sullivan 1996

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, American Journal of Obstetrics & Gynecology, 174, 1565-8, 1996

Tan 2010

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

Tan 2013

Tan, P. C., Norazilah, M. J., Omar, S. Z., Dextrose saline compared with normal saline rehydration of hyperemesis gravidarum: a randomized controlled trial, Obstetrics & Gynecology, 121, 291-8, 2013

Tan 2009

Tan, P. C., Yow, C. M., Omar, S. Z., A placebo-controlled trial of oral pyridoxine in hyperemesis gravidarum, Gynecologic & Obstetric Investigation, 67, 151-7, 2009

Vutyavanich 2001

Vutyavanich, T., Kraisarin, T., Ruangsri, R., Ginger for nausea and vomiting in pregnancy: randomized, double-masked, placebo-controlled trial, Obstetrics and gynecology, 97, 577-82, 2001

Vutyavanich 1995

Vutyavanich, T., Wongtrangan, S., Ruangsri, R., Pyridoxine for nausea and vomiting of pregnancy: a randomized, double-blind, placebo-controlled trial, American Journal of Obstetrics and Gynecology, 173, 881-4, 1995

Werntoft 2001

Werntoft, E., Dykes, A. K., Effect of acupressure on nausea and vomiting during pregnancy. A randomized, placebo-controlled, pilot study, The Journal of reproductive medicine, 46, 835-9, 2001

Willetts 2003

Willetts, K. E., Ekangaki, A., Eden, J. A., Effect of a ginger extract on pregnancy-induced nausea: A randomised controlled trial, Australian and New Zealand Journal of Obstetrics and Gynaecology, 43, 139-144, 2003

Yost 2003

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, Obstetrics and gynecology, 102, 1250-4, 2003

Zhang 2017

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

Ziaei 2004

Ziaei, S., Hosseiney, F. S., Faghihzadeh, S., The efficacy low dose of prednisolone in the treatment of hyperemesis gravidarum, Acta Obstetricia Gynecologica Scandinavica, 83, 272-5, 2004

Appendices

Appendix A – Review protocols

Review protocol for review question: What interventions are effective in treating nausea and vomiting during pregnancy?

Table 4: Review protocol

Field (based on PRISMA-P)	Content
Review question	What interventions are effective in treating nausea and vomiting during pregnancy? Note: the safety of pharmacological interventions to treat nausea and vomiting during pregnancy will not be covered in this review. For information on the safety of any pharmacological interventions, please consult the BNF/MHRA.
Type of review question	Intervention
Objective of the review	The aim of this review is to evaluate the pregnancy outcomes of different treatment interventions for nausea and vomiting during pregnancy and to establish whether there are any harms for the women or baby associated with them.
Eligibility criteria – population	Pregnant woman with nausea, vomiting and/or retching of any degree (including hyperemesis gravidarum). Note: Women with hyperemesis gravidarum will be analysed separately from those with mild or moderate nausea and vomiting.

Eligibility criteria – intervention(s)	Only the following listed interventions will be considered in this review:
	
	Mild and moderate nausea and vomiting
	Complementary therapies
	• Acupressure
	• Acupuncture
	
	Dietary supplements
	• Ginger
	
	Pharmacological interventions
	• Dopamine (D_2) receptor antagonists
	  ○ Domperidone
	  ○ Metoclopramide hydrochloride
	  ○ Prochlorperazine
	• Histamine H1-receptor antagonist
	  ○ Cyclizine hydrochloride
	  ○ Doxylamine succinate

Field (based on PRISMA-P)	Content
	○ Promethazine hydrochloride • Pyridoxine hydrochloride (Vitamin B_6) • Serotonin (5-HT) antagonists ○ Ondansetron **Severe nausea and vomiting (hyperemesis gravidarum)** Note: there is no standard definition of hyperemesis gravidarum but it generally includes intractable nausea/vomiting, signs of dehydration (for example ketonuria), high urine specific gravity, electrolyte imbalances, and weight loss of at least 5% of pre-pregnancy weight, excluding other diagnoses. See RCOG definition for more information. All interventions listed for mild and moderate nausea and vomiting above will be considered, plus the following: **Non-pharmacological interventions** • Intravenous fluids **Pharmacological interventions** • Any corticosteroid
Eligibility criteria – comparator(s)	**Mild and moderate nausea and vomiting** • Complementary therapy vs placebo (placebo pill, dietary advice, sham treatment [for example sham acupuncture] or no treatment) • Dietary supplement vs placebo • Complementary therapy vs dietary supplement • Complementary therapy + dietary supplement vs complementary therapy • Complementary therapy + dietary supplement vs dietary supplement • Pharmacological intervention (including combination of listed pharmacological interventions) vs placebo • Pharmacological intervention vs another pharmacological intervention (including combination of listed pharmacological therapies) **Hyperemesis gravidarum only** Note: all comparisons for mild and moderate nausea and vomiting will be considered plus the following: • Corticosteroid vs placebo • Corticosteroid vs pharmacological intervention listed for mild and moderate nausea and vomiting • Corticosteroid + pharmacological intervention listed for mild and moderate nausea and vomiting + vs pharmacological intervention listed for mild and moderate nausea and vomiting only • Intravenous fluids vs no intravenous fluids • Intravenous fluids in one setting (for example home) vs intravenous fluids in another setting (for example hospital) Note: for pharmacological interventions, both inter-class (for example histamine H1 receptor anatagonist vs serotonin 5-HT antagonist) and intra-class comparisons (for example doxylamine succinate vs cyclizie hydrochloride) will be considered.
Outcomes and prioritisation	**Critical Outcomes** • Symptomatic relief during pregnancy • Fetal death (at any stage of pregnancy, including miscarriage, still birth and termination of pregnancy) • Infant death up to 4 weeks chronological age

Field (based on PRISMA-P)	Content
	Important Outcomes • Adverse event that is not immediately due to nausea and vomiting and which requires hospitalisation during treatment • Number of days in hospital for treatment of nausea and vomiting • Women's experience and satisfaction of care during or at end of pregnancy • Pre-term birth (birth before 37^{+0} weeks) • Small for gestational age (SGA) Note: SGA is defined as having a birth weight below the 10th centile. Some studies will report this as Low Birth Weight (LBW) adjusted for Gestational Age (GA) rather than as SGA.
Eligibility criteria – study design	INCLUDE: • Systematic reviews • Randomised or quasi-randomised controlled trials If no evidence of these types is found for a listed class of intervention, the following non-randomised studies in order of priority will be considered: • Non-randomised controlled trials • Prospective cohort studies • Retrospective cohort studies Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
Other inclusion exclusion criteria	**Exclusion** POPULATION: • Multiple pregnancy • Pregnancy with known or pre-existing congenital anomalies STUDY DESIGN: • Case-control studies • Cross-over studies • Cross-sectional studies • Epidemiological reviews or reviews on associations • Non-comparative studies LANGUAGE: • Non-English PUBLICATION STATUS: • Conference abstract **Inclusion** COUNTRY: • No restriction

Field (based on PRISMA-P)	Content
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroup analysis according to World Bank status (High-income countries; Low- and middle-income countries) will be conducted (see https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups for classification of countries**)**. Note that the use of the World Bank definitions of low-, middle- and high-income countries in this guideline is consistent with its use in the Postnatal care up to 8 weeks after birth (update) NICE guideline CG37. In the presence of heterogeneity, the following sub-group analysis will also be conducted: • Parity status (nulliparous; primiparous; multiparous) This subgroup factor will be used as a confounding factor to assess risk of bias of any included cohort studies using the relevant checklist. Other confounding factors that will be considered in the risk of bias evaluation when including cohort studies are: • Age • BMI or body weight of woman • Smoking/Alcohol/substance misuse during pregnancy Statistical heterogeneity will be assessed by visually examining the forest plots and by calculating the I^2 inconsistency statistic (with an I^2 value≥50% indicating serious heterogeneity, and ≥80% indicating very serious heterogeneity).
Selection process – duplicate screening/selection/analysis	Studies included in the 2008 NICE guideline on antenatal care for uncomplicated pregnancies (CG62) that satisfy the review protocol will be included in this review. Review questions selected as high priorities for health economic analysis (and those selected as medium priorities and where health economic analysis could influence recommendations) will be subject to dual weeding and study selection; any discrepancies above 10% of the dual weeded resources will be resolved through discussion between the first and second reviewers or by reference to a third person. All data extraction will quality assured by a senior reviewer. Draft excluded studies and evidence tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.
Data management (software)	NGA STAR software will be used to generate bibliographies/citations, and perform conduct sifting and data extraction. Pairwise meta-analyses, if possible, will be conducted using Cochrane Review Manager (RevMan5). For details please see Supplement 1: methods. 'GRADEpro' will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (for example date, study design): • Date limit: 2006 (date of last search for CG 62). • Apply standard animal/non-English language exclusion • Limit to RCTs and systematic reviews in first instance but download all results.
Identify if an update	This antenatal care update will replace the 2008 NICE guideline on antenatal care for uncomplicated pregnancies (CG62) which will be taken down in due course. The following relevant recommendations in the 2008 NICE guideline on antenatal care for uncomplicated pregnancies (CG62) on treatment of nausea and vomiting were made: 1.4.1.1 Women should be informed that most cases of nausea and vomiting in pregnancy will resolve spontaneously within 16 to 20 weeks and that nausea and vomiting are not usually associated with a poor pregnancy outcome. If a woman requests or would like to consider treatment, the following interventions appear to be effective in reducing symptoms: non-pharmacological: ginger P6 (wrist) acupressure pharmacological: antihistamines. 1.4.1.2 Information about all forms of self-help and non-pharmacological treatments should be made available for pregnant women who have nausea and vomiting.
Author contacts	Developer: National Guideline Alliance.

Field (based on PRISMA-P)	Content
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix F.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix G (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix G (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs or quasi-RCTs • Cochrane ROBINS-I for non-randomised (clinical) controlled trials and cohort studies For details please see section 6.2 of Developing NICE guidelines: the manual. The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for analysis – combining studies and exploring (in)consistency	For details please see Supplement 1: methods.
Meta-bias assessment – publication bias, selective reporting bias	For details please see Supplement 1: methods and section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots. Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Kate Harding in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplement 1: methods.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.
PROSPERO registration number	This protocol is not registered with PROSPERO.

Appendix B – Literature search strategies

Literature search strategies for review question: What interventions are effective in treating nausea and vomiting during pregnancy?

Database(s): Medline & Embase (Multifile)
Last searched on **Embase Classic+Embase** 1947 to 2020 September 03, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to September 03, 2020
Date of last search: 4th September 2020
Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Pregnancy/ use ppez
2	Pregnant Women/ use ppez
3	pregnancy/ use emczd
4	pregnant woman/ use emczd
5	pregnan$.tw,kw.
6	1 or 2 or 3 or 4 or 5
7	exp Morning Sickness/ use ppez
8	morning sickness/ use emczd
9	hyperemesis gravidarum/ use emczd
10	retching/ use emczd
11	(morning adj sickness$).tw,kw.
12	((hyperemesis$ or hyperemisis$ or emesis$ or emisis$) adj gravid$).tw,kw.
13	retch$.tw,kw.
14	7 or 8 or 9 or 10 or 11 or 12 or 13
15	Nausea/ use ppez
16	Vomiting/ use ppez
17	15 and 16
18	nausea/ use emczd
19	vomiting/ use emczd
20	18 and 19
21	"nausea and vomiting"/ use emczd
22	(nause$ adj5 vomit$).tw,kw.
23	17 or 20 or 21 or 22
24	6 and 14
25	6 and 23
26	24 or 25
27	((nause$ or vomit$) adj3 pregnan$).tw,kw.
28	26 or 27
29	(antiemetic$ or antipyretic$).tw,kw.
30	6 and 29
31	28 or 30
32	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
33	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
34	meta-analysis/
35	meta-analysis as topic/
36	systematic review/
37	meta-analysis/
38	(meta analy* or metanaly* or metaanaly*).ti,ab.
39	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
40	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
41	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
42	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
43	(search* adj4 literature).ab.
44	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
45	cochrane.jw.
46	((pool* or combined) adj2 (data or trials or studies or results)).ab.

#	Searches
47	letter/
48	editorial/
49	news/
50	exp historical article/
51	Anecdotes as Topic/
52	comment/
53	case report/
54	(letter or comment*).ti.
55	47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56	randomized controlled trial/ or random*.ti,ab.
57	55 not 56
58	animals/ not humans/
59	exp Animals, Laboratory/
60	exp Animal Experimentation/
61	exp Models, Animal/
62	exp Rodentia/
63	(rat or rats or mouse or mice).ti.
64	57 or 58 or 59 or 60 or 61 or 62 or 63
65	letter.pt. or letter/
66	note.pt.
67	editorial.pt.
68	case report/ or case study/
69	(letter or comment*).ti.
70	65 or 66 or 67 or 68 or 69
71	randomized controlled trial/ or random*.ti,ab.
72	70 not 71
73	animal/ not human/
74	nonhuman/
75	exp Animal Experiment/
76	exp Experimental Animal/
77	animal model/
78	exp Rodent/
79	(rat or rats or mouse or mice).ti.
80	72 or 73 or 74 or 75 or 76 or 77 or 78 or 79
81	64 use ppez
82	80 use emczd
83	81 or 82
84	32 use ppez
85	33 use emczd
86	84 or 85
87	(or/34-35,38,40-45) use ppez
88	(or/36-39,41-46) use emczd
89	87 or 88
90	31 and 83
91	31 not 90
92	limit 91 to english language
93	limit 92 to yr="2006 -Current"
94	86 or 89
95	93 and 94 [RCT/SR data]
96	93 not 95 [Non-RCT/SR data]

Database(s): Cochrane Library
Last searched on **Cochrane Database of Systematic Reviews**, Issue 9 of 12, September 2020, **Cochrane Central Register of Controlled Trials**, Issue 9 of 12, September 2020
Date of last search: 4th September 2020

#	Searches
#1	MeSH descriptor: [Pregnancy] this term only
#2	MeSH descriptor: [Pregnant Women] this term only
#3	(pregnan*):ti,ab,kw
#4	#1 OR #2 OR #3
#5	MeSH descriptor: [Morning Sickness] explode all trees
#6	((morning NEXT sickness*)):ti,ab,kw
#7	(((hyperemesis* or hyperemisis* or emesis* or emisis*) NEXT gravid*)):ti,ab,kw
#8	(retch*):ti,ab,kw
#9	#5 OR #6 OR #7 OR #8

#	Searches
#10	MeSH descriptor: [Nausea] this term only
#11	MeSH descriptor: [Vomiting] this term only
#12	#10 AND #11
#13	((nause* NEAR/5 vomit*)):ti,ab,kw
#14	#12 OR #13
#15	#4 AND #9
#16	#4 AND #14
#17	#15 OR #16 Publication Year from 2006 to current

Database(s): CRD: Database of Abstracts of Reviews of Effects (DARE), HTA Database
Date of last search: 4th September 2020

#	Searches
1	MeSH DESCRIPTOR Pregnancy EXPLODE ALL TREES IN DARE,HTA
2	MeSH DESCRIPTOR Pregnant Women EXPLODE ALL TREES IN DARE,HTA
3	((pregnan*)) IN DARE, HTA
4	#1 OR #2 OR #3
5	MeSH DESCRIPTOR Morning Sickness EXPLODE ALL TREES IN DARE,HTA
6	(morning sickness*) IN DARE, HTA
7	((((hyperemesis* or hyperemisis* or emesis* or emisis*) NEAR gravid*))) IN DARE, HTA
8	((retch*)) IN DARE, HTA
9	#5 OR #6 OR #7 OR #8
10	MeSH DESCRIPTOR Nausea EXPLODE ALL TREES IN DARE,HTA
11	MeSH DESCRIPTOR Vomiting EXPLODE ALL TREES IN DARE,HTA
12	#10 AND #11
13	(((nause* NEAR vomit*))) IN DARE, HTA
14	#12 OR #13
15	#4 AND #9
16	#4 AND #14
17	#15 OR #16 Publication Year from 2006 to current

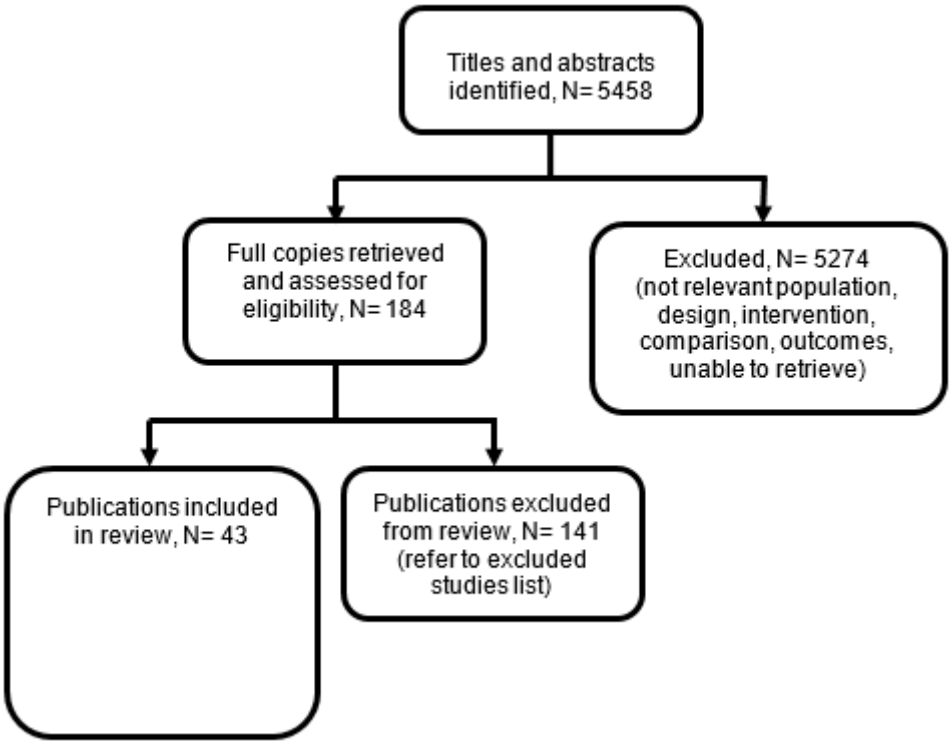
Database(s): Cinahl Plus
Date of last search: 4th September 2020

#	Searches
S15	S13 OR S14 Limiters - Publication Year: 2006-2020; English Language;
S14	TI ((nause* or vomit*) N3 pregnan*) OR AB ((nause* or vomit*) N3 pregnan*)
S13	S4 AND S12
S12	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S11	TI (antiemetic* or antipyretic*) OR AB (antiemetic* or antipyretic*)
S10	TI (nause* N5 vomit*) OR AB (nause* N5 vomit*)
S9	(MH "Nausea and Vomiting")
S8	TI retch* OR AB retch*
S7	TI ((hyperemesis* or hyperemisis* or emesis* or emisis*) N1 gravid*) OR AB ((hyperemesis* or hyperemisis* or emesis* or emisis*) N1 gravid*)
S6	TI (morning N1 sickness*) OR AB (morning N1 sickness*)
S5	(MH "Hyperemesis Gravidarum")
S4	S1 OR S2 OR S3
S3	TI pregnan* or AB pregnan*
S2	(MH "Expectant Mothers")
S1	(MH "Pregnancy")

Appendix C – Clinical evidence study selection

Study selection for: What interventions are effective in treating nausea and vomiting during pregnancy?

Figure 1: Study selection flow chart:



Appendix D – Clinical evidence tables

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)	

Appendix E – Forest plots

Forest plots for review question: What interventions are effective in treating nausea and vomiting during pregnancy?

This section includes Forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Mild to moderate nausea and vomiting

Ginger versus placebo for pregnant women with mild to moderate nausea and vomiting

Figure 2: Symptomatic relief during pregnancy - Overall relief (Total Rhodes Index score)

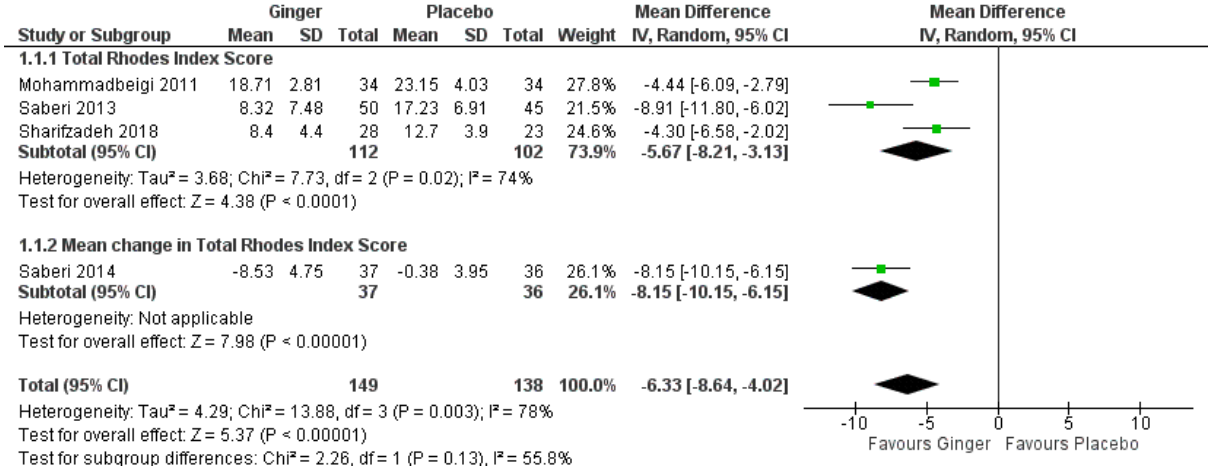


Figure 3: Symptomatic relief during pregnancy – Nausea relief (Rhodes Index score)

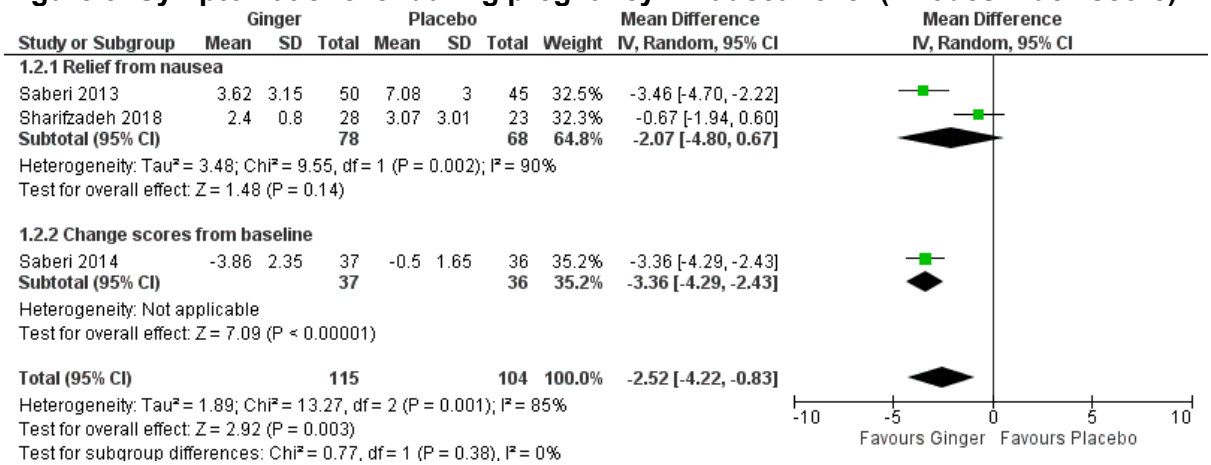


Figure 4: Symptomatic relief during pregnancy - Nausea intensity (Rhodes Index score)

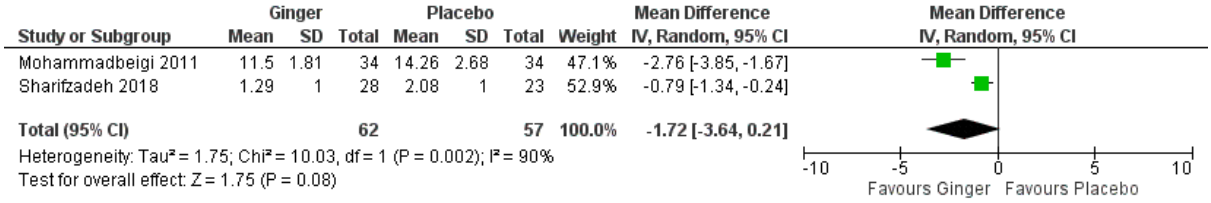


Figure 5: Symptomatic relief during pregnancy - Nausea intensity (VAS score)

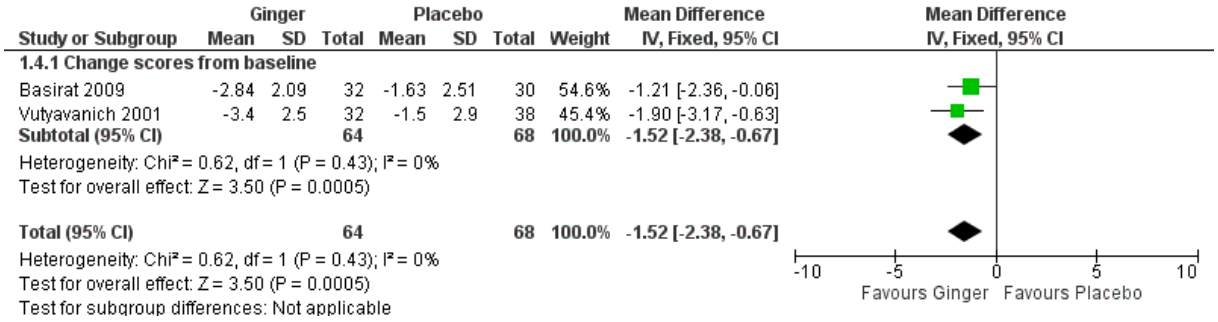


Figure 6: Symptomatic relief during pregnancy – Vomiting relief (Rhodes Index score)

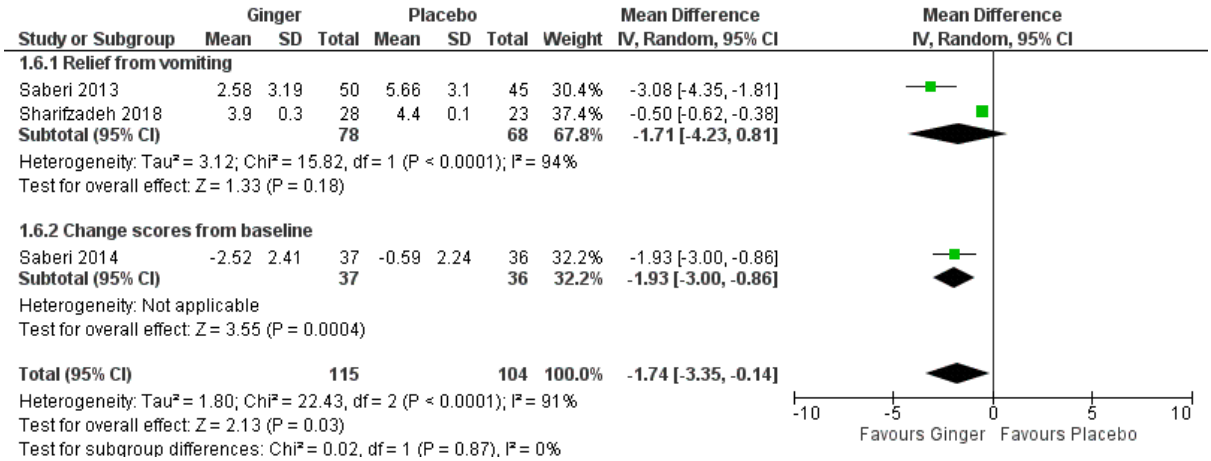


Figure 7: Symptomatic relief during pregnancy - Vomiting intensity (Rhodes Index score)

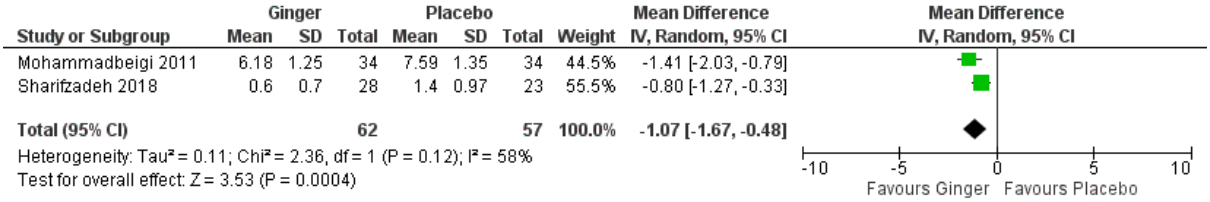


Figure 8: Symptomatic relief during pregnancy - Vomiting frequency in the last 24 hours (Patient reported)

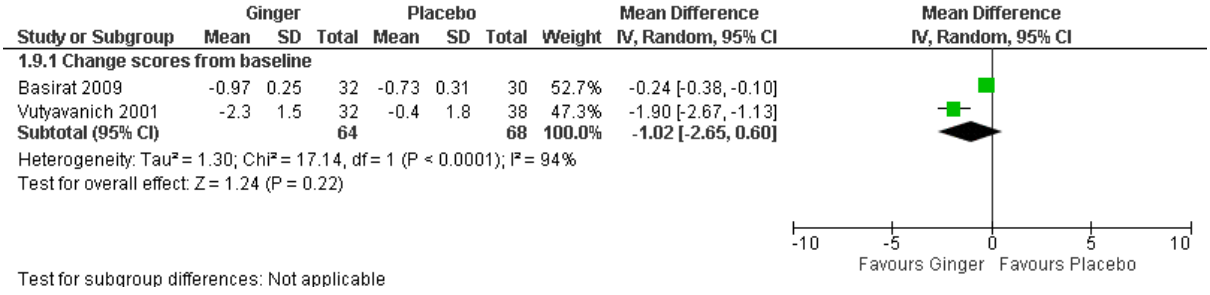


Figure 9: Symptomatic relief during pregnancy – Retching relief (Rhodes Index score)

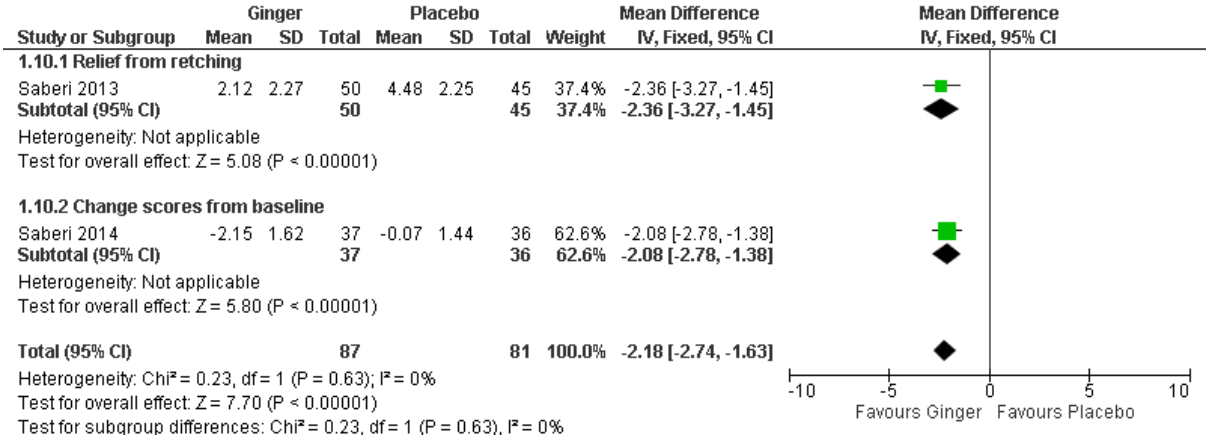


Figure 10: Adverse events requiring hospitalisation

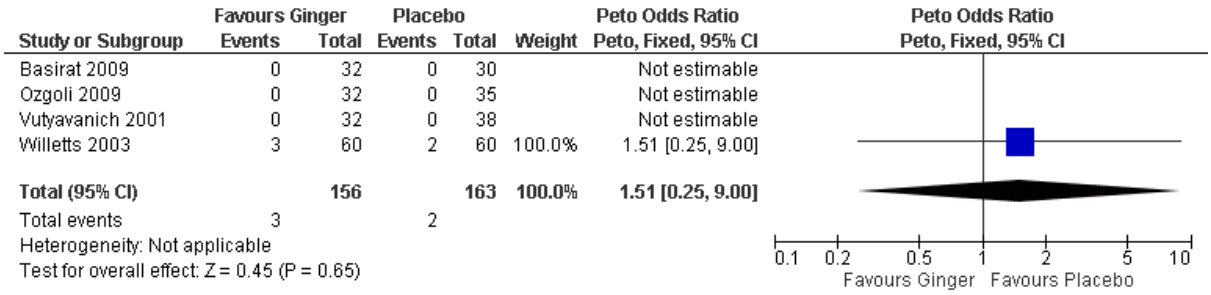
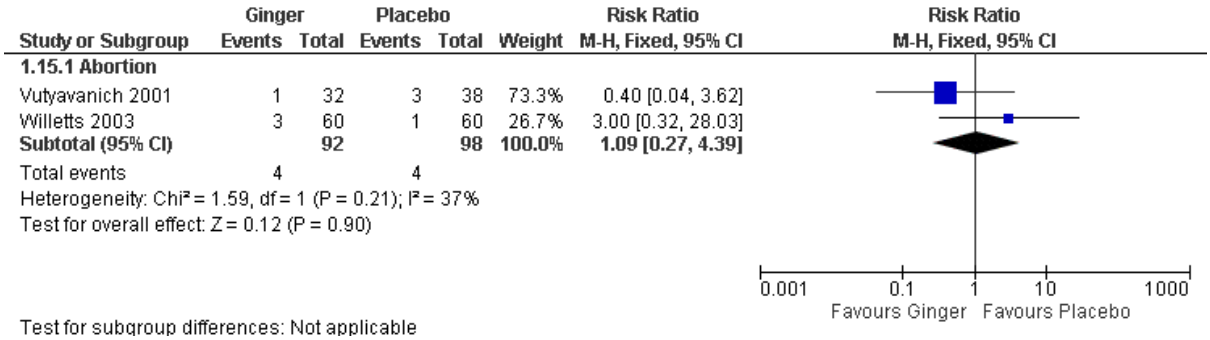


Figure 11: Fetal death

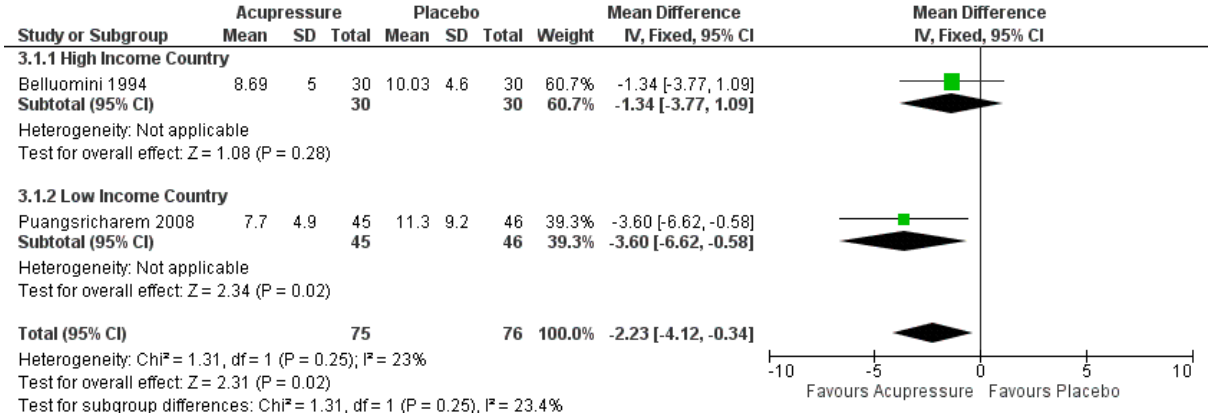


Acupressure versus acupressure for pregnant women with mild to moderate nausea and vomiting

There are no forest plots for this comparison because no meta-analysis was performed.

Acupressure versus placebo for pregnant women with mild to moderate nausea and vomiting

Figure 12: Symptomatic relief during pregnancy – Overall relief (Total Rhodes Index score)



Acupressure versus control for pregnant women with mild to moderate nausea and vomiting

There are no forest plots for this comparison because no meta-analysis was performed.

Acupressure versus ginger for pregnant women with mild to moderate nausea and vomiting

There are no forest plots for this comparison because no meta-analysis was performed.

Acupuncture versus placebo for pregnant women with mild to moderate nausea and vomiting

There are no forest plots for this comparison because no meta-analysis was performed.

Dopamine D2-receptor antagonists versus placebo for pregnant women with mild to moderate nausea and vomiting

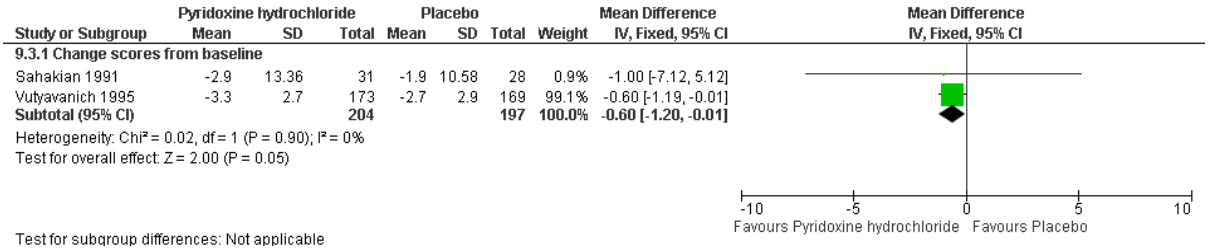
There are no forest plots for this comparison because no meta-analysis was performed.

Histamine H1-recepter antagonist versus placebo for pregnant women with mild to moderate nausea and vomiting

There are no forest plots for this comparison because no meta-analysis was performed.

Pyridoxine hydrochloride versus placebo for pregnant women with mild to moderate nausea and vomiting

Figure 13: Symptomatic relief during pregnancy - Nausea intensity (VAS score)



Pyridoxine hydrochloride versus histamine H1-recepter antagonist for pregnant women with mild to moderate nausea and vomiting

There are no forest plots for this comparison because no meta-analysis was performed.

Pyridoxine hydrochloride + dopamine D2-receptor antagonist versus histamine H1-receptor antagonist for pregnant women with mild to moderate nausea and vomiting

There are no forest plots for this comparison because no meta-analysis was performed.

Pyridoxine hydrochloride + histamine H1-receptor antagonist versus placebo for pregnant women with mild to moderate nausea and vomiting

Figure 14: Symptomatic relief during pregnancy – Relief from nausea and vomiting (Patient reported)

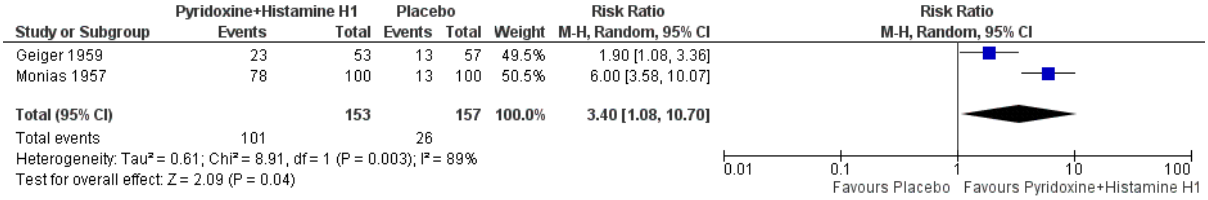
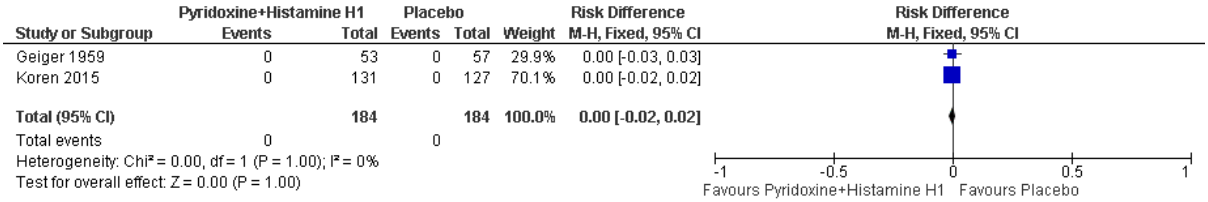


Figure 15: Adverse event requiring hospitalisation



Pyridoxine hydrochloride + histamine H1-receptor antagonist vs pyridoxine hydrochloride for pregnant women with mild to moderate nausea and vomiting

There are no forest plots for this comparison because no meta-analysis was performed.

Pyridoxine hydrochloride + histamine H1-receptor antagonist vs histamine H1-receptor antagonist for pregnant women with mild to moderate nausea and vomiting

There are no forest plots for this comparison because no meta-analysis was performed.

Serotonin 5-HT antagonist + placebo versus pyridoxine hydrochloride + histamine H1-receptor antagonist for pregnant women with mild to moderate nausea and vomiting

There are no forest plots for this comparison because no meta-analysis was performed.

Hyperemesis gravidarum

Acupressure vs placebo for pregnant women with hyperemesis gravidarum

There are no forest plots for this comparison because no meta-analysis was performed.

Acupuncture vs placebo for pregnant women with hyperemesis gravidarum

There are no forest plots for this comparison because no meta-analysis was performed.

Pyridoxine hydrochloride vs placebo for pregnant women with hyperemesis gravidarum

There are no forest plots for this comparison because no meta-analysis was performed.

Dopamine D2 receptor antagonist vs histamine H1-receptor antagonist for pregnant women with hyperemesis gravidarum

There are no forest plots for this comparison because no meta-analysis was performed.

Serotonin 5-HT antagonist vs dopamine D2 receptor antagonist for pregnant women with hyperemesis gravidarum

There are no forest plots for this comparison because no meta-analysis was performed.

Serotonin 5-HT antagonist vs histamine H1-receptor antagonist for pregnant women with hyperemesis gravidarum

There are no forest plots for this comparison because no meta-analysis was performed.

Corticosteroid vs placebo for pregnant women with hyperemesis gravidarum

Figure 16: Fetal death

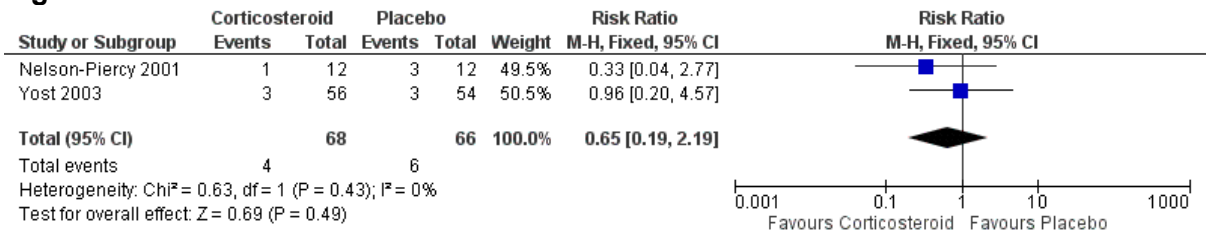


Figure 17: Pre-term birth (before 37 weeks)

Corticosteroid vs dopamine D2 receptor antagonist for pregnant women with hyperemesis gravidarum

There are no forest plots for this comparison because no meta-analysis was performed.

Corticosteroid vs histamine H1-receptor antagonist for pregnant women with hyperemesis gravidarum

There are no forest plots for this comparison because no meta-analysis was performed.

Intravenous fluids vs intravenous fluids for pregnant women with hyperemesis gravidarum

There are no forest plots for this comparison because no meta-analysis was performed.

Intravenous fluids in one setting vs intravenous fluids in another setting for pregnant women with hyperemesis gravidarum

There are no forest plots for this comparison because no meta-analysis was performed.

Appendix F – GRADE tables

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

Mild to moderate nausea and vomiting

Table 7: Clinical evidence profile for ginger versus placebo for treating mild to moderate nausea and vomiting

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ginger	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Overall relief (Total Rhodes Index score) (follow-up 0-7 days; measured with: Total or change score on Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
4‡	randomised trials	serious[1]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	none	149	138	-	MD 6.33 lower (8.64 to 4.02 lower)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Nausea relief (Rhodes Index score) (follow-up 0-7 days; measured with: Total or change score on Rhodes Index of Nausea and Vomiting Form 2 ; range of scores: 0-32; Better indicated by lower values)												
3‡	randomised trials	serious[3]	very serious[4]	no serious indirectness	no serious imprecision	none	115	104	-	MD 2.52 lower (4.22 to 0.83 lower)	⊕OOO VERY LOW	CRITICAL
Symptomatic relief during pregnancy - Nausea intensity (Rhodes Index score) (measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
2‡	randomised trials	serious[5]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	none	62	57	-	MD 1.72 lower (3.64 lower to 0.21 higher)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Nausea intensity (VAS score) (follow-up 7 days; measured with: Total or change score on Visual Analogue Score Scale ; range of scores: 0-10; Better indicated by lower values)												
2‡	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6,7]	none	64	68	-	MD 1.52 lower (2.38 to 0.67 lower)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Nausea frequency (Rhodes Index score) (measured with: Rhodes Index of Nausea and Vomiting Form 2; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ginger	Placebo	Relative (95% CI)	Absolute		
1 (Sharifzadeh 2018)	randomised trials	serious	no serious inconsistency	no serious indirectness	serious[6,7]	none	28	23	-	MD 0.57 lower (1.08 to 0.06 lower)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Vomiting relief (Rhodes Index score) (follow-up median 0-7 days; measured with: Total or change score on Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
3‡	randomised trials	serious[3]	no serious inconsistency[2]	no serious indirectness	serious[6,7]	reporting bias[8]	115	104	-	MD 1.74 lower (3.35 to 0.14 lower)	⊕OOO VERY LOW	CRITICAL
Symptomatic relief during pregnancy - Vomiting intensity (Rhodes Index score) (measured with: Rhodes Index of Nausea and Vomiting Form 2 ; range of scores: 0-32; Better indicated by lower values)												
2‡	randomised trials	serious[5]	no serious inconsistency[9]	no serious indirectness	serious[6,7]	none	62	57	-	MD 1.07 lower (1.67 to 0.48 lower)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Vomiting frequency (Rhodes Index score) (measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Sharifzadeh 2018)	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[6,7]	none	28	23	-	MD 0.9 lower (1.32 to 0.48 lower)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Vomiting frequency in the last 24 hours (Patient reported) (follow-up 7 days; measured with: Total or change scores of patient reports; Better indicated by lower values)												
2‡	randomised trials	no serious risk of bias	very serious[4]	no serious indirectness	very serious[7,11]	none	64	68	-	MD 1.02 lower (2.65 lower to 0.6 higher)	⊕OOO VERY LOW	CRITICAL
Symptomatic relief during pregnancy - Retching relief (Rhodes Index score) (measured with: Total or change scores on Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
2‡	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6,7]	none	87	81	-	MD 2.18 lower (2.74 to 1.63 lower)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Retching frequency (Rhodes Index score) (measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Sharifzadeh 2018)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6,7]	none	28	23	-	MD 0.40 lower (1 lower to 0.2 higher)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ginger	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - No improvement in nausea intensity (assessed with: VAS score)												
1 (Ozgoli 2009)	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	very serious[13]	none	3/32 (9.4%)	7/35 (20%)	RR 0.47 (0.13 to 1.66)	106 fewer per 1000 (from 174 fewer to 132 more)	⊕OOO VERY LOW	CRITICAL
Symptomatic relief during pregnancy - No or little improvement on nausea intensity scale - 2-point or less improvement (day 9 and 14)												
1 (Keating 2002)	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	serious[15]	none	0/13 (0%)	7/10 (70%)	Peto OR 0.04 (0.01 to 0.24)	672 fewer per 1000 (from 532 fewer to 693 fewer)	⊕⊕OO LOW	CRITICAL
Fetal death - Abortion (follow-up 0-7 days)												
2‡	randomised trials	serious[16]	no serious inconsistency	no serious indirectness	very serious[13]	none	4/92 (4.3%)	4/98 (4.1%)	RR 1.09 (0.27 to 4.39)	4 more per 1000 (from 30 fewer to 138 more)	⊕OOO VERY LOW	CRITICAL
Adverse events requiring hospitalisation (follow-up 0-7 days)												
4‡	randomised trials	serious[16]	no serious inconsistency	no serious indirectness	very serious[13]	none	3/156 (1.9%)	2/163 (1.2%)	Peto OR 1.51 (0.25 to 9)	6 more per 1000 (from 9 fewer to 98 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events requiring hospitalisation - High Income Country												
1 (Willets 2003)	randomised trials	serious[16]	no serious inconsistency	no serious indirectness	very serious[13]	none	3/60 (5%)	2/60 (3.3%)	RR 1.50 (0.26 to 8.66)	17 more per 1000 (from 25 fewer to 255 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events requiring hospitalisation - Low Income Country												
3‡	randomised trials	serious[16]	no serious inconsistency	no serious indirectness	very serious[17]	none	0/96 (0%)	0/103 (0%)	Not estimable	-	⊕OOO VERY LOW	IMPORTANT

Abbreviations: CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio; VAS: Visual analogue scale

[1] Downgraded by 1 level due to unclear risk of bias regarding allocation concealment (insufficient detail for all 4 studies) and blinding of participants in Mohammadbeigi 2011 and Saberi 2014.

[2] Although there was high heterogeneity (i2=/>75%) all results favoured ginger and the evidence was therefore not downgraded.

[3] Downgraded by 1 level due to unclear risk of selection bias in all studies, and high risk of performance and attrition bias.

[4] Downgraded by 2 levels due to very serious heterogeneity (i2=/>80%).

[5] Downgraded by 1 level due to unclear risk of selection bias in all studies, and high risk of attrition bias in Sharifzadeh 2018.

[6] *Evidence downgraded by 1 level because 95% CI crosses 1 MID for this outcome.*
[7] *The calculated MIDs for symptomatic relief during pregnancy were calculated as 0.5 times the median/mean* of the SD at baseline. The specific MIDs for the outcomes, are as follows: Overall relief (Total Rhodes Index Score): +/- 2.34 Nausea relief (Rhodes Index Score): +/- 1.20 Nausea intensity (Rhodes Index Score): +/- 1.77 Nausea intensity (VAS score): +/- 0.95 Nausea frequency (Rhodes Index Score): +/- 0.50 Vomiting relief (Rhodes Index Score): +/- 1.25 Vomiting intensity (Rhodes Index Score): +/- 1.49 Vomiting frequency (Rhodes Index Score): +/- 0.60 Vomiting frequency in the last 24 hours (Patient reported): +/- 0.59 Retching relief (Rhodes Index Score): +/- 1.89 Retching frequency (Rhodes Index Score): +/- 0.45 *Note, mean used when 2 studies are present, and median used when 3 or more studies are present.*
[8] *Downgraded by 1 level due to asymmetrical Funnel Plot and imprecise studies.*
[9] *Although there is moderate heterogeneity (i2=/>50%) all results favoured ginger and the evidence was therefore not downgraded.*
[10] *Downgraded by 1 level due to high risk of attrition bias and unclear risk of selection bias.*
[11] *Evidence downgaded by 2 levels because 95% CIs cross 2 MIDs for this outcome.*
[12] *Downgraded by 1 level due to high risk of selection bias and reporting bias and unclear risk of selection bias.*
[13] *Evidence downgraded by 2 levels because 95% CI crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).*
[14] *Downgraded by 1 level due to high risk of attrition bias and reporting bias and unclear risk of selection and performance bias.*
[15] *Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (0.8).*
[16] *Downgraded by 1 level due to high risk of reporting bias.*
[17] *Evidence downgraded 2 levels due to very serious imprecision surrounding small sample size.*
‡ *For references see corresponding forest plot*

Table 8: Clinical evidence profile for acupressure versus acupressure for treating mild to moderate nausea and vomiting

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupressure	Acupressure	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy- Nausea severity- Change score from baseline (follow-up 4 days; measured with: VAS scale; range of scores: 0-10; Better indicated by lower values)												
1 (Galeshi 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	40	42	-	MD 0.52 lower (1.08 lower to 0.04 higher)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy- Vomiting severity- Change score from baseline (follow-up 4 days; measured with: VAS scale; range of scores: 0-10; Better indicated by lower values)												
1 (Galeshi 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	42	-	MD 0.22 higher (0.26 lower to 0.7 higher)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI: confidence interval; MD: mean difference; VAS: Visual analogue scale
[1] *Downgraded by 1 level due to some concerns with measurement of the outcome and selection of the reported result.*
[2] *Evidence downgraded by 1 level because 95% CI crosses 1 MID for this outcome.*
[3] *The calculated MIDs for symptomatic relief during pregnancy were calculated as 0.5 times the median/mean* of the SD at baseline. The specific MIDs for the outcomes, are as follows: Nausea severity- change score from baseline (VAS score): +/-0.83 Vomiting severity- change score from baseline (VAS score): +/- 0.87 *Note, mean used when 2 studies are present, and median used when 3 or more studies are present.*

Table 9: Clinical evidence profile for acupressure versus placebo for treating mild to moderate nausea and vomiting

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupressure	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Overall relief (Total Rhodes Index score) (follow-up 0-7 days; measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
2‡	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	123	121	-	MD 2.34 lower (3.97 to 0.72 lower)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Overall relief (Total Rhodes Index score) - High Income Country (measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Belluomini 1994)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3,4]	none	30	30	-	MD 1.34 lower (3.77 lower to 1.09 higher)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Overall relief (Total Rhodes Index score) - Low Income Country (follow-up 7 days; measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Puangsricharem 2008)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3,4]	none	45	46	-	MD 3.60 lower (6.62 to 0.58 lower)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Nausea relief (Rhodes Index score) (follow-up 0-7 days; measured with: Rhodes Index of Nausea and Vomiting Form 2 ; range of scores: 0-32; Better indicated by lower values)												
1 (Belluomini 1994)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3,4]	none	30	30	-	MD 1.24 lower (2.63 lower to 0.15 higher)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Nausea frequency - Change score from baseline (follow-up 4 days; measured with: 0-4 scale; range of scores: 0-4; Better indicated by lower values)												
1 (Mobarakabadi 2019)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[3,4]	none	25	25	-	MD 2.49 lower (4.41 to 0.57 lower)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupressure	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Nausea intensity (VAS score) (measured with: Visual Analogue Scale Score; range of scores: 0-100; Better indicated by lower values)												
1 (Werntoft 2001)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[3,4]	none	20	20	-	MD 1.70 lower (3.25 to 0.15 lower)	⊕OOO VERY LOW	CRITICAL
Symptomatic relief during pregnancy - Nausea intensity (VAS score) (measured with: Visual Analogue Scale Score; range of scores: 0-10; Better indicated by lower values)												
1 (Rad 2012)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	40	40	-	median 3 higher (2 to 8 higher)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Nausea intensity- Change score from baseline (follow-up 4 days; measured with: 0-4 scale; range of scores: 0-4; Better indicated by lower values)												
1 (Mobarak abadi 2019)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[3,4]	none	25	25	-	MD 6.39 lower (12.37 to 0.41 lower)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Vomiting relief (Rhodes Index score) (follow-up 0-7 days; measured with: Rhodes Index of Nausea and Vomiting Form 2 ; range of scores: 0-32; Better indicated by lower values)												
1 (Belluomini 1994)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 0.35 lower (1.42 lower to 0.72 higher)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Vomiting frequency (Patient reported) (measured with: Patient report; range of scores: 0-10; Better indicated by lower values)												
1 (Rad 2012)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	40	40	-	median 1 higher (0 to 2 higher)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Vomitng frequency - Change score from baseline (follow-up 4 days; measured with: 0-4 scale; range of scores: 0-4; Better indicated by lower values)												
1 (Mobarak abadi 2019)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	25	-	MD 0.38 lower (1.57 lower to 0.81 higher)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupressure	Placebo	Relative (95% CI)	Absolute		
Women's experience and satisfaction of care during or at end of pregnancy- Satisfaction with intervention (Yes)												
1 (Mobarak abadi 2019)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[9]	none	15/25 (60%)	6/25 (24%)	RR 2.50 (1.16 to 5.39)	360 more per 1000 (from 38 more to 1000 more)	⊕⊕OO LOW	IMPORTANT
Women's experience and satisfaction of care during or at end of pregnancy- Satisfaction with intervention (No)												
1 (Mobarak abadi 2019)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[10]	none	1/25 (4%)	0/25 (0%)	Peto OR 7.39 (0.15 to 372.38)	-	⊕OOO VERY LOW	IMPORTANT
Women's experience and satisfaction of care during or at end of pregnancy- Satisfaction with intervention (Almost)												
1 (Mobarak abadi 2019)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[9]	none	9/25 (36%)	19/25 (76%)	RR 0.47 (0.27 to 0.84)	403 fewer per 1000 (from 122 fewer to 555 fewer)	⊕⊕OO LOW	IMPORTANT

Abbreviations: CI: confidence interval; IQR: interquartile range; MD: mean difference; OR: odds ratio; RR: risk ratio

[1] Downgraded by 1 level due to high risk of performance bias and unclear risk of selection bias.

[2] Downgraded by 1 level due to high risk of attrition and reporting bias, and unclear risk of selection bias.

[3] Evidence downgraded by 1 level because 95% CI crosses 1 MID for this outcome.

[4] The calculated MIDs for symptomatic relief during pregnancy were calculated as 0.5 times the median/mean of the SD at baseline. The specific MIDs for the outcomes, are as follows: Overall relief (Total Rhodes Index Score): +/- 6.9 Overall relief - High income (Total Rhodes Index Score): +/- 2.30 Overall relief - Low income (Total Rhodes Index Score): +/- 4.60 Nausea relief (Rhodes Index Score): +/- 1.30 Vomiting relief (Rhodes Index Score): +/- 1.65 Retching relief (Rhodes Index Score): +/- 1.26 Nausea intensity (VAS Score): +/- 1.20 Nausea frequency- change score from baseline of placebo (0-4 scale): +/-2.61 Nausea intensity- change score from baseline of placebo (0-4 scale): +/-7.31 Vomiting frequency- change score from baseline of placebo (0-4 scale): +/-2.19 *Note, mean used when 2 studies are present, and median used when 3 or more studies are present.*

[5] Downgraded by 1 level due unclear risk of selection bias.

[6] Downgraded by 1 level due to some concerns with measurement of the outcome and other biases.

[7] Downgraded by 2 levels due to serious risk of attrition bias and other bias, and unclear risk of selection and performance bias.

[8] Evidence downgraded by 2 levels due to very serious imprecision surrounding sample size.

[9] Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).

[10] Evidence downgraded by 2 levels because 95% CI crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).

‡ For references see corresponding forest plot

Table 10: Clinical evidence profile for acupressure versus control for treating mild to moderate nausea and vomiting

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupressure	Control (no treatment)	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Overall relief (Total Rhodes Index score) (follow-up 0-7 days; measured with: Rhodes Index score; range of scores: 0-32; Better indicated by lower values)												
1 (Saberi 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	48	45	-	MD 2.67 lower (5.84 lower to 0.50 higher)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Nausea relief (Rhodes Index score) (follow-up 0-7 days; measured with: Rhodes Index of Nausea and Vomiting Form 2 ; range of scores: 0-32; Better indicated by lower values)												
1 (Saberi 2013)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2,3]	none	30	30	-	MD 0.95 higher (0.51 lower to 2.41 higher)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy- Nausea frequency- Change score from baseline (0-4 scale) (follow-up 4 days; measured with: 0-4 scale; range of scores: 0-4; Better indicated by lower values)												
1 (Mobarakabadi 2019)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	25	-	MD 5.5 lower (7.24 to 3.76 lower)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Nausea intensity (VAS score) (measured with: Visual Analogue Scale Score; range of scores: 0-100; Better indicated by lower values)												
1 (Werntoft 2001)	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[2,3]	none	20	20	-	MD 2.30 lower (3.79 to 0.81 lower)	⊕OOO VERY LOW	CRITICAL
Symptomatic relief during pregnancy- Nausea intensity- Change score from baseline (0-4 scale) (follow-up 4 days; measured with: 0-4 scale; range of scores: 0-4; Better indicated by lower values)												
1 (Mobarakabadi 2019)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	25	-	MD 14.3 lower (20.02 to 8.58 lower)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Vomiting relief (Rhodes Index score) (follow-up 0-7 days; measured with: Rhodes Index of Nausea and Vomiting Form 2 ; range of scores: 0-32; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupressure	Control (no treatment)	Relative (95% CI)	Absolute		
1 (Saberi 2013)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2,3]	none	48	45	-	MD 1.41 lower (2.73 to 0.09 lower)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy- Vomiting frequency- Change score from baseline (0-4 scale) (follow-up 4 days; measured with: 0-4 scale; range of scores: 0-4; Better indicated by lower values)												
1 (Mobarakabadi 2019)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[2,3]	none	25	25	-	MD 1.39 lower (2.37 to 0.41 lower)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Retching relief (Rhodes Index score) (follow-up 7 days; measured with: Rhodes Index of Nausea and Vomiting Form 2 ; range of scores: 0-32; Better indicated by lower values)												
1 (Saberi 2013)	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[2,3]	none	48	45	-	MD 0.82 lower (1.78 lower to 0.14 higher)	⊕⊕OO LOW	CRITICAL
Women's experience and satisfaction of care during or at end of pregnancy- Satisfaction with intervention (Yes)												
1 (Mobarakabadi 2019)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/25 (60%)	3/25 (12%)	RR 5 (1.65 to 15.15)	480 more per 1000 (from 78 more to 1000 more)	⊕⊕⊕O MODERATE	IMPORTANT
Women's experience and satisfaction of care during or at end of pregnancy- Satisfaction with intervention (No)												
1 (Mobarakabadi 2019)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/25 (4%)	16/25 (64%)	RR 0.06 (0.01 to 0.44)	602 fewer per 1000 (from 358 fewer to 634 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Women's experience and satisfaction of care during or at end of pregnancy- Satisfaction with intervention (Almost)												
1 (Mobarakabadi 2019)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[8]	none	9/25 (36%)	6/25 (24%)	RR 1.50 (0.63 to 3.59)	120 more per 1000 (from 89 fewer to 622 more)	⊕OOO VERY LOW	IMPORTANT

Abbreviations: CI: confidence interval; MD: mean difference; RR: risk ratio

[1] Downgraded by 1 level due to high risk of performance bias.

[2] Evidence downgraded by 1 level because 95% CI crosses 1 MID for this outcome.

[3] The calculated MIDs for symptomatic relief during pregnancy were calculated as 0.5 times the median/mean* of the SD at baseline. The specific MIDs for the outcomes, are as follows: Overall relief (Rhodes Index): +/- 3.45 Nausea relief (Rhodes Index): +/- 1.50 Nausea frequency- change score from baseline of control (0-4 scale): +/-1.75 Nausea intensity (VAS score): +/- 1.10 Nausea

intensity- change score from baseline of control (0-4 scale): +/-3.71 Vomiting relief (Rhodes Index): +/- 1.55 Vomiting frequency- change score from baseline of control (0-4 scale): +/-1.14 Retching relief (Rhodes Index): +/-1.14 *Note, mean used when 2 studies are present, and median used when 3 or more studies are present.
[4] Downgraded by 1 level due unclear risk of selection bias.
[5] Downgraded by 1 level due to some concerns with measurement of the outcome and other biases.
[6] Downgraded by 2 levels due to serious risk of attrition bias and other bias, and unclear risk of selection and performance bias.
[7] Downgraded by 1 level due to high risk of performance bias and unclear risk of selection bias.
[8] Evidence downgraded by 2 levels because 95% CI crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).

Table 11: Clinical evidence profile for acupressure versus ginger for treating mild to moderate nausea and vomiting

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupressure	Ginger	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Overall relief (Total Rhodes Index score) (follow-up 7 days; measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Saberi 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	50	-	MD 6.24 higher (3.03 to 9.45 higher)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Relief from nausea (Rhodes Index Score) (follow-up 7 days; measured with: Rhodes Index of Nausea and Vomiting Form 2 ; range of scores: 0-32; Better indicated by lower values)												
1 (Saberi 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	50	-	MD 4.41 higher (2.96 to 5.86 higher)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Relief from vomiting (Rhodes Index Score) (follow-up 7 days; measured with: Rhodes Index of Nausea and Vomiting Form 2 ; range of scores: 0-32; Better indicated by lower values)												
1 (Saberi 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	48	50	-	MD 1.67 higher (0.37 to 2.97 higher)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Relief from retching (Rhodes Index Score) (follow-up 7 days; measured with: Rhodes Index of Nausea and Vomiting Form 2 ; Better indicated by lower values)												
1 (Saberi 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	48	50	-	MD 1.54 higher (0.6 to 2.48 higher)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI: confidence interval; MD: mean difference
[1] Downgraded by 1 level due to high risk of performance bias and unknown risk of selection bias and other bias.
[2] Evidence downgraded 1 level because 95% CI crosses 1 MID for this outcome.
[3] The calculated MIDs for symptomatic relief during pregnancy were calculated as 0.5 times the median/mean of the SD at baseline. The specific MIDs for the outcomes, are as follows: Overall relief*

(Total Rhodes Index Score): +/- 2.58 Relief from nausea (Rhodes Index Score): +/- 1.20 Relief from vomiting (Rhodes Index Score): +/- 1.27 Relief from retching (Rhodes Index Score): +/- 1.26
**Note, mean used when 2 studies are present, and median used when 3 or more studies are present.*

Table12: Clinical evidence profile for acupuncture versus placebo for treating mild to moderate nausea and vomiting

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupuncture	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Nausea relief (Rhodes Index score) - P6 vs Placebo (measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Smith 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	148	297	-	MD 0.35 lower (0.98 lower to 0.28 higher)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Nausea relief (Rhodes Index score) - Traditional vs Placebo (measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Smith 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	148	297	-	MD 0.95 lower (1.54 to 0.36 lower)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Nausea intensity (VAS score) - Traditional vs Placebo (measured with: Visual Analogue Scale Score ; range of scores: 0-100; Better indicated by lower values)												
1 (Knight 2001)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	28	27	-	acupuncture 47.5 (IQR 29.25-69.5), placebo 48 (IQR 14.0 to 80.0), p=0.90	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Vomiting relief (Rhodes Index score) - P6 vs Placebo (measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Smith 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	148	297	-	MD 0.3 lower (0.66 lower to 0.06 higher)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Vomiting relief (Rhodes Index score) - Traditional vs Placebo (measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Smith 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	148	297	-	MD 0.3 lower (0.62 lower to 0.02 higher)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupuncture	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Retching relief (Rhodes Index score) - P6 vs Placebo (measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Smith 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	148	297	-	MD 0.35 lower (0.63 to 0.07 lower)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Retching relief (Rhodes Index score) - Traditional vs Placebo (measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Smith 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	148	297	-	MD 0.45 lower (0.74 to 0.16 lower)	⊕⊕⊕O MODERATE	CRITICAL
Fetal death - P6 vs Placebo												
1 (Smith 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	6/148 (4.1%)	24/297 (8.1%)	RR 0.5 (0.21 to 1.2)	40 fewer per 1000 (from 64 fewer to 16 more)	⊕⊕OO LOW	CRITICAL
Fetal death - Traditional vs Placebo												
1 (Smith 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	6/148 (4.1%)	24/297 (8.1%)	RR 0.5 (0.21 to 1.2)	40 fewer per 1000 (from 64 fewer to 16 more)	⊕⊕OO LOW	CRITICAL
Adverse events requiring hospitalisation												
1 (Knight 2001)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	0/28 (0%)	0/27 (0%)	RD 0.00 (-0.07 to 0.07)	-	⊕⊕OO LOW	IMPORTANT

Abbreviations: CI: confidence interval; IQR: interquartile range; MD: mean difference; RD: risk difference; RR: risk ratio; VAS: Visual analogue scale

[1] Downgraded by 1 level due to unclear risk of selection, performance, attrition, and other biases.

[2] Evidence downgraded 1 level because 95% CI crosses 1 MID for this outcome.

[3] The calculated MIDs for symptomatic relief during pregnancy were calculated as 0.5 times the median/mean of the SD at baseline. The specific MIDs for the outcomes, are as follows: Nausea relief (Rhodes Index Score, P6 and traditional): +/- 1.20 Vomiting relief (Rhodes Index Score, P6 and traditional): +/- 1.38 Retching relief (Rhodes Index Score, P6 and traditional): +/- 0.98 *Note, mean used when 2 studies are present, and median used when 3 or more studies are present.*

[4] Evidence downgraded 2 levels due to very serious imprecision surrounding small sample size

[5] Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).

Table13: Clinical evidence profile for acupuncture + component versus sham acupuncture + placebo component for treating mild to moderate nausea and vomiting

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupuncture	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Overall relief (Total Rhodes Index score) (measured with: Total on Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Ghule 2020)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	52	-	MD 6.32 lower (8.21 to 4.43 lower)	⊕⊕OO LOW	CRITICAL
Women's experience and satisfaction of care during or at end of pregnancy (measured with: Nausea Vomiting of Pregnancy Quality of Life; range of scores: 0-120; Better indicated by higher values)												
1 (Ghule 2020)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	52	-	MD 34.65 lower (40.64 to 28.66 lower)	⊕⊕OO LOW	IMPORTANT

Abbreviations: CI: confidence interval; IQR: interquartile range; MD: mean difference; RD: risk difference; RR: risk ratio; VAS: Visual analogue scale
[1] Evidence downgraded 2 levels due to some concerns with the randomisation process, deviations from intended interventions, measurement of the outcome, and selection of the report result.

Table14: Clinical evidence profile for dopamine D2-receptor antagonists versus placebo for treating mild to moderate nausea and vomiting

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dopamine D2-receptor antagonists	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Overall relief (Total Rhodes Index score) (measured with: Rhodes Index of Nausea and Vomiting Form 2 ; range of scores: 0-32; Better indicated by lower values)												
1 (Mohammadbeigi 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	none	34	34	-	MD 4.62 lower (6.83 to 2.41 lower)	⊕⊕⊕⊕ HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dopamine D2-receptor antagonists	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Nausea intensity (Rhodes Index score) (measured with: Rhodes Index of Nausea and Vomiting Form 2 ; range of scores: 0-32; Better indicated by lower values)												
1 (Mohammadbeigi 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	34	34	-	MD 3.05 lower (4.5 to 1.6 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Symptomatic relief during pregnancy - Vomiting intensity (Rhodes Index score) (measured with: Rhodes Index of Nausea and Vomiting Form 2 ; range of scores: 0-32; Better indicated by lower values)												
1 (Mohammadbeigi 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	34	34	-	MD 1.06 lower (1.82 to 0.3 lower)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI: confidence interval; MD: mean difference
[1] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 2.32.
[2] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 1.27.
[3] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 0.89. Downgraded by 1 level because 95% CI crosses 1 MID (-0.89).

Table15: Clinical evidence profile for histamine H1-receptor antagonist versus placebo for treating mild to moderate nausea and vomiting

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Histamine H1-receptor antagonist	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Number of women with improvements in symptoms- physician evaluations - Improvement in nausea (assessed with: Physician evaluation)												
1 (Zhang 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	144/209 (68.9%)	94/181 (51.9%)	RR 1.33 (1.12 to 1.57)	171 more per 1000 (from 62 more to 296 more)	⊕OOO VERY LOW	CRITICAL
Symptomatic relief during pregnancy - Number of women with improvements in symptoms- physician evaluations - Improvement in vomiting (assessed with: Physician evaluation)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Histamine H1-receptor antagonist	Placebo	Relative (95% CI)	Absolute		
1 (Zhang 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	163/209 (78%)	119/181 (65.7%)	RR 1.19 (1.04 to 1.35)	125 more per 1000 (from 26 more to 230 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; RR: risk ratio
[1] Downgraded by 2 levels due to serious risk of attrition, reporting, and other biases. There is also an unclear risk of selection bias.
[2] Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (1.25).

Table16: Clinical evidence profile for pyridoxine hydrochloride versus placebo for treating mild to moderate nausea and vomiting

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pyridoxine hydrochloride	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Overall relief (Total Rhodes Index score) (measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Sharifzadeh 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	23	-	MD 5.5 lower (7.66 to 3.34 lower)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Nausea intensity (Rhodes Index score) (measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Sharifzadeh 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	26	23	-	MD 0.89 lower (1.38 to 0.4 lower)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Nausea intensity (VAS score) (follow-up 0-7 days; measured with: Visual Analogue Scale Score; range of scores: 0-10; Better indicated by lower values)												
2‡	randomised trials	serious[4]	no serious inconsistency[5]	no serious indirectness	no serious imprecision	none	204	197	-	MD 0.60 lower (1.2 to 0.01 lower)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pyridoxine hydrochloride	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Nausea frequency (Rhodes Index score) (measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Sharifzadeh 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	26	23	-	MD 0.67 lower (1.08 to 0.26 lower)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Vomiting intensity (Rhodes Index score) (measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Sharifzadeh 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	26	23	-	MD 0.7 lower (1.14 to 0.26 lower)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Vomiting frequency (Rhodes Index score) (measured with: Rhodes Index of Nausea and Vomiting Form 2; range of scores: 0-32; Better indicated by lower values)												
1 (Sharifzadeh 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	26	23	-	MD 0.97 lower (1.43 to 0.51 lower)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Change in vomiting frequency (Patient reported) - Change scores from baseline (measured with: Patient report; Better indicated by lower values)												
1 (Vutyavanich 1995)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	173	169	-	MD 0.1 lower (0.62 lower to 0.42 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Symptomatic relief during pregnancy - Number of patients vomiting on last day of treatment												
1 (Sahakian 1991)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	8/31 (25.8%)	15/28 (53.6%)	RR 0.48 (0.24 to 0.96)	279 fewer per 1000 (from 21 fewer to 407 fewer)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Number of women with improvements in symptoms- physician evaluations - Improvement in nausea (assessed with: Physician evaluation)												
1 (Zhang 2017)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[8]	none	130/191 (68.1%)	94/181 (51.9%)	RR 1.31 (1.11 to 1.55)	161 more per 1000 (from 57 more to 286 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pyridoxine hydrochloride	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Number of women with improvements in symptoms- physician evaluations - Improvement in vomiting (assessed with: Physician evaluation)												
1 (Zhang 2017)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	126/191 (66%)	119/181 (65.7%)	RR 1 (0.87 to 1.16)	0 fewer per 1000 (from 85 fewer to 105 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI: confidence interval; MD: mean difference; RR: risk ratio; VAS: Visual analogue scale
[1] Downgraded by 1 level due to serious risk of attrition bias and unclear risk of selection bias.
[2] The calculated MIDs for symptomatic relief during pregnancy were calculated as 0.5 times the median/mean of the SD at baseline. The specific MIDs for the outcomes, are as follows: Overall relief (Total Rhodes Index Score): +/- 2.35 Nausea intensity (Rhodes Index Score): +/- 0.5 Nausea intensity (VAS Score): +/- 6.74 Nausea frequency (Rhodes Index Score): +/- 0.5 Vomiting intensity (Rhodes Index Score): +/- 0.6 Vomiting frequency (Rhodes Index Score): +/- 0.6 Change in vomiting frequency (Patient reported): +/- 1.25 *Note, mean used when 2 studies are present, and median used when 3 or more studies are present.*
[3] Evidence downgraded by 1 level because 95% CI crosses 1 MID.
[4] Downgraded by 1 level due to serious risk of attrition bias and unclear risk of selection bias in all studies.
[5] Although one study has a CI that crosses line of no effect, evidence not downgraded as heterogeneity is low and overall effect estimate favours pyridoxine hydrochloride.
[6] Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (0.8).
[7] Downgraded by 2 levels due to serious risk of attrition, reporting, and other biases. There is also an unclear risk of selection bias.
[8] Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (1.25).
‡ For references see corresponding forest plot

Table17: Clinical evidence profile for pyridoxine hydrochloride versus histamine H1-recepter antagonist for treating mild to moderate nausea and vomiting

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pyridoxine hydrochloride	Histamine H1-recepter antagonist	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Number of women with improvements in symptoms- physician evaluations - Improvement in nausea (assessed with: Physician evaluation)												
1 (Zhang 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	130/191 (68.1%)	144/209 (68.9%)	RR 0.99 (0.86 to 1.13)	7 fewer per 1000 (from 96 fewer to 90 more)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pyridoxine hydrochloride	Histamine H1-recepter antagonist	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Number of women with improvements in symptoms- physician evaluations - Improvement in vomiting (assessed with: Physician evaluation)												
1 (Zhang 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	126/191 (66%)	163/209 (78%)	RR 0.85 (0.75 to 0.96)	117 fewer per 1000 (from 31 fewer to 195 fewer)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; RR: risk ratio
[1] Downgraded by 2 levels due to serious risk of attrition, reporting, and other biases. There is also an unclear risk of selection bias.
[2] Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (0.80).

Table18: Clinical evidence profile for pyridoxine hydrochloride + dopamine D2-receptor antagonist versus histamine H1-receptor antagonist for treating mild to moderate nausea and vomiting

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pyridoxine hydrochloride + Dopamine D2-receptor antagonist	Histamine H1-receptor antagonist	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Vomiting frequency (Patient reported) (measured with: Patient report; Better indicated by lower values)												
1 (Bsat 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,2]	none	54	52	-	MD 0.2 lower (0.5 lower to 0.1 higher)	⊕⊕⊕O MODERATE	CRITICAL

[1] Evidence downgraded by 1 level because 95% CI crosses 1 MID.
[2] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 0.4. Evidence downgraded by 1 because 95% CI crosses 1 MID (-0.4).

Table19: Clinical evidence profile for pyridoxine hydrochloride + histamine H1-receptor antagonist versus placebo for nausea and vomiting in pregnancy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pyridoxine hydrochloride + Histamine H1-receptor antagonist	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Overall relief (PUQE score) (follow-up 15 days; measured with: Change scores with Pregnancy Unique Quantification of Emesis/Nausea Index Score; range of scores: 3-25; Better indicated by lower values)												
1 (Koren 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	131	125	-	MD 0.9 lower (1.55 to 0.25 lower)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Complete relief from nausea and vomiting (Patient reported) (assessed with: Patient report)												
2‡	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	101/153 (66%)	26/157 (16.6%)	RR 3.40 (1.08 to 10.7)	397 more per 1000 (from 13 more to 1000 more)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Number of women with improvements in symptoms- physician evaluations - Improvement in nausea symptoms (assessed with: Physician evaluation)												
1 (Zhang 2017)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[4]	none	160/213 (75.1%)	94/181 (51.9%)	RR 1.45 (1.23 to 1.7)	234 more per 1000 (from 119 more to 364 more)	⊕OOO VERY LOW	CRITICAL
Symptomatic relief during pregnancy - Number of women with improvements in symptoms- physician evaluations - Improvement in vomiting symptoms (assessed with: Physician evaluation)												
1 (Zhang 2017)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[4]	none	155/213 (72.8%)	119/181 (65.7%)	RR 1.11 (0.97 to 1.26)	72 more per 1000 (from 20 fewer to 171 more)	⊕OOO VERY LOW	CRITICAL
Adverse event requiring hospitalisation												
2‡	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[6]	none	0/184 (0%)	0/184 (0%)	RD 0.00 (-0.02 to 0.02)	-	⊕⊕OO LOW	IMPORTANT

Abbreviations: CI: confidence interval; MD: mean difference; PUQE: pregnancy unique quantification of emesis and nausea; RD: risk difference; RR: risk ratio

[1] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 1.3. Evidence downgraded one level because 95% CI crosses 1 MID (-1.3).

[2] Downgraded by 1 level due to unclear risk of other biases in both studies, and unclear/high risk of reporting bias. Additionally, unclear risk of selection, performance, detection, and attrition bias.

[3] Although there is high heterogeneity, evidence is not downgraded because all results favour same side.

[4] Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (1.25).
[5] Downgraded by 2 levels due to serious risk of attrition, reporting, and other biases. There is also an unclear risk of selection bias.
[6] Evidence downgraded by 1 level due to serious imprecision surrounding small sample size.
‡ For references see corresponding forest plot

Table20: Clinical evidence profile for pyridoxine hydrochloride + histamine H1-receptor antagonist versus pyridoxine hydrochloride for treating mild to moderate nausea and vomiting

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pyridoxine hydrochloride + Histamine H1-receptor antagonist	Pyridoxine hydrochloride	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Number of women with improvements in symptoms- physician evaluations - Improvement in nausea (assessed with: Physician evaluation)												
1 (Zhang 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	160/213 (75.1%)	130/191 (68.1%)	RR 1.1 (0.97 to 1.25)	68 more per 1000 (from 20 fewer to 170 more)	⊕OOO VERY LOW	CRITICAL
Symptomatic relief during pregnancy - Number of women with improvements in symptoms- physician evaluations - Improvement in vomiting (assessed with: Physician evaluation)												
1 (Zhang 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	155/213 (72.8%)	126/191 (66%)	RR 1.10 (0.97 to 1.26)	66 more per 1000 (from 20 fewer to 172 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; RR: risk ratio
[1] Downgraded by 2 levels due to serious risk of attrition, reporting, and other biases. There is also an unclear risk of selection bias.
[2] Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).

Table21: Clinical evidence profile for pyridoxine hydrochloride + histamine H1-receptor antagonist versus histamine H1-receptor antagonist for treating mild to moderate nausea and vomiting

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pyridoxine hydrochloride + Histamine H1-receptor antagonist	Histamine H1-receptor antagonist	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Number of women with improvements in symptoms- physician evaluations - Improvement in nausea (assessed with: Physician evaluation)												
1 (Zhang 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	160/213 (75.1%)	144/209 (68.9%)	RR 1.09 (0.97 to 1.23)	62 more per 1000 (from 21 fewer to 158 more)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Number of women with improvements in symptoms- physician evaluations - Improvement in vomiting (assessed with: Physician evaluation)												
1 (Zhang 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	155/213 (72.8%)	163/209 (78%)	RR 0.93 (0.84 to 1.04)	55 fewer per 1000 (from 125 fewer to 31 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI: confidence interval; RR: risk ratio

[1] Downgraded by 2 levels due to serious risk of attrition, reporting, and other biases. There is also an unclear risk of selection bias.

Table22: Clinical evidence profile for serotonin 5-HT antagonist + placebo versus pyridoxine hydrochloride + histamine H1-receptor antagonist for treating mild to moderate nausea and vomiting

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Serotonin 5-HT antagonist + Placebo	Pyridoxine hydrochloride + H1-receptor antagonist	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Nausea intensity (VAS score) (follow-up 7 days; measured with: Change scores from baseline from Visual Analogue Scale Score; range of scores: 0-100; Better indicated by lower values)												
1 (Oliveira 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	13	17	-	serotonin 5-HT antagonist + placebo median 51 (IQR 37 to 64), pyridoxine hydrochloride + doxylamine succinate median 20 (IQR 8 to 51), p=0.019	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Vomiting intensity (VAS score) (follow-up 7 days; measured with: Change scores from baseline from Visual Analogue Scale Score; range of scores: 0-100; Better indicated by lower values)												
1 (Oliveira 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	13	17	-	serotonin 5-HT antagonist + placebo median 41 (IQR 17 to 57), pyridoxine hydrochloride + doxylamine succinate median 17 (IQR -4 to 38), p=0.049	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Number of women with improvement in symptoms (score on VAS ≥25 mm) - Clinically significant improvement - Nausea (follow-up 7 days; assessed with: Visual Analogue Scale Score [2])												
1 (Oliveira 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	12/13 (92.3%)	7/17 (41.2%)	RR 2.24 (1.24 to 4.04)	511 more per 1000 (from 99 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Number of women with improvement in symptoms (score on VAS ≥25 mm) - Clinically significant improvement - Vomiting (follow-up 7 days; assessed with: Visual Analogue Scale Score[2])												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Serotonin 5-HT antagonist + Placebo	Pyridoxine hydrochloride + H1-receptor antagonist	Relative (95% CI)	Absolute		
1 (Oliveira 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	10/13 (76.9%)	6/17 (35.3%)	RR 2.18 (1.07 to 4.43)	416 more per 1000 (from 25 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events requiring hospitalisation (follow-up 7 days)												
1 (Oliveira 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/13 (0%)	0/17 (0%)	RD 0 (-0.12 to 0.12)	-	⊕⊕OO LOW	IMPORTANT

Abbreviations: CI: confidence interval; IQR: interquartile range; RD: risk difference; RR: risk ratio; VAS: Visual analogue scale
[1] Evidence downgraded by 2 levels due to very serious imprecision surrounding small sample size.
[2] Scale from 0-100 with lower score indicating better result.
[3] Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (1.25).

Hyperemesis gravidarum

Table23: Clinical evidence profile for acupressure versus placebo for hyperemesis gravidarum

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupressure	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Overall relief (PUQE score) (measured with: Pregnancy Unique Quantification of Emesis Score ; range of scores: 3-15; Better indicated by lower values)												
1 (Adlan 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	60	60	-	MD 2.7 lower (3.28 to 2.12 lower)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupressure	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Nausea severity (PUQE score) (measured with: Pregnancy Unique Quantification of Emesis Score ; range of scores: 3-15; Better indicated by lower values)												
1 (Adlan 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	60	60	-	MD 1.01 lower (1.32 to 0.7 lower)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Vomiting severity (PUQE score) (measured with: Pregnancy Unique Quantification of Emesis Score ; range of scores: 3-15; Better indicated by lower values)												
1 (Adlan 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	60	60	-	MD 1.1 lower (1.33 to 0.87 lower)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Retching severity (PUQE score) (measured with: Pregnancy Unique Quantification of Emesis Score ; range of scores: 3-15; Better indicated by lower values)												
1 (Adlan 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	60	60	-	MD 0.58 lower (0.81 to 0.35 lower)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Number of women with disappearance of symptoms (follow-up 2 weeks)												
1 (Habek 2004)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/11 (63.6%)	0/7 (0%)	Peto OR 12.54 (1.9 to 82.93)	-	⊕⊕⊕O MODERATE	CRITICAL
Fetal death - Miscarriage before 20 weeks												
1 (Heazell 2006)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/29 (3.4%)	2/28 (7.1%)	RR 0.48 (0.05 to 5.03)	37 fewer per 1000 (from 68 fewer to 288 more)	⊕OOO VERY LOW	CRITICAL
Fetal death - Termination of pregnancy												
1 (Heazell 2006)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[7]	none	3/29 (10.3%)	4/28 (14.3%)	RR 0.72 (0.18 to 2.95)	40 fewer per 1000 (from 117 fewer to 279 more)	⊕OOO VERY LOW	CRITICAL
Fetal death - Intra-uterine fetal death after 20 weeks												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupressure	Placebo	Relative (95% CI)	Absolute		
1 (Heazell 2006)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/23 (4.3%)	1/13 (7.7%)	RR 0.57 (0.04 to 8.3)	33 fewer per 1000 (from 74 fewer to 562 more)	⊕OOO VERY LOW	CRITICAL
Number of days in hospital for treatment of nausea and vomiting (Better indicated by lower values)												
1 (Adlan 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[8]	none	60	60	-	MD 1.05 lower (1.32 to 0.78 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Number of days in hospital for treatment of nausea and vomiting (Better indicated by lower values)												
1 (Heazell 2006)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[9]	none	40	40	-	acupressure median 3 (IQR 2 to 4), placebo median 3 (IQR 2 to 5), p=not stated	⊕OOO VERY LOW	IMPORTANT
Women's experience and satisfaction of care during or at end of pregnancy												
1 (Adlan 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[10]	none	43/60 (71.7%)	51/60 (85%)	RR 0.84 (0.7 to 1.02)	136 fewer per 1000 (from 255 fewer to 17 more)	⊕⊕OO LOW	IMPORTANT
Pre-term birth (before 37 weeks)												
1 (Heazell 2006)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/23 (0%)	2/13 (15.4%)	Peto OR 0.06 (0 to 1.08)	145 fewer per 1000 (from 154 fewer to 12 more)	⊕⊕⊕O MODERATE	IMPORTANT

Abbreviations: CI: confidence interval; IQR: interquartile range; MD: mean difference; OR: odds ratio; PUQE: pregnancy unique quantification of emesis and nausea; RR: risk ratio

[1] Downgraded by 1 level due to unclear risk of selection, detection, and reporting bias.
[2] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 0.94.
[3] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 0.40.
[4] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 0.71. Evidence downgraded by 1 level because 95% CI crosses 1 MID (-0.71)
[5] Downgraded by 1 level becase of unclear risk of selection, attrition and other biases.
[6] Downgraded by 1 level due to unclear risk of detection, attrition, and other biases.
[7] Evidence downgraded by 2 levels because 95% CI crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).
[8] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 0.44.

[9] *Evidence downgraded by 2 levels due to very serious imprecision surrounding small sample size.*
[10] *Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (0.8).*

Table24: Clinical evidence profile for acupuncture versus placebo for hyperemesis gravidarum

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupuncture	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Number of women with relief from symptoms (follow-up 2 weeks)												
1 (Habek 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/10 (90%)	1/8 (12.5%)	RR 7.2 (1.14 to 45.56)	775 more per 1000 (from 17 more to 1000 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI: confidence interval; RR: risk ratio
[1] *Downgraded by 1 level due to unclear risk of selection, attrition, and other biases.*
[2] *Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (1.25).*

Table25: Clinical evidence profile for pyridoxine hydrochloride versus placebo for hyperemesis gravidarum

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pyridoxine hydrochloride	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Nausea intensity (VAS score) (follow-up 2 weeks; measured with: Visual Analgoue Scale Score ; range of scores: 0-10; Better indicated by lower values)												
1 (Tan 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	24	28	-	pyridoxine hydrochloride median 2 (IQR 3 – as reported), placebo median 2.5 (IQR 4 – as reported), p=0.69	⊕OOO VERY LOW	CRITICAL
Symptomatic relief during pregnancy - Daily mean vomiting episodes (Patient reported) (follow-up 2 weeks; measured with: Patient report; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pyridoxine hydrochloride	Placebo	Relative (95% CI)	Absolute		
1 (Tan 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	24	28	-	MD 0 higher (0.79 lower to 0.79 higher)	⊕OOO VERY LOW	CRITICAL
Symptomatic relief during pregnancy - Number of women vomiting in the last 24 hours before discharge (follow-up 2 weeks)												
1 (Tan 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	19/47 (40.4%)	13/45 (28.9%)	RR 1.4 (0.79 to 2.49)	116 more per 1000 (from 61 fewer to 430 more)	⊕OOO VERY LOW	CRITICAL
Fetal death (follow-up 2 weeks)												
1 (Tan 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/32 (0%)	1/36 (2.8%)	Peto OR 0.15 (0 to 7.67)	24 fewer per 1000 (from 28 fewer to 185 more)	⊕OOO VERY LOW	CRITICAL
Adverse event requiring hospitalisation (follow-up 2 weeks)												
1 (Tan 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/24 (0%)	0/28 (0%)	RD 0.00 (-0.07 to 0.07)	-	⊕OOO VERY LOW	IMPORTANT
Women's experience and satisfaction of care during or at end of pregnancy- Overall wellbeing score (VAS score) (follow-up 2 weeks; measured with: Visual Analogue Scale Score ; range of scores: 0-10; Better indicated by higher values)												
1 (Tan 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	24	28	-	pyridoxine hydrochloride median 8 (IQR 1 – as reported), placebo median 9 (IQR 1 –as reported), p=0.73	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; IQR: interquartile range; MD: mean difference; OR: odds ratio; RR: risk ratio

[1] Downgraded 1 level due to high risk of performance and reporting bias. Unclear risk of other bias.

[2] Evidence downgraded by 2 levels due to very serious imprecision surrounding small sample size.

[3] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 0.55. Evidence downgraded by 2 levels because 95% CI crosses 2 MIDs (-0.55 and 0.55).

[4] Evidence downgraded by 2 levels because 95% CI crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).

Table26: Clinical evidence profile for dopamine D2 receptor antagonist versus histamine H1-receptor antagonist for hyperemesis gravidarum

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dopamine D2 receptor antagonist	Histamine H1-receptor antagonist	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Nausea severity (VNRS score) - Metoclopramide vs Promethazine (measured with: Visual Numerical Rating Scale; range of scores: 1-10; Better indicated by lower values)												
1 (Tan 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	73	76	-	dopamine D2 receptor antagonist median 2 (IQR 1 to 5), histamine H1 receptor antagonist median 2 (IQR 1 to 4), p=0.99	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Vomiting frequency (Patient reported) - Metoclopramide vs Promethazine (measured with: Patient report; Better indicated by lower values)												
1 (Tan 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	73	76	-	dopamine D2 receptor antagonist median 1 (IQR 0 to 5), histamine H1 receptor antagonist median 2 (IQR 0 to 3), p=0.81	⊕⊕OO LOW	CRITICAL
Number of days in hospital for treatment of nausea and vomiting - Metoclopramide vs Promethazine (Better indicated by lower values)												
1 (Tan 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	73	76	-	dopamine D2 receptor antagonist median 1.8 (IQR 1.5 to 2.5), histamine H1 receptor antagonist median 1.7 (IQR 1.5 to 2.4), p=0.71	⊕⊕OO LOW	IMPORTANT
Women's experience and satisfaction of care during or at end of pregnancy - Patient wellbeing (VNRS scale) - Metoclopramide vs Promethazine (measured with: Visual Numerical Rating Scale ; range of scores: 0-10; Better indicated by higher values)												
1 (Tan 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	73	76	-	MD 0.5 higher (0.22 lower to 1.22 higher)	⊕⊕⊕O MODERATE	IMPORTANT

Abbreviations: CI: confidence interval; IQR: interquartile range; MD: mean difference; VNRS: visual numerical rating scale

[1] Evidence downgraded by 2 levels due to very serious imprecision surrounding small sample size.

[2] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 1.15. Evidence downgraded by 1 level because 95% CI crosses 1 MID (1.15).

Table27: Clinical evidence profile for serotonin 5-HT antagonist versus dopamine D2 receptor antagonist for hyperemesis gravidarum

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Serotonin 5-HT antagonist	Dopamine D2 receptor antagonist	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Nausea severity (VAS score) - Ondansetron vs Metoclopramide (follow-up 7 days; measured with: Visual Analogue Scale Score ; range of scores: 0-10; Better indicated by lower values)												
1 (Kashifard 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	none	34	49	-	MD 0.7 lower (1.97 lower to 0.57 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Symptomatic relief during pregnancy - Nausea severity (VNRS score) - Ondansetron vs Metoclopramide (measured with: Visual Numerical Rating Scale ; range of scores: 0-10; Better indicated by lower values)												
1 (Abas 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	60	60	-	serotonin 5-HT antagonist median 1 (IQR 1 to 3), dopamine D2 receptor antagonist median 2 (IQR 1 to 3), p=0.68	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Vomiting severity (VAS score) - Ondansetron vs Metoclopramide (follow-up 7 days; measured with: Visual Analogue Scale Score ; range of scores: 0-10; Better indicated by lower values)												
1 (Kashifard 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	none	34	49	-	MD 0 higher (1.24 lower to 1.24 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Symptomatic relief during pregnancy - Number of women vomit free during 24 hour treatment - Ondansetron vs Metoclopramide												
1 (Abas 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	39/60 (65%)	34/60 (56.7%)	RR 1.15 (0.86 to 1.53)	85 more per 1000 (from 79 fewer to 300 more)	⊕⊕⊕O MODERATE	CRITICAL
Number of days in hospital for treatment of nausea and vomiting - Ondansetron vs Metoclopramide (Better indicated by lower values)												
1 (Abas 2014)	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious[2]	none	60	60	-	serotonin 5-HT antagonist median 1.9 (IQR 1.5 to 2.4), dopamine D2	⊕⊕OO LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Serotonin 5-HT antagonist	Dopamine D2 receptor antagonist	Relative (95% CI)	Absolute		
		risk of bias								receptor antagonist median 2 (IQR 1.7 to 2.7), p=0.10		
Women's experience and satisfaction of care during or at end of pregnancy - Patient wellbeing (VNRS score) - Ondansetron vs Metoclopramide (measured with: Visual Numerical Rating Scale; range of scores: 0-10; Better indicated by higher values)												
1 (Abas 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	80	80	-	MD 0.4 higher (0.03 lower to 0.83 higher)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI: confidence interval; IQR: interquartile range; MD: mean difference; RR: risk ratio; VAS: Visual analogue scale; VNRS: visual numerical rating scale
[1] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 2.05
[2] Evidence downgraded by 2 levels due to very serious imprecision surrounding small sample size.
[3] Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (1.25).
[4] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 0.80. Evidence downgraded by 1 level because 95% CI crosses 1 MID (-0.80).

Table28: Clinical evidence profile for serotonin 5-HT antagonist versus histamine H1-receptor antagonist for hyperemesis gravidarum

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Serotonin 5-HT antagonist	Histamine H1-receptor antagonist	Relative (95% CI)	Absolute		
Adverse event requiring hospitalisation - Sedation - Ondansetron vs Promethazine												
1 (Sullivan 1996)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/15 (0%)	8/15 (53.3%)	Peto OR 0.07 (0.01 to 0.35)	496 fewer per 1000 (from 347 fewer to 528 fewer)	⊕⊕OO LOW	IMPORTANT
Number of days in hospital for treatment of nausea and vomiting - Ondansetron vs Promethazine (Better indicated by lower values)												

1 (Sullivan 1996)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	15	15	-	MD 0 higher (1.39 lower to 1.39 higher)	⊕OOO VERY LOW	IMPORTANT

Abbreviations: CI: confidence interval; MD: mean difference; OR: odds ratio
[1] Downgraded by 1 level because unclear risk of selection, performance, detectionm reporting, and other biases.
[2] Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (0.8).
[3] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 0.75. Evidence downgraded 2 levels because 95% CI crosses 2 MIDs (-0.75 and +0.75).

Table29: Clinical evidence profile for corticosteroid versus placebo for hyperemesis gravidarum

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid	Placebo	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Improvement in nausea intensity - Prednisolone vs Placebo (follow-up 7 days; measured with: Numerical scale; range of scores: 0-10; Better indicated by lower values)												
1 (Nelson-Piercy 2001)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	12	12	-	corticosteroid median 6.5 (range 2 to 10), placebo median 4 (range -5 to 9), p=0.10	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Reduction in vomiting intensity - Prednisolone vs Placebo (follow-up 7 days; measured with: Numerical scale; range of scores: 0-10; Better indicated by lower values)												
1 (Nelson-Piercy 2001)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	12	12	-	corticosteroid median 2 (range -1 to 4), placebo median 1.5 (range -3 to 4), p=0.26	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Vomiting frequency (Patient reported) - Prednisolone vs Placebo (follow-up 7 days)												
1 (Nelson-Piercy 2001)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/12 (16.7%)	5/12 (41.7%)	RR 0.4 (0.1 to 1.67)	250 fewer per 1000 (from 375 fewer to 279 more)	⊕⊕OO LOW	CRITICAL
Fetal death (follow-up 0-7 days)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid	Placebo	Relative (95% CI)	Absolute		
2‡	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/68 (5.9%)	6/66 (9.1%)	RR 0.65 (0.19 to 2.19)	32 fewer per 1000 (from 74 fewer to 108 more)	⊕OOO VERY LOW	CRITICAL
Number of days in hospital for treatment of nausea and vomiting - Prednisolone vs Placebo (follow-up 7 days; Better indicated by lower values)												
1 (Nelson-Piercy 2001)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	12	12	-	corticosteroid median 7 (range 2 to 21), placebo median 7 (range 2 to 26), p=0.84	⊕⊕OO LOW	IMPORTANT
Number of days in hospital for treatment of nausea and vomiting - Corticosteroids vs Placebo (Better indicated by lower values)												
1 (Yost 2003)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	56	54	-	MD 3.3 higher (1.55 lower to 8.15 higher)	⊕⊕OO LOW	IMPORTANT
Pre-term birth (before 37 weeks) (follow-up 0-7 days)												
2‡	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/68 (13.2%)	8/66 (12.1%)	RR 1.1 (0.45 to 2.67)	12 more per 1000 (from 67 fewer to 202 more)	⊕⊕⊕O MODERATE	IMPORTANT

Abbreviations: CI: confidence interval; IQR: interquartile range; MD: mean difference; RR: risk ratio

[1] Evidence downgraded by 2 levels due to very serious imprecision surrounding small sample size.

[2] Evidence downgraded by 2 levels because 95% CI crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).

[3] Downgraded by 1 level due to high or unclear risk of other bias in all studies.

[4] Downgraded by 1 level due to unclear risk of selection, detection, and other biases.

[5] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 2.15. Evidence downgraded by 1 level because 95% CI crosses 1 MID (2.15).

‡ For references see corresponding forest plot

Table30: Clinical evidence profile for corticosteroid versus dopamine D2 receptor antagonist for hyperemesis gravidarum

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid	Dopamine D2 receptor antagonist	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Reduction in mean number of vomiting episodes (Patient reported) (follow-up 2 weeks; measured with: Patient report; Better indicated by lower values)												
1 (Bondok 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20	20	-	SMD 1.37 lower (2.06 to 0.68 lower)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI: confidence interval; SMD: standardised mean difference
[1] Evidence downgraded by 1 level because 95% CI croses 1 MID for SMD (-0.50).

Table31: Clinical evidence profile for corticosteroid versus histamine H1-receptor antagonist for hyperemesis gravidarum

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid	Histamine H1-receptor antagonist	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Number of women with severe nausea - Prednisolone vs Promethazine (follow-up 7 days)												
1 (Ziaei 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/39 (56.4%)	27/39 (69.2%)	RR 0.81 (0.58 to 1.15)	132 fewer per 1000 (from 291 fewer to 104 more)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Vomiting frequency (Patient reported) - Prednisolone vs Promethazine (follow-up 7 days; measured with: Patient report; Better indicated by lower values)												
1 (Ziaei 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	39	39	-	corticosteroid median 3 (IQR 0 to 6), histamine H1-receptor antagonist median 3 (IQR 0 to 5), p=1.00	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid	Histamine H1-receptor antagonist	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Number of patients with complete or partial relief - Prednisolone vs Promethazine - Prednisolone vs Promethazine (follow-up 7 days)												
1 (Ziaei 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	20/39 (51.3%)	12/39 (30.8%)	RR 1.67 (0.95 to 2.92)	206 more per 1000 (from 15 fewer to 591 more)	⊕⊕OO LOW	CRITICAL
Symptomatic relief during pregnancy - Number of women with improvement of symptoms - Methylprednisolone vs Promethazine (follow-up 2 weeks)												
1 (Safari 1998)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	17/20 (85%)	18/20 (90%)	RR 0.94 (0.75 to 1.19)	54 fewer per 1000 (from 225 fewer to 171 more)	⊕⊕OO LOW	CRITICAL
Adverse event requiring hospitalisation - Prednisolone vs Promethazine - Abdominal pain (follow-up 7 days)												
1 (Safari 1998)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	0/40 (0%)	4/40 (10%)	Peto OR 0.13 (0.02 to 0.92)	87 fewer per 1000 (from 8 fewer to 98 fewer)	⊕⊕OO LOW	IMPORTANT
Adverse event requiring hospitalisation - Prednisolone vs Promethazine - Drowsiness (follow-up 7 days)												
1 (Ziaei 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/40 (0%)	6/40 (15%)	Peto OR 0.12 (0.02 to 0.62)	132 fewer per 1000 (from 57 fewer to 147 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse event requiring hospitalisation (non-event) - Methylprednisolone vs Promethazine (follow-up 2 weeks)												
1 (Ziaei 2004)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/20 (0%)	0/20 (0%)	RD 0 (-0.09 to 0.09)	-	⊕OOO VERY LOW	IMPORTANT
Number of days in hospital for treatment of nausea and vomiting - Methylprednisolone vs Promethazine (follow-up 2 weeks)												
1 (Safari 1998)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/17 (0%)	5/17 (29.4%)	Peto OR 0.10 (0.02 to 0.67)	265 fewer per 1000 (from 97 fewer to 288 fewer)	⊕⊕⊕O MODERATE	IMPORTANT

Abbreviations: CI: confidence interval; IQR: interquartile range; OR: odds ratio; RR: risk ratio

[1] Downgraded 1 level due to unclear risk of selection performance, detection, reporting and other biases.
[2] Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (0.8).
[3] Evidence downgraded by 2 levels due to very serious imprecision surrounding small sample size
[4] Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (1.25).
[5] Downgraded by 1 level due to high risk of other bias, and unclear risk of detection and reporting bias.

Table32: Clinical evidence profile for intravenous fluids vs intravenous fluids for hyperemesis gravidarum

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intravenous fluids	Intravenous fluids	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Nausea intensity (VNRS score) (measured with: Visual Numerical Rating Scale Score ; range of scores: 1-10; Better indicated by lower values)												
1 (Tan 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	102	101	-	dextrose saline median 2 (IQR 1 to 4), normal saline median 2 (IQR 2 to 4), p=0.39	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic relief during pregnancy - Vomiting frequency (Patient reported) (measured with: Patient report; Better indicated by lower values)												
1 (Tan 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	102	101	-	dextrose saline median 0 (IQR 0 to 2), normal saline median 0 (IQR 0 to 2), p=0.66	⊕⊕⊕O MODERATE	CRITICAL
Women's experience and satisfaction of care during or at end of pregnancy - Dextrose saline vs Normal saline (measured with: Visual Numerical Rating Scale ; range of scores: 1-10; Better indicated by higher values)												
1 (Tan 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	102	101	-	MD 0.1 higher (0.33 lower to 0.53 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

Abbreviations: CI: confidence interval; IQR: interquartile range; MD: mean difference; VNRS: visual numerical rating scale
[1] Evidence downgraded by 1 level due to serious imprecision surrounding small sample size.
[2] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 0.75.

Table33: Clinical evidence profile for intravenous fluids in one setting vs intravenous fluids in another setting for hyperemesis gravidarum

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intravenous fluids in one setting	Intravenous fluids in another setting	Relative (95% CI)	Absolute		
Symptomatic relief during pregnancy - Overall relief (PUQE score) - Maternity Assessment Unit vs Antenatal Ward (measured with: Pregnancy Unique Quantification of Emesis/Nausea Index Score; range of scores: 3-15; Better indicated by lower values)												
1 (McParlin 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13	18	-	MD 0.7 higher (1.77 lower to 3.17 higher)	⊕OOO VERY LOW	CRITICAL
Fetal death - Spontaneous abortions - Maternity Assessment Unit vs Antenatal Ward												
1 (McParlin 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/27 (7.4%)	2/26 (7.7%)	RR 0.96 (0.15 to 6.34)	3 fewer per 1000 (from 65 fewer to 411 more)	⊕OOO VERY LOW	CRITICAL
Fetal death - Termination of pregnancy - Maternity Assessment Unit vs Antenatal Ward												
1 (McParlin 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/27 (3.7%)	0/26 (0%)	Peto OR 7.12 (0.14 to 359.1)	-	⊕OOO VERY LOW	CRITICAL
Number of days in hospital for treatment of nausea and vomiting - Inpatient care vs Day care (Better indicated by lower values)												
1 (McCarthy 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	56	42	-	inpatient care median 2 (IQR 1 to 4), day care median 0 (IQR 0 to 2), p=0.001	⊕⊕OO LOW	IMPORTANT
Women's experience and satisfaction of care during or at end of pregnancy - Inpatient care vs Day care (measured with: Client Satisfaction Questionnaire; range of scores: 0-100; Better indicated by higher values)												
1 (McCarthy 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	56	42	-	inpatient care median 67 (IQR 57 to 69), day care median 63 (IQR 58 to 71), p=0.70	⊕⊕OO LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intravenous fluids in one setting	Intravenous fluids in another setting	Relative (95% CI)	Absolute		
Women's experience and satisfaction of care during or at end of pregnancy - Maternity Assessment Unit vs Antenatal Ward (measured with: Short Satisfaction Survey; Better indicated by lower values)												
1 (McParlin 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	12	17	-	MD 0.60 lower (3.51 lower to 2.31 higher)	⊕⊕OO LOW	IMPORTANT
Small for gestational age - Maternity Assessment Unit vs Antenatal Ward												
1 (McParlin 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/27 (11.1%)	3/26 (11.5%)	RR 0.96 (0.21 to 4.35)	5 fewer per 1000 (from 91 fewer to 387 more)	⊕OOO VERY LOW	IMPORTANT

Abbreviations: CI: confidence interval; IQR: interquartile range; MD: mean difference; OR: odds ratio; PUQE: pregnancy unique quantification of emesis and nausea; RR: risk ratio

[1] Downgraded by 1 level due to high risk of other bias and unclear risk of selection and detection bias.

[2] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 1.15. Evidence downgraded by 2 levels because 95% CI crosses 2 MIDs (-1.15 and 1.15).

[3] Evidence downgraded 2 levels as 95% CI crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).

[4] Evidence downgraded by 2 levels due to very serious imprecision surrounding small sample size.

[5] MID for this outcome, calculated as 0.5 times the SD of the control arm at baseline, is +/- 2.35. Evidence downgraded by 1 level because 95% CI crosses 1 MID (-2.35).

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What interventions are effective in treating nausea and vomiting during pregnancy?

A single economic search was undertaken for all topics included in the scope of this guideline. One economic study was identified which was applicable to this review question. See supplementary material 2 for details.

Appendix H – Economic evidence tables

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

Table34: Economic evidence tables for inpatient versus day care treatment for women with nausea and vomiting

Study details	Treatment strategies	Study population, design and data sources	Results	Comments	Study details
Author & year: Murphy 2015 **Country:** Ireland **Type of economic analysis:** Cost Utility Analysis (CUA) **Source of funding:** eported.	**Intervention in detail** The intervention was day care management of nausea and vomiting during pregnancy (NVP). Treatment took place in the day ward (Monday-Friday, 8pm-4pm) or in the emergency room in Cork University Maternity Hospital (CUMH). Patients randomised to day care received 2 L of fluid (normal saline) intravenously over 5 hours. Antiemetics were administered when patients failed to	**Population characteristics:** Women experiencing NVP. **Modelling approach:** Economic evaluation alongside an RCT. The economic analysis employs a Markov model which consists of three health states: Healthy Discharged, Moderate and Severe NVP over 52 days. **Source of base-line and effectiveness data:**	**Mean cost per patient** Intervention: €609 Control: €2135 Difference: -€1526 **Mean QALYs per patient:** Intervention: 9.49 QALYs Control: 9.42 QALYs Difference: 0.070 QALYs Day care *dominates* inpatient management **Subgroup analysis:**	**Perspective:** Healthcare payer and patient perspective (healthcare payer reported separately) **Currency:** Euros (€) (EUR) **Cost year:** Not stated **Time horizon:** 52 days – Appropriate for this type of study **Discounting:**	**Author & year:** Murphy et al. 2015 **Country:** Ireland **Type of economic analysis:** Cost Utility Analysis (CUA) **Source of funding:** eported.

Study details	Treatment strategies	Study population, design and data sources	Results	Comments	Study details
	respond to intravenous fluid administration and administered using a standardised, pretyped stepwise drug ProForma **Comparator in detai:** The comparator were those assigned to inpatient management for NVP. nts randomised to inpatient admission received 1 L of fluid (normal saline) administered over 3 h. The patient then received 1 L of fluid (normal saline) intravenously every 6 h until able to tolerate oral fluids. Similar to day care, antiemetics were administered in an identical stepwise approach.	RCT (n = 98) between day care and inpatient management using computer-generated randomisation. Initial evaluation was identical, after which patients were consented and randomised to either initial treatment with day care or in patient management. The clinical trial (McCarthy 2014) was the source of base-line and effectiveness data. The transition probabilities between each cycle are also informed by the attached clinical trial. **Source of cost data:** Whilst costs were assessed from both a health care provider and patient perspective, only health care provider costs are relevant for this review	Not conducted. **Sensitivity analysis:** Not reported **Probabilistic sensitivity analysis:** babilistic sensitivity analysis was reported. The authors report all input parameters were assigned probability distributions (Gamma distribution on costs and a Beta distribution on utilities and transition probabilities). This follows standard convention. The mean values of these distributions are used to calculate the ICER. Whilst the ICER is not reported, the study includes a scatterplot of 10,000 ICER's and a cost effectiveness acceptability curve (CEAC). Against a ceiling threshold of €45,000 per QALY, the probability that day	N/A as this study was over a time period of less than 12 months **Applicability:** This study is deemed as *directly applicable* for the following reasons: the study population is in accordance with that specified in the protocol; the interventions are appropriate to the review question; the study was conducted in a system sufficiently similar to the UK (Ireland; a healthcare payers perspective was undertaken for costs and the study utilises QALYs as a measure of effectiveness. **Limitations:** The overall methodological quality of the study can be classified as having *minor limitations*.	

Study details	Treatment strategies	Study population, design and data sources	Results	Comments	Study details
		(See NICE guidelines manual). Health care costs included the cost of treatment as a day care patient and inpatient. The source of cost data is not explicitly stated but appears to have been obtained from the 'Irish Case mix Programme' in 2011. Resource use was calculated from the attached clinical RCT **Source of QoL data:** D data was extracted directly from the original RCT for the Severe NVP state. Owing to coding errors in the original trial, SF-36 QoL data used for the remaining health states. The source of these values were based on values derived from a US population (Attard et al., 2002). These results were converted	care is cost effective is 73% whereas the probability that inpatient management is cost effective is 23%.	Firstly, despite using an RCT as a vehicle for an economic evaluation, it is not clear from where the unit cost data is derived from. Secondly, utilities for the Moderate and Severe NVP health states are derived from non-preference based health-quality of life measurements. Whilst the collection of primary utility data is preferable, mapping is standard practice and is justified by the authors as being due to data constraints. It is unlikely that these would impact on the conclusions made about cost effectiveness. **Other comments:** Whilst a probabilistic sensitivity analysis is reported, it is not clear where cost savings occur in day care management – though it is clear that they are	

Study details	Treatment strategies	Study population, design and data sources	Results	Comments	Study details
		into utilities using an algorithm by Ara & Brazier (2008), using a cross walk value set from the EQ-5D instrument.		the driver for day care management being cost effective.	

Appendix I – Health economic evidence profiles

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

Table35: Economic evidence profiles for inpatient versus day care treatment for women with nausea and vomiting

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects		Uncertainty	Applicability and limitations
Murphy 2015	Women experiencing NVP.	Day care vs. inpatient management of nausea and committing of pregnancy (NVP)						The study included a probabilistic sensitivity analysis with 10,000 simulations. The results are displayed on a cost effectiveness acceptability curve, showing that at a ceiling threshold of €45,000 per QALY, day care management is cost effective at 73% while the probability that inpatient management is cost effective is 23%. A deterministic sensitivity analysis was not reported.	The study was deemed *directly applicable* to the UK because the study population is in accordance with that specified in the protocol and the Irish healthcare system is sufficiently similar to the NHS in England and Wales. This study is classified as having *minor limitations*. The source of cost data is not clear, nor is an explanation explicit as to what drives the cost reduction of day care management.
		Day-care	€609	9.49 QALYs					
		Inpatient	€2135	9.42 QALYs	€1526	0.07 QALYs			

Appendix J – Health economic analysis

Economic analysis for review question: What interventions are effective in treating nausea and vomiting during pregnancy?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: What interventions are effective in treating nausea and vomiting during pregnancy?

Table 36:Clinical studies

Study	Reason for exclusion
Adibah, I; Khursiah, D; A Amir, I; NM, Zaki;, Fluid therapy in the treatment of hyperemesis gravidarum: normal saline or ringer's lactate, does it really matter? , The Malaysian Journal of Medical Sciences, 15, 201, 2008	Study design does not meet protocol eligibility criteria - conference abstract.
Aga-Miri, Z, Hosseini, N, Ramazanadeh, F, Hagollah, F, Vijeh, M, Effect of acupressure on the frequency and severity of nausea in pregnancy, J Payesh, 7, 370-4, 2008	Non-English language article.
Aghadam, S. K. Z., Mahfoozi, B., Evaluation of the effects of acupressure by sea band on nausea and vomiting of pregnancy, Iranian journal of obstetrics, gynecology and infertility, 13, 39 44, 2010	Non-English language publication.
Aleyasin, A., Saffarieh, E., Torkamandi, H., Hanafi, S., Sadeghi, F., Mahdavi, A., Bahmaei, F., Javadi, M., Comparison of Efficacy of Granisetron and Promethazine in Control of Hyperemesis Gravidarum, Journal of Obstetrics and Gynecology of India, 66, 409-414, 2016	Study comparisons do not meet protocol eligibility criteria - 5-HT3 receptor antagonis (Granisetron) versus H1 receptor-blocking agent (promethazine).
Alhajri, L., AlFalasi, M., Abdelrahim, M., AlKaabi, R., The efficacy of ginger for pregnancy-induced nausea and vomiting: A systematic review, Journal of Natural Remedies, 17, 48-56, 2017	Systematic review including eligible and non-eligible comparisons - references checked, no additional evidence identified.
Babaei, A. H., Foghaha, M. H., A randomized comparison of vitamin B6 and dimenhydrinate in the treatment of nausea and vomiting in early pregnancy, Iranian Journal of Nursing and Midwifery ResearchIran J Nurs Midwifery Res, 19, 199-202, 2014	Study comparison does not meet protocol eligibility criteria - antihistamine/anticholinergic (dimenhydrinate) versus pyridoxine (vitamin B6).
Basirat, Z., Barat, S., Moghadamnia, A. A., Comparing the effects of prednisolone and promethazine in the treatment of hyperemesis gravidarum: a double-blind, randomized clinical trial, Feyz journal of kashan university of medical sciences, 16, 414 419, 2012	Full text article is not available in English.
Bergamo, T. R., Latorraca, C. O. C., Pachito, D. V., Martimbianco, A. L. C., Riera, R., Findings and methodological quality of systematic reviews focusing on acupuncture for pregnancy-related acute conditions, Acupuncture in MedicineAcupunct Med, 36, 146-152, 2018	Systematic review of systematic reviews - references checked, no additional evidence identified.
Biswas, S. C., Dey, R., Kamliya, G. S., Bal, R., Hazra, A., Tripathi, S. K., A single-masked, randomized, controlled trial of ginger extract in the treatment of nausea and vomiting of pregnancy, Journal international medical sciences academy, 24, 167-169, 2011	Study comparison does not meet the protocol eligibility criteria - dietary supplement vs pharmacological intervention.

Study	Reason for exclusion
Boelig, R. C., Barton, S. J., Saccone, G., Kelly, A. J., Edwards, S. J., Berghella, V., Interventions for treating hyperemesis gravidarum, Cochrane Database of Systematic Reviews, 2016, CD010607, 2016	Cochrane review - 3 additional relevant studies were identified and included in our review.
Boelig, R. C., Barton, S. J., Saccone, G., Kelly, A. J., Edwards, S. J., Berghella, V., Interventions for treating hyperemesis gravidarum: A cochrane systematic review and meta-analysis, Journal of Maternal-Fetal and Neonatal Medicine, 31, 2492-2505, 2017	Journal article to Boelig (2016) Cochrane review - no additional evidence.
Bryer, E., A literature review of the effectiveness of ginger in alleviating mild-to-moderate nausea and vomiting of pregnancy, Journal of midwifery & women's health, 50, e1 e3, 2005	A review paper of 4 RCTs. All references checked and added to this review if relevant.
Buchberger, B., Krabbe, L., Evaluation of outpatient acupuncture for relief of pregnancy-related conditions, International Journal of Gynecology and Obstetrics, 141, 151-158, 2018	Systematic review of systematic reviews and RCTs for different pregnancy conditions - references checked, no additional evidence identified.
Campbell, K., Rowe, H., Azzam, H., Lane, C. A., The Management of Nausea and Vomiting of Pregnancy, Journal of Obstetrics and Gynaecology Canada, 38, 1127-1137, 2016	Clinical practice guideline - references checked, no additional relevant evidence.
Can Gurkan, O., Arslan, H., Effect of acupressure on nausea and vomiting during pregnancy, Complementary therapies in clinical practice, 14, 46-52, 2008	Insufficient data available for analysis.
Carstairs, S. D., Ondansetron Use in Pregnancy and Birth Defects: A Systematic Review, Obstetrics & GynecologyObstet Gynecol, 127, 878-83, 2016	Systematic review of registry data, case-controls and cohort studies (RCT data available for ondansetron). References checked, no additional evidence identified.
Chin, J. W. S., Gregor, S., Persaud, N., Re-analysis of safety data supporting doxylamine use for nausea and vomiting of pregnancy, American journal of perinatology, 31, 701-710, 2014	Study design does not meet protocol eligibility criteria - re-analysis of meta-analysis including case-control and cohort studies of different antihistamines for congenital malformations.
Chittumma,P., Kaewkiattikun,K., Wiriyasiriwach,B., Comparison of the effectiveness of ginger and vitamin B6 for treatment of nausea and vomiting in early pregnancy: A randomized double-blind controlled trial, Journal of the Medical Association of Thailand, 90, 15-20, 2007	Duplicate
Chittumma,P., Kaewkiattikun,K., Wiriyasiriwach,B., Comparison of the effectiveness of ginger and vitamin B6 for treatment of nausea and vomiting in early pregnancy: A randomized double-blind controlled trial, Journal of the Medical Association of Thailand, 90, 15-20, 2007	Study comparison does not meet protocol eligibility criteria - dietary supplement versus pharmacological intervention.
Collins, K. L., Wilson, M., Vincent, E. C., Safranek, S., How safe and effective is ondansetron for nausea and vomiting in	A review paper of 3 RCTs. All references checked and added to this review if relevant.

Study	Reason for exclusion
pregnancy?, Journal of Family Practice, 68, E12-E14, 2019	
Crawford-Faucher, A., Which drug is more effective for treating hyperemesis gravidarum?, American family physician, 83, 842, 2011	Study design does not meet protocol eligibility criteria - commentary.
Cunningham, K., Odansetron compared with doxylamine and pyridoxine for treatment of nausea in pregnancy: A randomized controlled trial, Obstetrics and gynecology, 125, 490-491, 2015	Study design does not meet protocol eligibility criteria - letter to the Editor.
Dante, G., Bellei, G., Neri, I., Facchinetti, F., Herbal therapies in pregnancy: what works?, Current Opinion in Obstetrics & GynecologyCurr Opin Obstet Gynecol, 26, 83-91, 2014	Systematic review on various herbal treatments - references checked for relevant studies; no additional evidence identified.
Dante, G., Pedrielli, G., Annessi, E., Facchinetti, F., Herb remedies during pregnancy: A systematic review of controlled clinical trials, Journal of Maternal-Fetal and Neonatal Medicine, 26, 306-312, 2013	Systematic review of eligible and non-eligible study comparisons - references checked, no additional evidence identified. updated by Dante 2014.
de Aloysio, D., Penacchioni, P., Morning sickness control in early pregnancy by Neiguan point acupressure, Obstet GynecolObstetrics and gynecology, 80, 852-4, 1992	Study design does not meet protocol eligibility criteria - cross-over design.
Dennehy,C., Omega-3 fatty acids and ginger in maternal health: pharmacology, efficacy, and safety, Journal of Midwifery and Women's Health, 56, 584-590, 2011	Study design does not meet protocol eligibility criteria - narrative review.
Ding, M., Leach, M., Bradley, H., The effectiveness and safety of ginger for pregnancy-induced nausea and vomiting: A systematic review, Women and Birth, 26, e26-e30, 2013	Systematic review of eligible and non-eligible comparisons - references checked, no additional evidence identified.
Dror, D. K., Allen, L. H., Interventions with vitamins B6, B12 and C in pregnancy, Paediatric and Perinatal Epidemiology, 26 Suppl 1, 55-74, 2012	Systematic review - not specifically on nausea and vomiting during pregnancy. References checked, no additional evidence identified.
Duggar, CR, Carlan, SJ, The efficacy of methylprednisolone in the treatment of hyperemesis gravidarum: a randomized double-blind controlled study [abstract]. , Obstetrics & Gynecology, 97, 45S, 2001	Study design does not meet protocol eligibility criteria - conference abstract.
Dundee, J. W., Sourial, F. B., Ghaly, R. G., Bell, P. F., P6 acupressure reduces morning sickness, J R Soc MedJournal of the Royal Society of Medicine, 81, 456-7, 1988	Study outcomes not presented in a useable format.
El-Deeb, A. M., Ahmady, M. S., Effect of acupuncture on nausea and/or vomiting during and after cesarean section in comparison with ondansetron, Journal of anesthesia, 25, 698-703, 2011	Study does not meet protocol eligibility criteria - interventions for post-operative nausea and vomiting.
Enblom, A., Johnsson, A., Type and frequency of side effects during PC6 acupuncture: observations from therapists and patients	Study population does not meet protocol eligibility criteria - patients with radiotherapy-induced nausea versus healthy participants.

Study	Reason for exclusion
participating in clinical efficacy trials of acupuncture, Acupuncture in medicine : journal of the British Medical Acupuncture Society, 35, 421-429, 2017	
Ensiyeh, J., Sakineh, M. A. C., Comparing ginger and vitamin B6 for the treatment of nausea and vomiting in pregnancy: a randomised controlled trial, Midwifery, 25, 649-653, 2009	Study comparison does not meet protocol eligibility criteria - dietary supplement versus pharmacological intervention.
Ensiyeh, J., Sakineh, M. A., Zingiber officinale (ginger) might be better than vitamin B<inf>6</inf> for treating nausea in pregnancy, Focus on Alternative and Complementary Therapies, 15, 121, 2010	Study comparison does not meet protocol eligibility criteria - dietary supplement versus pharmacological intervention.
Ernst, E., Lee, M. S., Choi, T. Y., Acupuncture in obstetrics and gynecology: An overview of systematic reviews, American Journal of Chinese Medicine, 39, 423-431, 2011	Study design does not meet protocol eligibility criteria - review of reviews. References checked, no additional evidence identified.
Ernst, E., Matthews, A., What works for morning sickness?, Focus on Alternative & Complementary Therapies, 16, 51-52, 2011	Study design does not meet protocol eligibility criteria - commentary on Cochrane Review (Matthews 2010).
Etwel, F., Faught, L. H., Rieder, M. J., Koren, G., The Risk of Adverse Pregnancy Outcome After First Trimester Exposure to H1 Antihistamines: A Systematic Review and Meta-Analysis, Drug SafetyDrug Saf, 40, 121-132, 2017	Systematic review of cohort and case-control studies. References checked, no additional evidence identified.
Ezzo, J., Streitberger, K., Schneider, A., Cochrane systematic reviews examine P6 acupuncture-point stimulation for nausea and vomiting, Journal of Alternative and Complementary Medicine, 12, 489-495, 2006	Narrative review.
Farazmand, T., Khadem, N., Comparison of the effect of methylprednisolone and promethazine in the treatment of hyperemesis gravidarum (2001-2002), International Journal of Gynecology and Obstetrics, 2), S523, 2009	Study design does not meet protocol eligibility criteria - conference abstract.
Festin, M., Nausea and Vomiting in Early Pregnancy, American Family Physician, 92, 516-7, 2015	Study design does not meet protocol eligibility criteria - chapter from handbook.
Festin, M., Nausea and vomiting in early pregnancy, Clinical EvidenceClin Evid (Online), 19, 19, 2014	Systematic review - references checked, one additional relevant study was identified and included in our review.
Firouzbakht, M., Nikpour, M., Jamali, B., Omidvar, S., Comparison of ginger with vitamin B6 in relieving nausea and vomiting during pregnancy, AyuAyu, 35, 289-93, 2014	Serious risk surrounding quality of data.
Fischer-Rasmussen, W, Kjaer, SK, Dahl, C, Asping, U, Ginger treatment of hyperemesis gravidarum., Eur J Obstet Gynecol Reprod Biol, 38, 19-24, 1991	Study design does not meet protocol eligibility criteria - cross-over trial.
Fletcher, S. J., Waterman, H., Nelson, L., Carter, L. A., Dwyer, L., Roberts, C., Torgerson, D., Kitchener, H., Holistic assessment of women	Study comparison does not meet protocol eligibility criteria - all women received IV

Study	Reason for exclusion
with hyperemesis gravidarum: A randomised controlled trial, International Journal of Nursing Studies, 52, 1669-1677, 2015	rehydration and antiemetic therapy (not specified).
Forouhari, S, Ghaemi, SZ, Roshandel, A, Moshfegh, Z, Rostambeigy, P, Mohaghegh, Z, The effect of acupressure on nausea and vomiting during pregnancy. , Researcher, 6, 27-34, 2014	Study does not specify how many women in each treatment group.
Gawande, S., Vaidya, M., Tadke, R., Kirpekar, V., Bhave, S., Progressive muscle relaxation in hyperemesis gravidarum, Journal of SAFOG, 3, 28-32, 2011	Study comparison does not meet protocol eligibility criteria - pharmacological intervention muscle relaxation versus pharmacological intervention alone.
Ghahiri, A. A., Abdi, F., Mastoo, R., Ghasemi, M., The effect of Ondansetron and Metoclopramide in nausea and vomiting of pregnancy, Journal of isfahan medical school, 29, 2011	Non-English language publication.
Giacosa, A., Morazzoni, P., Bombardelli, E., Riva, A., Bianchi Porro, G., Rondanelli, M., Can nausea and vomiting be treated with ginger extract?, European Review for Medical & Pharmacological SciencesEur Rev Med Pharmacol Sci, 19, 1291-6, 2015	Narrative review
Gilbey, A., Ernst, E., Tani, K., A systematic review of reviews of systematic reviews of acupuncture, Focus on Alternative and Complementary Therapies, 18, 8-18, 2013	Systematic review of reviews of reviews (not specifically nausea and vomiting during pregnancy). References checked, no additional studies were identified
Gilboa, S. M., Ailes, E. C., Rai, R. P., Anderson, J. A., Honein, M. A., Antihistamines and birth defects: A systematic review of the literature, Expert Opinion on Drug Safety, 13, 1667-1698, 2014	Systematic review of cohort and case-control studies, not specifically for nausea and vomiting.References checked, no additional studies were identified.
Gill, S. K., Einarson, A., The safety of drugs for the treatment of nausea and vomiting of pregnancy, Expert Opinion on Drug Safety, 6, 685-94, 2007	Narrative review
Gill,S.K., O'Brien,L., Koren,G., The safety of histamine 2 (H2) blockers in pregnancy: a meta-analysis, Digestive diseases and sciences, 54, 1835-1838, 2009	Study does not meet protocol eligibility criteria - H2 blockers.
Haji Seid Javadi, E., Salehi, F., Mashrabi, O., Comparing the effectiveness of vitamin b6 and ginger in treatment of pregnancy-induced nausea and vomiting, Obstetrics & Gynecology InternationalObstet Gynecol Int, 2013, 927834, 2013	Study comparison does not meet protocol eligibility criteria - dietary supplement versus pharmacological intervention.
Hall, Helen G., McKenna, Lisa G., Griffiths, Debra L., Complementary medicine for nausea and vomiting in pregnancy: a review of the evidence, Evidence Based Midwifery, 9, 84-88, 2011	Review - references checked; no additional evidence identified.
Hansen, L. B., Saseen, J. J., Teal, S. B., Levonorgestrel-only dosing strategies for emergency contraception,	Duplicate

Study	Reason for exclusion
Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy, 27, 278-84, 2007	
He, X. L., Zhong, G., He, Y., Clinical observation on treatment of hyperemesis gravidarum by integrative Chinese and Western medicine and its influence on serum motilin, Zhongguo zhong xi yi jie he za zhi zhongguo zhongxiyi jiehe zazhi = chinese journal of integrated traditional and western medicine, 29, 872 874, 2009	Non-English language publication.
Helmreich, R. J., Shiao, S. Y. P. K., Dune, L. S., Meta-analysis of Acustimulation Effects on Nausea and Vomiting in Pregnant Women, Explore: The Journal of Science and Healing, 2, 412-421, 2006	Systematic review including RCTs and crossover studies. References checked, no additional studies were identified
Holmgren, C., Aagaard-Tillery, K. M., Silver, R. M., Porter, T. F., Varner, M., Hyperemesis in pregnancy: An evaluation of treatment strategies with maternal and neonatal outcomes, American Journal of Obstetrics and Gynecology, 198, 56, 2008	Study does not meet protocol eligibility criteria - unclear which medications administered.
Hosseinkhani, N, Sadeghi, T, The effect of ginger on pregnancy induced nausea during first trimester. , Iran J Nurs, 22, 75-83, 2009	Non-English language article.
Hsu, E, Pei, V, Shofer, FS, A prospective randomized controlled trial of acupressure vs shamfor pregnancy-related nausea and vomiting in the emergency department. , Acad Emerg Med, 10, 437, 2003	Study design does not meet protocol eligibility criteria - conference abstract.
Hsu, Y. Y., Hung, H. Y., Chang, S. C., Chang, Y. J., O'Donnell, A., McParlin, C., Robson, S. C., Beyer, F., Moloney, E., Bryant, A., Bradley, J., Muirhead, C., Nelson-Piercy, C., Newbury-Birch, D., Norman, J., Simpson, E., Swallow, B., Yates, L., Vale, L., Early oral intake and gastrointestinal function after cesarean delivery: a systematic review and meta-analysis Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review and economic assessment, Obstetrics and Gynecology, 121, 1327-1334, 2013	Study does not answer the review question.
Hu, Y., Amoah, A. N., Zhang, H., Fu, R., Qiu, Y., Cao, Y., Sun, Y., Chen, H., Liu, Y., Lyu, Q., Effect of ginger in the treatment of nausea and vomiting compared with vitamin B6 and placebo during pregnancy: a meta-analysis, Journal of Maternal-Fetal & Neonatal MedicineJ Matern Fetal Neonatal Med, 1-10, 2020	A review paper of 13 RCTs. All references checked and added to this review if relevant.
Hyde, E., Acupressure therapy for morning sickness. A controlled clinical trial, J Nurse MidwiferyJournal of nurse-midwifery, 34, 171-8, 1989	Study design does not meet protocol eligibility criteria - cross-over design.
Hyde, E., Acupressure therpy for morning sickness: A controlled clinical trial. , J Nurse	Duplicate

Study	Reason for exclusion
MidwiferyJournal of nurse-midwifery, 34, 171-8, 1989	
Jackson, E. A., Is ginger root effective for decreasing the severity of nausea and vomiting in early pregnancy?, Journal of Family Practice, 50, 720 , 2001	Recommendations for clinical practice based on Vutyavanich 2001.
Jamigorn, M., Phupong, V., Acupressure and vitamin B6 to relieve nausea and vomiting in pregnancy: A randomized study, Archives of gynecology and obstetrics, 276, 245-249, 2007	Study comparison does not meet protocol eligibility criteria - complementary therapy versus pharmacological intervention.
Jenett-Siems, K., With ginger against nausea and vomiting: Asian root helps pregnant women better than placebo, Deutsche Apotheker Zeitung, 155, 2015	Non-English language publication.
Jiang, N. Q., The application of Sanyinjiao (SP 6) for acupuncture treatment of gynecological and obstetrical disorders, Journal of Traditional Chinese MedicineJ Tradit Chin Med, 30, 51-2, 2010	Study design does not meet protocol eligibility criteria - case report.
Jo, J., Lee, S. H., Lee, J. M., Lee, H., Kwack, S. J., Kim, D. I., Use and safety of Korean herbal medicine during pregnancy: A Korean medicine literature review, European Journal of Integrative Medicine, 8, 4-11, 2016	Systematic review of different herbal medicines for various conditions in pregnancy. References checked, no additional studies were identified
Kang,H.S., Jeong,D., Kim,D.I., Lee,M.S., The use of acupuncture for managing gynaecologic conditions: An overview of systematic reviews, Maturitas, 68, 346-354, 2011	Systematic review - not specifically pregnant women with nausea and vomiting. References checked, no additional studies were identified
Khavandizadeh, AS, Mahfouzi, B, Evaluation of the effects of acupressure by sea band on nausea and vomiting in pregnancy. , Iranian Journal of Obstetrics, Gynecology and Infertility., 13, 39-44, 2010	Not written in English
Khorasani, F., Aryan, H., Sobhi, A., Aryan, R., Abavi-Sani, A., Ghazanfarpour, M., Saeidi, M., Rajab Dizavandi, F., A systematic review of the efficacy of alternative medicine in the treatment of nausea and vomiting of pregnancy, Journal of Obstetrics and Gynaecology, 40, 10-19, 2020	A review paper of 11 RCTs. All references checked and added to this review if relevant.
Khresheh, R., How women manage nausea and vomiting during pregnancy: A Jordanian study, Midwifery, 27, 42-45, 2011	Study design does not meet protocol eligibility criteria - Cross-sectional study.
Klauser, C. K., Fox, N. S., Istwan, N., Rhea, D., Rebarber, A., Desch, C., Palmer, B., Saltzman, D., Treatment of severe nausea and vomiting of pregnancy with subcutaneous medications, American journal of perinatology, 28, 715-721, 2011	Study design does not meet protocol eligibility criteria - RCT data available for metoclopramide and ondansetron.
Koot, M. H., Boelig, R. C., van't Hooft, J., Limpens, J., Roseboom, T. J., Painter, R. C., Grooten, I. J., Variation in hyperemesis gravidarum definition and outcome reporting in randomised clinical trials: a systematic review,	Study outcomes do not meet protocol eligibility criteria - overview of definitions and outcomes, but results not reported. References checked.

Study	Reason for exclusion
BJOG: An International Journal of Obstetrics and Gynaecology, 125, 1514-1521, 2018	
Koren, G., Clark, S., Hankins, G. D., Caritis, S. N., Umans, J. G., Miodovnik, M., Mattison, D. R., Matok, I., Demonstration of early efficacy results of the delayed-release combination of doxylamine-pyridoxine for the treatment of nausea and vomiting of pregnancy, BMC Pregnancy & ChildbirthBMC Pregnancy Childbirth, 16, 371, 2016	Secondary analysis to Koren (2010); comparisons between different timepoints; no additional evidence.
Koren, G., Hankins, G. D., Clark, S., Caritis, S. N., Miodovnik, M., Umans, J. G., Mattison, D. R., Effectiveness of doxylamine-pyridoxine for morning sickness, American Journal of Obstetrics & GynecologyAm J Obstet Gynecol, 214, 664-6, 2016	Study design does not meet protocol eligibility criteria - research letter.
Lamondy, A. M., I.V. rounds. Managing hyperemesis gravidarum, Nursing, 37, 66-68, 2007	Narrative review.
Lavecchia, M., Chari, R., Campbell, S., Ross, S., Ondansetron in Pregnancy and the Risk of Congenital Malformations: A Systematic Review, Journal of Obstetrics and Gynaecology Canada, 40, 910-918, 2018	Systematic review - case-control, cohort and case series studies included. References checked, no additional studies were identified
Lee, E. J., Frazier, S. K., The efficacy of acupressure for symptom management: A systematic review, Journal of pain and symptom management, 42, 589-603, 2011	Systematic review - References checked, no additional studies were identified
London, V., Grube, S., Sherer, D. M., Abulafia, O., Hyperemesis gravidarum: A review of recent literature, Pharmacology, 100, 161-171, 2017	Narrative review.
Maltepe, C., Koren, G., Preemptive treatment of nausea and vomiting of pregnancy: results of a randomized controlled trial, Obstetrics & Gynecology InternationalObstet Gynecol Int, 2013, 809787, 2013	Study does not meet protocol eligibility criteria - compares pre-emptive Diclectin versus treatment with Diclectin.
Mansour, G. M., Nashaat, E. H., Helicobacter pylori and hyperemesis gravidarum.[Erratum appears in Int J Gynaecol Obstet. 2009 Nov;107(2):177], International Journal of Gynaecology & ObstetricsInt J Gynaecol Obstet, 106, 63-4, 2009	Study does not meet protocol eligibility criteria - brief communication; women with versus women without hyperemesis gravidarum.
Mao, Z. N., Liang, C. E., Observation on therapeutic effect of acupuncture on hyperemesis gravidarum, Zhongguo zhen jiu [Chinese acupuncture & moxibustion], 29, 973 976, 2009	Non-English language publication.
Matok, I., Clark, S., Caritis, S., Miodovnik, M., Umans, J. G., Hankins, G., Mattison, D. R., Koren, G., Studying the antiemetic effect of vitamin B6 for morning sickness: pyridoxine and pyridoxal are prodrugs, Journal of clinical pharmacology, 54, 1429-1433, 2014	Study outcomes do not meet protocol eligibility criteria - plasma concentrations.

Study	Reason for exclusion
Matthews, A., Haas, D. M., O'Mathúna, D. P., Dowswell, T., Interventions for nausea and vomiting in early pregnancy, Cochrane Database of Systematic Reviews, 2015	Cochrane review - References checked, no additional studies were identified
Matthews,A., Dowswell,T., Haas,D.M., Doyle,M., O'Mathuna,D.P., Interventions for nausea and vomiting in early pregnancy, Sao Paulo Medical Journal, 129, 55-, 2011	Cochrane review - replaced by 2015 update.
McGuiness, BW, Taylor Binns, D, Debendox in pregnancy sickness. , Journal of the Royal College of General Practitioners, 21, 500-3, 1971	Study examines combination of pyridoxine hydrochloride, doxylamine succinate, and dicyclomine (anti-cholinergic). However, anti-cholinergics are not an intervention of interest.
McParlin, C., O'Donnell, A., Robson, S. C., Beyer, F., Moloney, E., Bryant, A., Bradley, J., Muirhead, C. R., Nelson-Piercy, C., Newbury-Birch, D., Norman, J., Shaw, C., Simpson, E., Swallow, B., Yates, L., Vale, L., Treatments for Hyperemesis Gravidarum and Nausea and Vomiting in Pregnancy: A Systematic Review, JAMAJama, 316, 1392-1401, 2016	Systematic review - References checked, no additional studies were identified
Moghadam, Z. K., Najfabady, M. T., Abedi, P., Haghighizadeh, M. H., Investigating the effect of gingerpill on the treatment of nausea and vomiting of pregnancy (NVP) in pregnancy women, International Journal of Pharmaceutical and Phytopharmacological Research, 9, 9-15, 2019	The trial is not randomised and there is only one intervention arm studied.
Moreau, C., Trussell, J., Results from pooled Phase III studies of ulipristal acetate for emergency contraception, Contraception, 86, 673-80, 2012	Duplicate
Naeimi Rad, M., Lamyian, M., Heshmat, R., Asghari Jaafarabadi, M., Yazdani , S., A Randomized Clinical Trial of the Efficacy of KID21 Point (Youmen) Acupressure on Nausea and Vomiting of Pregnancy, Iran Red Crescent Med J, 14, 697-701, 2012	Duplicate
Naeimi Rad, M., Lamyian, M., Heshmat, R., Jaafarabadi, MA., Yazdani, S., A randomized clinical trial of the efficacy of KID21 point (youmen) acupressure on nausea and vomiting of pregnancy. , Iran Red Crescent Med J, 14, 697-701, 2012	Duplicate
Narenji, F., Delavar, M., Rafiei, M., Comparison the effects of the ginger fresh root and vitamin B6 on the nausea and vomiting in pregnancy , Iranian journal of obstetrics, gynecology and infertility, 15, 39 43, 2012	Article is unavailable
Nazari, S., Nazari, S., Shayan, A., Shobeiri, F., Tabesh, R. A. N., Comparison of the effects of ondansetron, Vitamin b6 and ginger rhizome in nausea and vomiting of pregnancy: a randomized clinical trial, Iranian journal of	Article in Farsi

Study	Reason for exclusion
obstetrics, gynecology and infertility, 21, 29-35, 2018	
Nihr, Hsric, Diclectin (doxylamine succinate and pyridoxine hydrochloride) for the treatment of nausea and vomiting in pregnancy, 2016	NIHR evidence summary on diclectin (xonvea).
Norheim, A. J., Pedersen, E. J., Fonnebo, V., Berge, L., Acupressure treatment of morning sickness in pregnancy. A randomised, double-blind, placebo-controlled study, Scand J Prim Health CareScandinavian journal of primary health care, 19, 43-7, 2001	Number of participants in each arm is unclear and not mentioned in the article.
O'Brien, B., Relyea, M. J., Taerum, T., Efficacy of P6 acupressure in the treatment of nausea and vomiting during pregnancy, Am J Obstet GynecolAmerican journal of obstetrics and gynecology, 174, 708-15, 1996	Study outcomes not presented in a useable format.
O'Donnell, A., McParlin, C., Robson, S. C., Beyer, F., Moloney, E., Bryant, A., Bradley, J., Muirhead, C., Nelson-Piercy, C., Newbury-Birch, D., Norman, J., Simpson, E., Swallow, B., Yates, L., Vale, L., Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: A systematic review and economic assessment, Health Technology Assessment, 20, 2016	HTA - References checked, no additional studies were identified
Ostenfeld, A., Petersen, T. S., Futtrup, T. B., Andersen, J. T., Jensen, A. K., Westergaard, H. B., Pedersen, L. H., Lokkegaard, E. C. L., Validating the effect of Ondansetron and Mirtazapine In Treating hyperemesis gravidarum (VOMIT): protocol for a randomised placebo-controlled trial, BMJ Open, 10, e034712, 2020	RCT protocol. The trial will compare ondansetron, mirtazapine, and placebo.
Ozgoli, G., Saei Ghare Naz, M., Effects of Complementary Medicine on Nausea and Vomiting in Pregnancy: A Systematic Review, International journal of preventive medicine, 9, 75, 2018	Systematic review of eligible and non-eligible studies - References checked, no additional studies were identified
Pakniat, H., Memarzadeh, M. R., Azh, N., Mafi, M., Ranjkesh, F., Comparison of the effect of chamomile, Ginger and vitamin B6 on treatment of nausea and vomiting in pregnancy: a randomized clinical trial, Iranian journal of obstetrics, gynecology and infertility, 21, 47 54, 2018	Article in Farsi
Park, J., Sohn, Y., White, A. R., Lee, H., The safety of acupuncture during pregnancy: a systematic review, Acupuncture in MedicineAcupunct Med, 32, 257-66, 2014	A review paper focusing on benefits/harms of acupuncture during pregnancy. No specific focus on use for NVP/HG.
Parker, S. E., Van Bennekom, C., Anderka, M., Mitchell, A. A., National Birth Defects Prevention, Study, Ondansetron for Treatment of Nausea and Vomiting of Pregnancy and the Risk of Specific Birth Defects, Obstetrics & GynecologyObstet Gynecol, 132, 385-394, 2018	Study design does not meet protocol eligibility criteria - two case-control studies.

Study	Reason for exclusion
Pei, K., Xiao, B., Jing, X., Lu, S., Wei, L., Zhao, H., Weekly contraception with mifepristone, Contraception, 75, 40-44, 2007	Duplicate
Persaud, N., Meaney, C., El-Emam, K., Moineddin, R., Thorpe, K., Doxylamine-pyridoxine for nausea and vomiting of pregnancy randomized placebo controlled trial: Prespecified analyses and reanalysis, Plos one, 13 (1) (no pagination), 2018	Re-analysis of Koren (2010) and comparison of outcomes with other publications.
Pope, E., Maltepe, C., Koren, G., Comparing pyridoxine and doxylamine succinate-pyridoxine HCl for nausea and vomiting of pregnancy: a matched, controlled cohort study, Journal of clinical pharmacology, 55, 809 814, 2015	Study design does not meet protocol eligibility criteria - cohort study (RCT data available for this comparison).
Richardson, A. R., Maltz, F. N., Ulipristal Acetate: Review of the Efficacy and Safety of a Newly Approved Agent for Emergency Contraception, Clinical therapeutics, 34, 24-36, 2012	Duplicate
Roddison, Ruth, Charlesworth, Karen, Using acupuncture for the treatment of nausea and vomiting in pregnancy and hyperemesis gravidarum, MIDIRS Midwifery Digest, 28, 173-176, 2018	Study design does not meet protocol eligibility criteria - single treatment arm; no comparison.
Rukh, L., Nazar, H., Usmanghani, K., Efficacy of Gingocap as compared to pyridoxine in the treatment of nausea and vomiting during pregnancy, Pakistan Journal of Pharmaceutical Sciences, 29, 1937-1943, 2016	Study comparison does not meet protocol eligibility criteria - compares dietary supplements (ginger extract) versus pharmacological intervention (pyridoxine).
Salam, R. A., Zuberi, N. F., Bhutta, Z. A., Pyridoxine (vitamin B6) supplementation during pregnancy or labour for maternal and neonatal outcomes, Cochrane Database of Systematic Reviews, 2016 (3) (no pagination), 2015	Cochrane review - outcomes do not meet protocol eligibility criteria (mean birthweight; pre-eclampsia; apgar scores; breast milk production; dental decay; non-significant adverse events). References checked, no additional studies were identified
Sanu, O., Lamont, R. F., Hyperemesis gravidarum: pathogenesis and the use of antiemetic agents, Expert Opinion on Pharmacotherapy, 12, 737-48, 2011	Narrative/general review.
Sarkar, N. N., Emergency contraception spearheading despite hurdles and hindrance, International Medical Journal, 16, 211-216, 2009	Duplicate
Sarkar, N. N., Emergency contraception: A contraceptive intervention approaching target despite controversy and opposition, Journal of Public Health, 14, 164-173, 2006	Duplicate
Schuster, K., Bailey, L. B., Dimperio, D., Mahan, C. S., Morning sickness and vitamin B6 status of pregnant women, Hum Nutr Clin NutrHuman nutrition. Clinical nutrition, 39, 75-9, 1985	Article is unavailable
Shahraki, Z., Bonjar, Z. S. H., Forghani, F., Nakhai, R., Comparing neonatal outcome following the use of ondansetron versus vitamin	Study outcomes do not meet protocol eligibility criteria - mean gestational age, mean birth

Study	Reason for exclusion
B6 in pregnant females with morning sickness: A randomized clinical trial, Journal of comprehensive pediatrics, 7 (4) (no pagination), 2016	weight, mean height, mean head circumference; congential abnormalities).
Shen, J., Che, Y., Showell, E., Chen, K., Cheng, L., Interventions for emergency contraception, Cochrane Database of Systematic Reviews, 2017	Duplicate
Shin, H. S., Song, Y. A., Seo, S., Effect of Nei-Guan point (P6) acupressure on ketonuria levels, nausea and vomiting in women with hyperemesis gravidarum, Journal of advanced nursing, 59, 510-519, 2007	Study outcomes not reported in useable format - means reported but not standard deviations.
Shrim,A., Boskovic,R., Maltepe,C., Navios,Y., Garcia-Bournissen,F., Koren,G., Pregnancy outcome following use of large doses of vitamin B6 in the first trimester, Journal of Obstetrics and Gynaecology, 26, 749-751, 2006	Study design does not meet protocol eligibility criteria - observational study assessing B6 (RCT evidence available).
Smith, C. A., Cochrane, S., Does acupuncture have a place as an adjunct treatment during pregnancy? A review of randomized controlled trials and systematic reviews, Birth, 36, 246-253, 2009	Systematic review of acupuncture for various conditions in pregnancy - References checked, no additional studies were identified
Smith, C., Crowther, C., Willson, K., Hotham, N., McMillian, V., A randomized controlled trial of ginger to treat nausea and vomiting in pregnancy, Obstet GynecolObstetrics and gynecology, 103, 639-45, 2004	No comparator of interest- Dietary supplement (ginger) vs. Vitamin B6
Solt Kirca, A., Kanza Gul, D., Effects of Acupressure Applied to P6 Point on Nausea Vomiting in Pregnancy: A Double-Blind Randomized Controlled, Alternative Therapies in Health & MedicineAltern Ther Health Med, 28, 28, 2020	Full text unavailable
Sonkusare, S., Hyperemesis gravidarum: a review, Medical Journal of MalaysiaMed J Malaysia, 63, 272-6; quiz 277, 2008	Narrative review.
Sridharan, K., Sivaramakrishnan, G., Interventions for treating hyperemesis gravidarum: a network meta-analysis of randomized clinical trials, Journal of maternal-fetal & neonatal medicine, 1-7, 2018	Systematic review - References checked, no additional studies were identified
Sridharan, K., Sivaramakrishnan, G., Interventions for treating hyperemesis gravidarum: a network meta-analysis of randomized clinical trials, Journal of Maternal-Fetal and Neonatal Medicine, 33, 1405-1411, 2020	A review paper of 20 RCTs. All references checked and added to this review if relevant.
Sridharan, K., Sivaramakrishnan, G., Interventions for treating nausea and vomiting in pregnancy: a network meta-analysis and trial sequential analysis of randomized clinical trials, Expert Review of Clinical Pharmacology, 1-8, 2018	Systematic review - References checked, no additional studies were identified

Study	Reason for exclusion
Stanisiere, J., Mousset, P. Y., Lafay, S., How Safe Is Ginger Rhizome for Decreasing Nausea and Vomiting in Women during Early Pregnancy?, FoodsFoods, 7, 01, 2018	Narrative review
Steele, N. M., French, J., Gatherer-Boyles, J., Newman, S., Leclaire, S., Effect of acupressure by Sea-Bands on nausea and vomiting of pregnancy, JOGNN - Journal of Obstetric, Gynecologic, & Neonatal Nursing, 30, 61-70, 2001	Study outcomes not presented in a useable format.
Stone, C. L., Acupressure wristbands for the nausea of pregnancy, Nurse PractThe Nurse practitioner, 18, 15, 18, 23, 1993	Study design does not meet protocol eligibility criteria - letter to the editor.
Streitberger, K., Ezzo, J., Schneider, A., Acupuncture for nausea and vomiting: An update of clinical and experimental studies, Autonomic Neuroscience: Basic and Clinical, 129, 107-117, 2006	General review, not specific to pregnant women with nausea and vomiting.
Sulak, P. J., Continuous oral contraception: changing times, Best Practice and Research: Clinical Obstetrics and Gynaecology, 22, 355-374, 2008	Duplicate
Tabatabaii, A., Sekhavat, L., Mojibian, M., A randomized, placebo-controlled trial of corticosteroids for hyperemesis gravidarum., Journal of Maternal-Fetal and Neonatal Medicine, 21, 225-226, 2008	Conference abstract
Tamay, A. G., Kuscu, N. K., Hyperemesis gravidarum: current aspect, Journal of Obstetrics & Gynaecology, 31, 708-12, 2011	Narrative review.
Tara, F, Azizi, H, Bahrami, H, Effects of pressure stimulation of the nei guan (PC6) point on the nausea and vomiting in pregnant women. , Avicenna J Phytomed, 5, 17-18, 2015	Study design does not meet protocol eligibility criteria - conference abstract.
Tara, F., Bahrami-Taghanaki, H., Amini Ghalandarabad, M., Zand-Kargar, Z., Azizi, H., Esmaily, H., Azizi, H., The Effect of Acupressure on the Severity of Nausea, Vomiting, and Retching in Pregnant Women: A Randomized Controlled Trial, Complementary Medical ResearchComplementary Med, 1-8, 2020	Article is unavailable
Tara, F., Bahrami-Taghanaki, H., Amini Ghalandarabad, M., Zand-Kargar, Z., Esmaily, H., Azizi, H., Wirkung der Akupressur auf den Schweregrad von Ubelkeit, Erbrechen und Wurgereiz bei Schwangeren: eine randomisierte kontrollierte Studie, The Effect of Acupressure on the Severity of Nausea, Vomiting, and Retching in Pregnant Women: A Randomized Controlled Trial, Complementary medicine research, 1-8, 2020	Duplicate.
Thomson, M., Corbin, R., Leung, L., Effects of ginger for nausea and vomiting in early pregnancy: a meta-analysis, Journal of the	Systematic review - references checked; no additional relevant evidence identified.

Study	Reason for exclusion
American Board of Family Medicine: JABFMJ Am Board Fam Med, 27, 115-22, 2014	
Van den Heuvel, E., Goossens, M., Vanderhaegen, H., Sun, H. X., Buntinx, F., Effect of acustimulation on nausea and vomiting and on hyperemesis in pregnancy: a systematic review of Western and Chinese literature, BMC Complementary & Alternative MedicineBMC Altern Med, 16, 13, 2016	Systematic review - References checked, no additional studies were identified
Viljoen, E., Visser, J., Koen, N., Musekiwa, A., A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting, Nutrition JournalNutr J, 13, 20, 2014	Systematic review - references checked; no additional evidence identified.
Wibowo, N., Purwosunu, Y., Sekizawa, A., Farina, A., Tambunan, V., Bardosono, S., Vitamin B6 supplementation in pregnant women with nausea and vomiting, International Journal of Gynaecology & ObstetricsInt J Gynaecol Obstet, 116, 206-10, 2012	Study comparison does not meet protocol eligibility criteria - compares high versus low dose pyridoxine hydrochloride.
Xu, J., MacKenzie, I. Z., The current use of acupuncture during pregnancy and childbirth, Current Opinion in Obstetrics & GynecologyCurr Opin Obstet Gynecol, 24, 65-71, 2012	Narrative review.

Economic studies

A single economic search was undertaken for all topics included in the scope of this guideline. No economic studies were identified which were applicable to this review question. See supplementary material 2 for details.

Appendix L – Research recommendations

Research recommendations for review question: What interventions are effective in treating nausea and vomiting during pregnancy?

Research question

What is the clinical and cost effectiveness of medication for women with mild to moderate nausea and vomiting in pregnancy?

Why this is important

Mild to moderate nausea and vomiting in pregnancy are common. The lack of high quality evidence on effectiveness (including benefits and harms) of commonly used pharmacological treatments raises potential for safety concerns, resource waste and a higher burden of disease than is necessary. As the provision of antenatal care by maternity units is increasingly delivered through streamlined protocol-driven services and the use of clinical pathways in general practice is increasingly common, there is a growing opportunity to conduct efficient multi-site randomised controlled trials of pharmacological treatments.

Table 37: Research recommendation rationale

Research question	What is the clinical and cost effectiveness of medication for women with nausea and vomiting in pregnancy?
Why is this needed	
Importance to 'patients' or the population	Mild to moderate nausea and vomiting in pregnancy are common, reduce quality of life and lead to significant economic costs. Little is known about the effectiveness, cost-effectiveness, and long-term safety on the unborn child of commonly used treatments during pregnancy.
Relevance to NICE guidance	Management of mild to moderate nausea and vomiting in pregnancy were considered in this guideline and there is a lack of data on effectiveness, cost-effectiveness, and long-term safety on the unborn child of several commonly used treatments.
Relevance to the NHS	The outcome would affect the types of treatment for nausea and vomiting in pregnancy provided by the NHS.
National priorities	High
Current evidence base	Minimal effectiveness and long-term safety data on the unborn child as a result of use during pregnancy.
Equality considerations	None known
Feasibility	Potential difficulty recruiting to a placebo-controlled trial given the potential for no treatment.
Other comments	-

Table 38: Research recommendation modified PICO table

Criterion	Explanation
Population	Women with mild to moderate nausea and vomiting during pregnancy
Interventions	Doxylamine/pyridoxine

Criterion	Explanation
	Cyclizine or promethazine Prochlorperazine or chlorpromazine Metoclopramide Ondansetron
Comparator	Other interventions listed above (ideally multi-arm trial comparing at least 3 of these commonly used options)
Outcomes	Symptomatic relief during pregnancy Fetal death (at any stage of pregnancy, including miscarriage, still birth and termination of pregnancy) Infant death up to 4 weeks chronological age Adverse events requiring hospitalisation during the pregnancy Duration of hospitalisation for treatment of nausea and vomiting Women's experience and satisfaction with care Pre-term birth Babies being born small for gestational age
Study design	RCT
Timeframe	At least 1 month of follow-up post-birth/term
Additional information	-

Research question

What is the clinical and cost effectiveness of corticosteroids for women with severe nausea and vomiting in pregnancy?

Why this is important

Severe nausea and vomiting in pregnancy (including hyperemesis gravidarum) is debilitating. The lack of high quality evidence on effectiveness (including benefits and harms) of commonly used pharmacological treatments raises potential for safety concerns, resource waste and a higher burden of disease than is necessary. As the provision of antenatal care by maternity units is increasingly delivered through streamlined protocol-driven services and the use of clinical pathways in general practice is increasingly common, there is a growing opportunity to conduct efficient multi-site randomised controlled trials of pharmacological treatments.

Table 39: Research recommendation rationale

Research question	What is the clinical and cost effectiveness of corticosteroids for women with severe nausea and vomiting in pregnancy?
Why is this needed	
Importance to 'patients' or the population	Severe nausea and vomiting in pregnancy (including hyperemesis gravidarum) significantly reduces quality of life and leads to significant economic costs. Little is known about the effectiveness, cost-effectiveness and long-term safety on the unborn child of commonly used treatments during pregnancy.
Relevance to NICE guidance	Management of severe nausea and vomiting in pregnancy (including hyperemesis gravidarum) in pregnancy were considered in this guideline and there is a lack of data on

Research question	What is the clinical and cost effectiveness of corticosteroids for women with severe nausea and vomiting in pregnancy?
	effectiveness, cost-effectiveness and long-term safety on the unborn child of several commonly used treatments.
Relevance to the NHS	The outcome would affect the types of treatment for severe nausea and vomiting in pregnancy (including hyperemesis gravidarum) provided by the NHS.
National priorities	High
Current evidence base	Minimal effectiveness data
Equality considerations	None known
Feasibility	Potential difficulty recruiting to a placebo-controlled trial given the potential for no treatment.
Other comments	-

Table 40: Research recommendation modified PICO table

Criterion	Explanation
Population	Women with severe nausea and vomiting in pregnancy (including hyperemesis gravidarum)
Intervention	Corticosteroids
Comparator	Any other conventional management option (which may include: doxylamine, pyridoxine, cyclizine, promethazine, prochlorperazine, chlorpromazine, metoclopramide, ondansetron)
Outcomes	Symptomatic relief during pregnancy Fetal death (at any stage of pregnancy, including miscarriage, still birth and termination of pregnancy) Infant death up to 4 weeks chronological age Adverse events requiring hospitalisation Duration of hospitalisation for treatment of nausea and vomiting Women's experience and satisfaction with care Pre-term birth Babies being born small for gestational age
Study design	RCT
Timeframe	At least 1 month of follow-up post-birth/term
Additional information	-