Bilaga till rapport

Behandling av extremt graviditetsillamående (hyperemesis gravidarum) / Treatments for extreme nausea and vomiting in pregnancy (hyperemesis gravidarum)
rapport 355 (2022)

Bilaga 5 Tabell över inkluderade studier/ Appendix 5 Tabel of included studies

Notes:

* Calculated in Review Manager [1] by SBU from values reported in the published article

C= control group; CI= confidence interval; F= F-value from analysis of variance (ANOVA) ANOVA; n= number of participants; I= intervention group; IQR= interquartile range; ITT= intention to treat; max= maximum ; MD= mean difference; min= minimum; NA= not available; NRSI= non-randomized study of interventions; p= probability value; RCT= randomized controlled trial; significant; RD= risk difference; RR= risk ratio; RD= standard deviation; SMD= standardized mean difference

Author	Abas
Year	2014
Country	Malaysia
Ref #	[2]
Study design	RCT
Setting	University hospital in Kuala Lumpur
Recruitment	Between November 2011 and August 29012, women first time hospitalized with HG were approached and enrolled by their providers
Population	**Mean age (SD)**: I = 29.7 (4.7) years, C = 29.2 (4.5) years **Severity of symptoms**: see nausea score under primary outcomes **Duration of symptoms**: not stated **Gestational week (SD)**: I = 9.6 (2.3), C = 9.4 (2.5) **Weight (SD)**: I = 57.0 (10.8) kg, C = 57.0 (10.7) kg

	Singleton/twin pregnancies: only singletons **Psychosocial health/socioeconomic status:** Employed (%), I = 75, C = 82.5 **Ethnicity (%)**: Malay, I = 77.5, C = 78.8 Indian, I = 5.0, C = 13.8 Chinese, I = 5.0, C = 2.5 Other, I = 12.5, C = 5.0
Inclusion criteria	Hospitalized with clinical diagnosis of HG with clinical dehydration and ketonuria (of 2+ or greater) on urine dipstick and gestation of 16 weeks or less. Diagnosis of HG required presence of nausea and intractable vomiting sufficient to cause dehydration and metabolic disturbance of a severity to require hospitalization, occurrence early in pregnancy, and with no other obvious cause. **Exclusion**: multiple gestations, established nonviable pregnancy, preexisting medical condition that could be associated with nausea and vomiting, known allergy to metoclopramide or ondansetron
Follow up	at 24h (end of trial) or at recruitment, 8 h, 16 h, and 24 h
Intervention	Ondansetron Intravenous 4 mg, given every 8 hours, thereafter open-label treatment of metoclopramide if antiemetic still needed, and standard care
Participants (n)	80
Drop-outs, n (%)	80-72= 8 (10%)
Comparison	Metoclopramide Intravenous 10 mg, given every 8 hours, thereafter open-label treatment of metoclopramide if antiemetic still needed, and standard care
Participants (n)	80
Drop-outs, n (%)	80-74= 6 (7.5%)
Primary outcomes	**Nausea** Visual numeric rating scale (min = 1; max = 10; higher= worse); Median (Interquartile range):

	- at recruitment I (n = 80) = 8 (7 to 9) C (n = 80) = 9 (7 to 10) Test of difference: p= 0.50 - at 8h I (n = 80) = 4 (3 to 6) C (n = 80) = 5 (4 to 6) Test of difference: p= 0.05 - at 16 h I (n = 80 or 79) = 3 (1 to 4) C (n = 80 or 79) = 3 (2 to 4.75) Test of difference: p= 0.28 - at 24 h I (n = between 80 and 75) = 1 (1 to 3) C (n = between 80 and 75) = 2 (1 to 3) Test of difference: p= 0.68 - overall repeated measures ANOVA (n=155); p=0.22 **Vomiting** Nr of vomiting episodes in the 24-hour study period; Median (Interquartile range): I (n = 80) = 1 (0 to 2) C (n = 80) = 1 (0 to 2.75) Test of difference: p= 0.38 **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment**

	Hospital stay in days; Median (Interquartile range): I (n=80) = 1.9 (1.5 to 2.4) C (n=80) = 2.0 (1.7 to 2.7) Test of difference: p= 0.10 **Health-related quality of life** Well-being; visual numeric rating scale (min = 1; max = 10; higher= greater); mean (SD): -at 24 hours I (n= from 80 to 78) = 8.7 (1.1) C (n=80) = 8.3 (1.6) Test of difference: p= 0.13 Effect size*: MD (95%CI) = 0.40 (-0.03 to 0.83), p = 0.07; SMD (95% CI) = 0.29 (-0.02 to 0.60), p = 0.07 **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** NA
Reported adverse events (overall)	Felt drowsy, Unable to sleep, had dry mouth, Felt dizzy, Had diarrhea, Had headache, Experienced palpitations, Noticed skin rash.
Comments **Risk of bias**	Open-label after the 24 h study period Low for outcomes during the 24 h study period (nausea, vomiting, health-related quality of life) Moderate for hospital treatment

Author	Adlan
Year	2017
Country	Malaysia

Ref #	[3]
Study design	RCT
Setting	Inpatient care at gynaecology ward of a hospital in Ipoh
Recruitment	Among eligible and symptomatic women requiring hospital admission from December 2012 to May 2013
Population	**Mean age (SD)**: I = 29.0 (4.92) years, C = 28.4 (4.34) years **Severity of symptoms**: see inclusion criteria (baseline PUQE not stated) **Duration of symptoms**: not stated **Gestational week (SD)**: I = 9.7 (2.09), C = 9.2 (2.03) **BMI or weight**: not stated **Singleton (%)**: 100 **Psychosocial health/socioeconomic status**: not stated **Ethnicity (%)**: Malay, I = 80.0, C = 65.0 Chinese, I = 6.7, C = 6.7 Indian, I = 11.7, C = 26.7 Other, I = 1.7, C = 1.7
Inclusion criteria	Spontaneously conceived singleton pregnancies between 5 and 14 weeks of gestation presenting with moderate to severe HG requiring hospital admission (severe NVP, unable to tolerate orally, ketonuria 3+, requiring intravenous fluids and antiemetics) **Exclusion**: multiple or molar pregnancy; prior knowledge of the acupressure band; presence of infections (such as urinary tract infection or gastroenteritis); medical conditions (such as hyperthyroidism); prior history of drug reaction toward metoclopramide
Follow up	Daily day 1 to 3, after 12 h of wearing the band
Intervention	Acupressure Acupressure wristband at Neiguan point (P6) 12 h daily first 3 days of admission as adjuvant treatment to standard inpatient care of HG, which include 1.5 L normal saline and 1.5 L Hartmann's solution per day, intravenous metoclopramide 10 mg tds, and thiamine supplements

Participants (n) **Drop-outs, n (%)**	60 0
Comparison **Participants (n)** **Drop-outs, n (%)**	Placebo Identical but non-stimulating wristband, adjuvant to standard treatment as the intervention group 60 0
Primary outcomes	**Nausea** Nausea over the past 24h (domain in PUQE) (min = 1; max = 5; higher= worse); Mean (SD): - at Day 1 I (n = 60) = 3.25 (1.05) C (n = 60) = 4.05 (0.79) Test of difference: p < 0.001 - at Day 2 I (n = 60) = 2.27 (0.90) C (n = 60) = 3.20 (0.70) Test of difference: p < 0.001 - at Day 3 I (n = 60) = 1.57 (0.81) C (n = 60) = 2.58 (0.93) Test of difference: p < 0.001 **Vomiting** Vomiting over the past 24h (domain in PUQE) (min = 1; max = 5; higher= worse); Mean (SD):

	- at Day 1 I (n = 60) = 3.02 (0.97) C (n = 60) = 3.92 (0.79) Test of difference: p < 0.001 - at Day 2 I (n = 60) = 2.03 (0.82) C (n = 60) = 3.17 (0.64) Test of difference: p < 0.001 - at Day 3 I (n = 60) = 1.48 (0.65) C (n = 60) = 2.58 (0.62) Test of difference: p < 0.001 **Retching** Retching over the past 24h (domain in PUQE) (min = 1; max = 5; higher= worse); Mean (SD): - at Day 1 I (n = 60) = 2.87 (1.19) C (n = 60) = 3.18 (1.41) Test of difference: p = 0.124 - at Day 2 I (n = 60) = 1.85 (0.69) C (n = 60) = 2.57 (0.83) Test of difference: p < 0.001 - at Day 3 I (n = 60) = 1.35 (0.52) C (n = 60) = 1.93 (0.73)

	Test of difference: p < 0.001 **Nausea/ Vomiting/Retching** Nausea, vomiting and retching over the past 24h (PUQE score) (min = 3; max = 15; higher= worse); Mean (SD): - at Day 1 I (n = 60) = 9.13 (2.02) C (n = 60) = 11.15 (1.87) Test of difference: p < 0.001 - at Day 2 I (n = 60) = 6.15 (1.93) C (n = 60) = 8.93 (1.51) Test of difference: p < 0.001 Effect size*: MD (95% CI) =-2.78 (-3.40 – -2.16), p < 0.00001 - at Day 3 I (n = 60) = 4.40 (1.63) C (n = 60) = 7.10 (1.61) Test of difference: p < 0.001 **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** Hospital stay (days); Mean (SD): I (n = 60) = 2.83 (0.62) C (n = 60) = 3.88 (0.87) Test of difference: p < 0.001 Effect size*: MD (95% CI) = -1.05 (-1.32 to -0.78), p < 0.00001 **Health-related quality of life**

	NA **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** NA
Reported adverse events (overall)	NA
Comments **Risk of bias**	 Moderate

Author	Aleyasin
Year	2016
Country	Iran
Ref #	[4]
Study design	RCT
Setting	Inpatient
Recruitment	Among women with presumed HG and determined to require an antiemetic, admitted to the obstetrics emergency ward between February 2011 and February 2012
Population	**Mean age (SD)**: I = 26.7 (4.4) years; C = 28.7 (7.0) years **Severity of symptoms**: mean (SD) number of vomiting episodes per day, I = 6.8 (3.0); C = 4.9 (3.0); mean nausea score (min = 0; max = 5; higher = worse), I = 4.9; C = 5.0 **Duration of symptoms**: not stated **Gestational week (SD)**: I = 9.8 (2.3); C = 9.8 (3.1) **BMI or weight**: not stated **Singleton/twin pregnancies**: not stated

	Psychosocial health/socioeconomic status: not stated **Ethnicity (%)**: not stated
Inclusion criteria	clinical hyperemesis gravidarum with detectable ketonuria by urine dipstick (more than +1 ketonuria) at a gestation of 20 weeks or less, and PUQE score of ≥13 24 h after admission to the ward **Exclusion**: evidence of hepatic and thyroid dysfunction, molar pregnancy, preexisting medical conditions that can cause nausea and vomiting (like urinary tract infections, gastrointestinal causes of vomiting, and diabetic ketoacidosis), hypersensitivity reaction to any of the study medications
Follow up	-after 48 hours -1 week after discharge -2 weeks after discharge Adverse drug effects also assessed 30 mins after intravenous administration
Intervention	Granisetron 24 hours after initial standard treatment (intravenous rehydration, with addition of potassium chloride as required, ranitidine and pyridoxine), 1 mg administered intravenously over 2 mins; from day 2, 1 mg every 12 h (plus two placebo tablets to maintain blinding) orally administered until 2 weeks after discharge; after discharge taken on an as-per-needed basis
Participants (n)	16
Drop-outs, n (%)	0
Comparison	Promethazine Orally and intravenously administered, following the same protocol as the intervention group, 25 mg administered intravenously over 2 mins; from day 2, 25 mg every 12 h orally administered until 2 weeks after discharge; after discharge taken on an as-per-needed basis
Participants (n)	16
Drop-outs, n (%)	0

Primary outcomes	**Nausea** Nausea score, after 48 hours (min = 0; max = 5; higher= worse); Mean (SD): I (n = 16) = 0.1 (NA) C (n = 16) = 2.5 (NA) Test of difference: 0.001 **Vomiting** Vomiting episodes per day (n), after 48 hours; Mean (SD): I (n = 16) = 1.1 (NA) C (n = 16) = 1.5 (NA) Test of difference: 0.007 **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** Hospital stay (day); Mean (SD): I (n = 16) = 3.2 (1.1) C (n = 16) = 2.2 (1.6) Test of difference: p= 0.108 Rehospitalization (number); n (%) I (n = 16) = 0 (0%) C (n = 16) = 1 (6%) Test of difference: p= 0.259 **Health-related quality of life** NA **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm**

	NA
Reported adverse events (overall)	Adverse drug reactions reported included somnolence, weakness, anorexia, and dry mouth.
Comments **Risk of bias**	 Moderate

Author	Bondok
Year	2006
Country	Egypt
Ref #	[5]
Study design	RCT
Setting	Intensive care unit (ICU)
Recruitment	Among pregnant women admitted to the ICU for intractable hyperemesis between March 2003 and July 2005
Population	**Mean age (SD)**: I = 28 (2.86) years; C = 28 (4.16) years **Severity of symptoms**: mean number of vomiting episodes Day 1 of therapy, I = 9.63*; C = 8.97* **Duration of symptoms**: not stated **Gestational week (SD)**: I = 10 (2.68); C = 11 (2.44) **BMI or weight**: not stated **Singleton/twin pregnancies**: only singleton (twin pregnancies were excluded) **Psychosocial health/socioeconomic status**: not stated **Ethnicity (%)**: not stated
Inclusion criteria	intrauterine pregnancy of ≤16 wks gestation with the diagnosis of intractable hyperemesis gravidarum (defined as severe persistent vomiting, ketonuria, and weight loss >5% of prepregnancy weight) necessitating ICU admission

	Exclusion: molar gestation, twin gestation or placental anomalies, or medical complications contraindicating or requiring steroid use
Follow up	- daily during 1 week of therapy - 2 weeks following discharge
Intervention	Hydrocortisone In addition to intravenous thiamine 100 mg and intravenous hydration, hydrocortisone 300 mg intravenously for 3 days, thereafter, tapered completely within 1 week
Participants (n)	20
Drop-outs, n (%)	0
Comparison	Metoclopramide In addition to thiamine and IV hydration as in the interventions group, metoclopramide intravenously 10 mg 3 times daily, continued without change for 1 week
Participants (n)	20
Drop-outs, n (%)	0
Primary outcomes	**Nausea** NA **Vomiting** Changes in mean number of vomiting episodes; Mean (SD): - at day2 I (n = 20) = 5.7 *(NA) C (n = 20) = 7.5*(NA) - at day3 I (n = 20) = 2.6*(NA)

	C (n = 20) = 4.3*(NA) - at day4 I (n = 20) = 1.5*(NA) C (n = 20) = 3.4*(NA) - at day5 I (n = 20) = 1.1*(NA) C (n = 20) = 2.7*(NA) - at day6 I (n = 20) = 0.5*(NA) C (n = 20) = 2.8*(NA) - at day7 I (n = 20) = 0.4*(NA) C (n = 20) = 2.1*(NA) Test of difference: NA **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** Rehospitalization (number); n (%) I (n = 16) = 0 (0%) C (n = 16) = 1 (6%) Test of difference: p= 0.259 **Health-related quality of life** NA **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm**

	NA
Reported adverse events (overall)	NA
Comments **Risk of bias**	randomization code broken after 1 week of therapy Low for vomiting Moderate for hospital treatment (assessed open-label)

* Data extracted from figure in the original paper

Author **Year** **Country** **Ref #**	Carlsson 2000 Sweden [6]
Study design **Setting** **Recruitment** **Population**	Crossover RCT Inpatient care Women with HG consecutively admitted between September 1995 and August 1997 (Reported for the 33 women who completed the study) **Mean age (range)**: 28.4 (23 to 37) years **Severity of symptoms**: see Nausea at day 0 under Primary outcomes **Duration of symptoms**: a mean of 4 weeks before admission **Gestational week (range)**: 9.9 (6 to 16) weeks **BMI or weight**: not stated **Singleton/twin pregnancies**: not stated **Psychosocial health/socioeconomic status**: not stated **Ethnicity (%)**: not stated

Inclusion criteria	Women with HG not responding to conventional outpatient treatment, otherwise healthy and mastering the Swedish language **Exclusion**: women asking for legal abortion, refusing acupuncture, not speaking Swedish and with other diseases were not randomized
Follow up	At recruitment (day 0) and after treatment (day 3). Also before crossover (day 4) and after cross-over treatment (day 7) (not reported here)
Intervention	Acupuncture Group A first received active (deep) acupuncture 30 mins x 3 daily for two days on PC6, in addition to parenteral nutrition with 5% glucose, "wash-out-period" days 3 and 4 with no acupuncture, thereafter groups switched treatments, no medicines allowed during the study period
Participants (n)	19
Drop-outs, n (%)	2 (11%)
Comparison	Placebo Group B first received superficial acupuncture for two days, otherwise same protocol as the intervention group
Participants (n)	21
Drop-outs, n (%)	5 (24%)
Primary outcomes	**Nausea** Visual Analogue Scale (min = 0 "no nausea at all"; max = 10 "worst possible nausea"; higher= worse); Extracted Mean from figure (SD=NA): - Before treatment (day 0) I (n = 17) = 8.3* C (n = 16) = 6.9* Test of difference: NA - after treatment (day 3)

	I (n = 17) = 4.7* C (n = 16) = 5.3* Test of difference: NA **Vomiting** Number of women vomiting; N (%): - Before treatment (day 0) I (n = 17) = 17 C (n = 16) = 16 Test of difference: NA - after treatment (day 3) I (n = 17) = 7 (41%) C (n = 16) = 12 (75%) Test of difference: p= 0.049, Chi^2-test. **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** NA **Health-related quality of life** NA **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** NA
Reported adverse events (overall)	No side effects reported.

Comments	
Risk of bias	Moderate

* Data extracted from figure in the original paper

Author	Ditto
Year	1999
Country	Italy
Ref #	[7]
Study design	RCT
Setting	Inpatient care
Recruitment	Among women admitted to the hospital between 1993 and 1997
Population	**Mean age (SD)**: I = 27.8 (7.14) years; C = 28.6 (5.04) years **Severity of symptoms**: weight loss (>5% on admission) I = 52%; C = 56% **Duration of symptoms**: persistent nausea and vomiting for a week before (inclusion criteria) **Gestational week (SD)**: I = 11.2 (3.17); C = 11.5 (2.96) **Weight**: I = 59.9 (8.97) kg; C = 58.1 (8.13) kg **Singleton/twin pregnancies**: not stated **Psychosocial health/socioeconomic status**: education, I = 12.1 (5.3) years; C = 12.8 (5.5) years **Ethnicity (%)**: non-European, I = 6 (24%); C = 8 (32%)
Inclusion criteria	less than 16 weeks of gestation, persistent nausea and vomiting for a week, associated with one or more of the following symptoms: weight loss exceeding 5% since the beginning of symptoms, ketonuria (3% increase), serum potassium less than 3.4 mEq/l **Exclusion**: psychological instability, gastrointestinal complaints, liver disease and known thyroid disorders, receiving other types of treatment for HG
Follow up	-at day 1 -at day 2

	-at day 3 -every week -at delivery
Intervention **Participants (n)** **Drop-outs, n (%)**	Parenteral fluids with vitamins plus diazepam 10 mg diazepam added to the first and last infusion of normal saline, glucose, and vitamins each day for a mean daily dose of 20 mg; after resolved symptoms, discharged with diazepam tablets 5 mg twice daily for a week 25 0
Comparison **Participants (n)** **Drop-outs, n (%)**	Parenteral fluid with vitamins without diazepam after resolved symptoms, discharged with placebo tablets 5 mg twice daily for a week 25 0
Primary outcomes	**Nausea** Number of patients with severe nausea; N(%): -at day 1 I (n = 25) = 24 (96%)* C (n = 25) = 25 (100%)* Test of difference: NA -at day 2 I (n = 25) = 6 (24%)* C (n = 25) = 18 (72%)* Test of difference: NA -at day 3

	I (n = 25) = 1 (4%)* C (n = 25) = 9 (36%)* Test of difference: NA **Vomiting** Number of patients with a reduction in emesis; N (%) - at day 1 I (n = 25) = 25 (100%)* C (n = 25) = 25 (100%)* Test of difference: NA -at day 2 I (n = 25) = 2 (8%)* C (n = 25) = 13 (12%)* Test of difference: NA -at day 3 I (n = 25) = 2 (8%)* C (n = 25) = 1 (4%)* Test of difference: NA **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** Stay in hospital, (days); Mean (SD): I (n = 25) = 4.5 (1.9) C (n = 25) = 5.6 (1.6) Test of difference: $p < 0.05$ Women requiring a second admission; N (%): I (n = 25) = 1 (4%)

	C (n = 25) = 6 (24%) Test of difference: p < 0.05 **Health-related quality of life** NA **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** Incidence of preterm delivery; n (%) I (n = 25) = 1 (4%) C (n = 25) = 2 (8%) Test of difference: p > 0.05
Reported adverse events (overall)	Termination of pregnancy No side effects or congenital neonatal malformations reported
Comments **Risk of bias**	 Moderate

* Data extracted from figure in the original paper

Author	Fischer-Rasmussen
Year	1990
Country	Denmark
Ref #	[8]
Study design	Crossover RCT
Setting	Inpatient care
Recruitment	Consecutively, among women delivering in the department over a period of 26 months, ending April 1988
Population	**Mean age (range)**: I = 27.1 (20 to 39), C = 25.6 (18 to 36)

	Severity of symptoms: Degree of nausea Morning sickness only: I = 1, C = 0 More episodes of nausea through the day: I = 3, C = 4 Constant nausea: I = 10, C = 9 **Duration of symptoms**: Duration of vomiting (days) ≤ 5 days: I = 0, C = 1 6-7 days: I = 4, C = 1 >7 days: I = 10, C = 11 **Gestational week (mean)**: I = 11.0, C = 10.8 **BMI or weight**: not stated; weight loss ≥5 kg: I = 5, C = 6 **Singleton/twin pregnancies**: not stated **Psychosocial health/socioeconomic status**: not stated **Ethnicity (%)**: not stated
Inclusion criteria	Admitted to the hospital with hyperemesis before the 20th week of gestation, persisting symptoms after two days (at least 10 points on a composite severity score), condition allowing oral intake of capsules **Exclusion**: women whose symptoms might have originated from gallbladder or liver disease, duodenal ulcer, pancreatitis, etc.
Follow up	for period 1: day 0 and day 5
Intervention	Ginger first Oral capsules with 250 mg ginger x 4 daily during the first four days of treatment, other antiemetic medication withdrawn, but parenteral fluids (dextrose, dextrose-saline) allowed to be continued, a 2-day wash-out period before crossover to the second 4-day period
Participants (n)	15
Drop-outs, n (%)	15-14=1 (7%)
Comparison	Placebo first Oral capsules with 250 mg lactose x 4 daily during the first four days of treatment, other antiemetic medication withdrawn, but parenteral fluids

	(dextrose, dextrose-saline) allowed to be continued, a 2-day wash-out period before crossover to the second 4-day period
Participants (n)	15
Drop-outs, n (%)	15-13= 2 (13%)
Primary outcomes	**Nausea/Vomiting** Composite relief measure of vomiting, nausea, change in body weight, patient's opinion about the treatment (min = -10; max = 13; higher= better); Mean (SD): I (n = 14) = 4.07 (5.65*) C (n = 13) = 0.92 (5.16*) Test of difference: NA **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** NA **Health-related quality of life** NA **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** NA
Reported adverse events (overall)	Spontaneous abortion, abortion. No side effects reported. All infants without deformities and discharged in good condition. All had Apgar scores of 9-10 after 5 minutes.
Comments **Risk of bias**	 Moderate

* calculated by SBU from data reported in the article

Author	Fletcher
Year	2015
Country	United Kingdom
Ref #	[9]
Study design	RCT
Setting	inpatient care
Recruitment	Among women admitted to four hospitals with a diagnosis of HG between June 2008 and December 2010
Population	**Mean age (SD)**: I = 26.5 (5.6); C = 25.8 (4.9) **Severity of symptoms**: PUQE (min = 0, max = 15, more = worse), I = 8.4 (3.1); C = 9.1 (3.0), indicating moderate symptoms **Duration of symptoms**: not stated **Gestational week (SD)**: I = 9.2 (2.6); C = 9.2 (2.6) **BMI**: I = 24.0 (5.5); C = 24.3 (5.8) **Singleton/twin pregnancies**: not stated **Psychosocial health/socioeconomic status**: employment status (%) Full time, I = 38.2%; C = 40.1% Part-time, I = 21.4%; C = 22.5% Unemployed, I = 9.9%; C = 7.8% Full time parent, I = 22.9%; C = 22.5% Student, I = 7.6%; C = 7.0% **Ethnicity (%)**: White British, I = 58%; C = 59% White European, I = 1.5%; C = 2.1% Bangladeshi, I = 1.5%; C = 4.9% Indian, I = 8.4%; C = 9.2%

	Pakistani, I = 13%; C = 10.6% Black African, I = 8.4%; C = 4.9% Black Caribbean, I = 2.3%; C = 0.8% Middle Eastern, I = 0.8%; C = 1.4% Other, I = 3.1%; C = 2.8% Missing, I = 3%; C = 4.2%
Inclusion criteria	admission with nausea and vomiting in early pregnancy within the previous 24 h, being aged 16 years or over and able to give informed consent **Exclusion**: if nausea and vomiting in pregnancy had commenced after 14 weeks gestation or if they were diabetic
Follow up	-at 2 weeks -at 4 weeks -at 6 weeks
Intervention	Usual care plus holistic assessment and tailored care plan In addition to standard medical care (intravenous rehydration and antiemetic therapy) according to each hospital's protocol, assessment using the Hyperemesis Impact of Symptoms (HIS) questionnaire; based on the responses, practical and supportive care was tailored, including dietary advice, symptom management, and psychological impact of symptoms
Participants (n)	131
Drop-outs, n (%)	27 (20.6%) complete loss
Comparison	Usual care Standard medical care (intravenous rehydration and antiemetic therapy) according to each hospital's protocol
Participants (n)	142
Drop-outs, n (%)	30 (21.1%) complete loss

Primary outcomes	**Nausea/Vomiting** PUQE (min = 3; max = 15; higher = worse); Mean (SD): -at 2 weeks I (n = 93) = 7.6 (3.20) C (n = 107) = 7.8 (3.3) Test of difference (adjusted for age, previous hyperemesis, gestational age, PUQE score and baseline value of social functioning): mean difference (95% Bootstrap CI) = 0.04 (-0.83 to 0.97); p= 0.923 -at 4 weeks I (n = 64) = 6.2 (2.5) C (n = 63) = 6.6 (2.7) Test of difference (adjusted for age, previous hyperemesis, gestational age, PUQE score and baseline value of social functioning): mean difference (95% Bootstrap CI) = -0.24 (-1.18 to 0.62); p= 0.614 -at 6 weeks I (n = 54) = 5.6 (2.5) C (n = 67) = 5.3 (2.2) Test of difference (adjusted for age, previous hyperemesis, gestational age, PUQE score and baseline value of social functioning): mean difference (95% Bootstrap CI) = 0.43(-0.50, 1.23); p= 0.312 **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** NA **Health-related quality of life** Social functioning, subscale from SF-36 (min = 0; max = 100; higher= better); Mean (SD): -at 2 weeks

	I (n = 93) = 34.7 (30.8) C (n = 105) = 32.7 (31.6) Test of difference (adjusted for age, previous hyperemesis, gestational age, PUQE score and baseline value of social functioning): mean difference (95% Bootstrap CI) = 4.95 (-3.50 to 13.30); p= 0.254 -at 4 weeks I (n = 66) = 50.0 (35.8) C (n = 64) = 46.3 (36.6) Test of difference (adjusted for age, previous hyperemesis, gestational age, PUQE score and baseline value of social functioning): mean difference (95% Bootstrap CI) = 5.25 (-6.16 to 17.19); p= 0.386 -at 6 weeks I (n = 55) = 59.8 (32.6) C (n = 69) = 60.5 (32.3) Test of difference (adjusted for age, previous hyperemesis, gestational age, PUQE score and baseline value of social functioning): mean difference (95% Bootstrap CI) = -2.35 (-12.98 to 9.02); p= 0.685 **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** NA
Reported adverse events (overall)	NA
Comments **Risk of bias**	Moderate, except for hospital treatment (with high risk due to missing data)

Author	Grooten et al

Year	2017
Country	The Netherlands
Ref #	[10]
Study design	Multicenter RCT
Setting	inpatient care in 16 hospitals
Recruitment	Among women admitted to hospital because of HG, between October 2014 and March 2016
Population	**Mean age (SD)**: I = 28.2 (5.0) years; C = 28.7 (4.6) years **Severity of symptoms, mean PUQE score (SD)**: I = 11.5 (3.0); C = 10.4 (3.0) (missing data: 35%) **Duration of symptoms**: mean (SD) gestational age at onset of symptoms, I = 6 (2); C = 5 (1) (missing data: 17%) **Gestational week (SD)**: I = 9 (3); C = 9 (3) **Weight at inclusion**: I = 70.3 (16.6) kg; C = 65.6 (13.4) kg **Twin pregnancies, n (%)**: I = 2 (3.4%), C = 2 (3.6%) **Psychosocial health/socioeconomic status**: Educational level (missing data: 23%) Primary: I = 3.4%; C = 0% Secondary: I = 39.0%; C = 53.6% Higher: I = 27.1%; C = 32.1% **Ethnicity (%)**: (missing data: 15%) Western: I = 57.6%; C =67.0% Non-western: I = 25.4%; C = 26.8%
Inclusion criteria	Women admitted to the hospital with a diagnosis of HG (a diagnoses made if excessive NVP necessitating hospital admission in the absence of any other obvious cause such as drug-induced vomiting or infection) and a gestational age between 5 and 19 weeks; severe weight loss, electrolyte imbalance, or severe dehydration were not required **Exclusion**: known molar or nonvital pregnancy, acute infection causing vomiting, contraindication for enteral tube feeding, HIV infection, women <18 years of age

Follow up	1 week, 3 weeks, at birth, 6 weeks postpartum
Intervention	Enteral tube feeding in addition to standard care Received a nasogastric polyurethane feeding tube as soon as possible after random assignment; tube placement and feeding regimens followed a local protocol under the guidance of a dietitian; standard care consisted of intravenous rehydration for the time needed to reach maximum feeding rates, and antiemetic medication, electrolytes, and vitamin supplements according to local protocol. As soon as tube feeding was tolerated, discharge home with tube feeding was encouraged. Tube feeding was continued for ≥7 days or until the woman was able to maintain an oral intake of 1000 kcal/d. Energy intake was estimated by hospital dietitians with whom women receiving tube feeding had ≥1 consultation/week. In cases of tube dislocation, a nasoduodenal or nasojejunal tube could be placed
Participants (n)	59
Drop-outs, n (%)	ITT analysis= 0 (0%), 51 received tube feeding; per protocol= 59 -28 = 31 (59%),
Comparison	Standard care Intravenous rehydration, antiemetic medication, electrolytes, vitamin supplements, and dietetic advice according to local protocol. In women with severe symptoms necessitating prolonged admission or readmission, additional tube feeding could be provided, but only if the attending physician deemed it necessary.
Participants (n)	57
Drop-outs, n (%)	ITT analysis= 57-56= 1 (2%), 15 received tube feeding, 8 of which within 7 days of randomization; per protocol=57-48= 9 (16%)
Primary outcomes	**Nausea, vomiting (PUQE)** not reported here because of high risk of bias **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** Readmission; n (%) I= 22 (37.9%)

	C= 20 (37.0%) Test of difference: p= 0.92 Duration all admissions, days; median (IQR) I= 6 (3–8) C= 5 (4–9) Test of difference: p= 0.87 **Health-related quality of life** not reported here because of high risk of bias **Babies born small-for-gestational-age (SGA)** Birth weight, 10th percentile; n (%) I= 5 (8.6%) C= 4 (7.3%) Test of difference: p= 0.82 **Babies born preterm** Prematurity, < 37 weeks; n (%) I= 7 (12.1%) C= 7 (13.0%) Test of difference: p= 0.89
Reported adverse events (overall)	phlebitis, pain at insertion location (of IV), nose-throat irritation, obstruction, tube dislocation, miscarriage, termination of pregnancy, perinatal death, NICU admission
Comments **Risk of bias**	Major discrepancy in number of participants between ITT and per protocol analysis Moderate for hospital treatment, small-for-gestational-age and babies born preterm High for symptoms data (PUQE) and health-related quality of life (SF-36) (not tabulated here)

Author	Heazell
Year	2006
Country	United Kingdom
Ref #	[11]
Study design	RCT
Setting	Inpatient care at a secondary care center serving a diverse inner-city population including a high proportion of recent immigrants
Recruitment	Women admitted to the hospital between December 2002 and July 2004
Population	**Mean age (range)**: I = 25.4 (17 to 35) years, C = 27.7 (17 to 40) years **Severity of symptoms**: not stated regarding nausea or vomiting, among inclusion criteria were ketonuria ≥2+ **Duration of symptoms**: not stated **Gestational week (range)**: I = 8.5 (6 to 14), C = 9.0 (5 to 14) **BMI or weight**: not stated **Singleton/twin pregnancies**: not stated **Psychosocial health/socioeconomic status**: not stated **Ethnicity (%)**: >50% of pregnant patients in the catchment area were of Asian origin
Inclusion criteria	Women with NVP on their first inpatient admission between 5 and 14 weeks of gestation, and at least 2+ ketonuria, need of intravenous fluids due to inability to tolerate oral fluids, and a requirement for antiemetic medication **Exclusion**: prior knowledge of or use of acupressure, urinary tract or gastroenterologic infection, inability to communicate with the medical team (which included staff members who were able to speak Asian languages)
Follow up	Until discharge regarding hospital treatment, at 9 months regarding pregnancy outcomes
Intervention	Acupressure Acupressure wristbands bilaterally at P6 meridian point 8 h daily until fit for discharge, in addition to standard inpatient care of HG, which include 3 L of intravenous fluid in 24 h and parenteral antiemetic medication (orally when

	tolerated) according to defined protocol, and thiamine 100 mg orally once daily
Participants (n)	40
Drop-outs, n (%)	primary outcomes: 0; secondary outcomes: 40-38=2 (5%); pregnancy outcomes: 40-27=13 (33%)
Comparison	Placebo Acupressure wristbands bilaterally at a dorsal aspect of the forearm not thought to be effective, 8 h daily until fit for discharge, adjuvant to same standard inpatient care as I-group
Participants (n)	40
Drop-outs, n (%)	primary outcomes: 0; secondary outcomes: 40-39=1 (3%); pregnancy outcomes: 40-18=22 (55%)
Primary outcomes	**Nausea** NA **Vomiting** NA **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** Length of hospital stay (days); Median (Interquartile range): I (n = 40) = 3 (2-4) C (n = 40) = 3 (2-5) Test of difference: NA Number of women staying > 4 days; N (%) I (n = 40) = 11 (11/40=28%) C (n = 40) = 18 (18/40= 45%) Test of difference: $p < 0.05$

	Health-related quality of life NA **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** (live delivery before 37 weeks not reported here due to high risk of bias)
Reported adverse events (overall)	Intra-uterine fetal death after 20 weeks, termination of pregnancy, miscarriage before 20 weeks, non-normal anomaly scan, live delivery before 37 weeks.
Comments **Risk of bias**	 Moderate High for birth outcomes, thus not reported here

Author	McCarthy
Year	2014
Country	Ireland
Ref #	[12]
Study design	RCT
Setting	Day care and inpatient units
Recruitment	Among women presenting to the maternity hospital between April 2009 and March 2012
Population	**Mean age (SD)**: I = 31.9 (5.5) years, C = 32.7 (5.5) years **Severity of symptoms**: mean (range) frequency of vomiting/day, I = 6 (4-8), C = 5 (4-10) **Duration of symptoms**: No. of days with severe nausea (interfering with daily activities) before first presentation to the hospital, mean (range): I = 10 (6-21), C = 9.5 (5-21) **Gestational week (range)**: I = 8 (7-11), C = 8 (7-10)

	BMI, mean (SD): I = 24.1 (4.3) kg/m^2, C = 25.4 (5.0) kg/m^2 **Singleton pregnancy (%)**: I = 97.5, C = 98.1 **Psychosocial health/socioeconomic status**: not stated **Ethnicity (%)**: Irish nationality, I = 92.6, C = 83.9
Inclusion criteria	Women with ≥2 of the following criteria: ongoing viable intrauterine pregnancy before 22 weeks of gestation, persistent vomiting (>3 episodes of vomiting per 24 hours), severe nausea, dehydration diagnosed by the presence of ketonuria, or electrolyte imbalance not attributable to other causes **Exclusion**: confirmed urinary tract infection, molar pregnancy, nonviable pregnancy, women who had already received treatment for nausea and vomiting of pregnancy outside of the trial, women living too far from the hospital for day care treatment to be an option
Follow up	until resolution of nausea and vomiting of pregnancy
Intervention	Initial day care At day care unit or emergency department, after which patients returned home with instruction to present on a daily basis to the day care unit until resolution of symptoms. Included 2 L of fluid (normal saline) intravenously over 5 h, plus antiemetics and vitamins, administered according to a standardized stepwise protocol, as needed.
Participants (n)	42
Drop-outs, n (%)	42-39= 3 (7%)
Comparison	Inpatient management Included 1 L of fluid (normal saline) intravenously over 3 h, followed by 1 L every 6 h, plus the same stepwise protocol for antiemetics and vitamins as the I-group
Participants (n)	56
Drop-outs, n (%)	56-54= 2 (4%)
Primary outcomes	**Nausea**

	NA **Vomiting** NA **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** No. of overnight stays; Median (interquartile range): I (n = 42) = 0 (0 to 2) C (n = 56) = 2 (1 to 4) Test of difference: p < 0.001 Total no. of day care visits for hyperemesis gravidarum; Median (interquartile range): I (n = 42) = 2 (1 to 4) C (n = 56) = 1 (1 to 4) Test of difference: p= 0.30 Total no. of inpatient admissions for hyperemesis gravidarum; Median (interquartile range): I (n = 42) = 0 (0 to 1) C (n = 56) = 1 (1 to 2) Test of difference: p < 0.001 **Health-related quality of life** NA **Babies born small-for-gestational-age (SGA)** Neonatal birth weight (g); Mean (SD): I (n = 39) = 3.327 (774) C (n = 54) = 3.556 (692) Test of difference: p = 0.15

	Babies born preterm NA
Reported adverse events (overall)	NA
Comments **Risk of bias**	 Moderate

Author	Mitchell-Jones
Year	2017
Country	United Kingdom
Ref #	[13]
Study design	RCT (non-randomised preference trial arm not reported here)
Setting	Outpatient and inpatient care
Recruitment	Among pregnant women presenting to secondary care for treatment between February 2014 and March 2016 (from June 2014 including a preference arm)
Population	(baseline reported without drop-outs, I: n=39, C: n=32) **Mean age (SD)**: I = 28.0 (4.6) years, C = 28.8 (6.7) years **Severity of symptoms**: PUQE score, mean (SD), I = 12.5 (2.2); C = 12.9 (2.3) **Duration of symptoms**: not stated **Gestational week (SD)**: I = 10.0 (2.7), C = 9.6 (2.7) **BMI, mean (SD)**: I = 23.9 (5.1) kg/m^2, C = 24.1 (6.1) kg/m^2 **Singleton/twin pregnancies**: not stated **Psychosocial health/socioeconomic status**: Employment status (%) Employed, I = 61.5, C = 46.9 Unemployed, I = 15.4, C = 25.0

	Primary care of children, I = 23.1, C = 28.1 **Ethnicity (%)**: Caucasian, I = 35.9%, C = 37.5% Asian, I = 23.1%, C = 15.5% Black, I = 23.1%, C = 21.9% Other, I = 17.9%, C = 25.0%
Inclusion criteria	(1) up to 20 weeks' gestation, (2) persistent severe nausea and vomiting and (3) ketonuria (≥1+ urinary ketones on dipstick) **Exclusion**: (1) gestation > 20 weeks, (2) any medical condition that may manifest as nausea and vomiting (eg, urinary tract infection), (3) pre-existing medical condition requiring higher level monitoring (eg, diabetes mellitus, cardiac disease), (4) serum potassium ≤3.2mmol/L and/or serum sodium level ≤130mmol/L, (5) abnormal thyroid function associated with symptoms of hyperthyroidism (goitre, tremor and heat intolerance) and (6) transaminase levels (alkaline phosphatase (ALT) or aspartate aminotransferase (AST) of ≥250IU/L
Follow up	24 hours postpresentation 48 hours postpresentation 7 days postdischarge (compare presentation) 7 days postdischarge (compare discharge) (not reported here)
Intervention	Ambulatory (outpatient) treatment Attended a care unit daily, treated with 2 L of 0.9% sodium chloride solution with 20 mmol potassium chloride intravenously over 4 h, bolus dose(s) of antiemetic(s) intravenous or intramuscular while at the care unit, and regular oral medication while at home
Participants (n)	41
Drop-outs, n (%)	41-39= 2 (5%)
Comparison	Inpatient care Admitted to gynaecology ward, treated with intravenous 0.9% sodium chloride solution with 20 mmol potassium chloride (1 L over 2 h, 1 L over 4 h, 1 L over 6 h, each subsequent 1 L over 8 h), antiemetics given by mouth, intramuscular or intravenous injection

Participants (n) **Drop-outs, n (%)**	36 36-32= 4 (11%)
Primary outcomes	**Nausea and vomiting** Nausea, vomiting and retching (PUQE-score), reduction compared to presentation (min = 3; max = 15; higher= worse); Mean (SD): - 24 hours post presentation I (n = 39) = 4.7 (2.6) C (n = 32) = 5.2 (3.0) Test of difference: p= 0.483 Effect size*: MD (95% CI) = -0.50 (-1.82 – 0.82), p = 0.46 - 48 hours post presentation I (n = 38) = 7.3 (2.7) C (n = 31) = 7.0 (3.1) Test of difference: p= 0.595 - 7 days post discharge I (n = 36) = 6.2 (4.1) C (n = 31) = 5.7 (3.5) Test of difference: p= 0.608 **Inability to tolerate oral fluids or food** Eating score, (1= normal, 2= nearly normal, 3= less than normal, 4= virtually nothing, 5= nothing), reduction from presentation; Mean (SD): - 24 hours post presentation I (n = 39) = 1.1 (1.1) C (n = 32) = 1.3 (1.3) Test of difference: p= 0.353 Effect size*: MD (95% CI) = -0.20 (-0.77 – 0.37), p = 0.49

	- 48 hours post presentation I (n = 38) = 1.9 (1.1) C (n = 32) = 2.1 (1.2) Test of difference: p= 0.479 - 7 days post discharge I (n = 36) = 2.1 (1.3) C (n = 31) = 1.8 (1.5) Test of difference: p= 0.376 Drinking score, (1= normal, 2= nearly normal, 3= less than normal, 4= virtually nothing, 5= nothing), reduction from presentation; Mean (SD): - 24 hours post presentation I (n = 39) = 1.3 (1.2) C (n = 32) = 1.4 (1.3) Test of difference: p= 0.824 Effect size*: MD (95% CI) = -0.10 (-0.69 – 0.49), p = 0.74 - 48 hours post presentation I (n = 38) = 2.0 (1.1) C (n = 32) = 2.1 (0.9) Test of difference: p= 0.969 - 7 days post discharge I (n = 36) = 2.2 (1.2) C (n = 31) = 1.7 (1.3) Test of difference: p= 0.063
Secondary outcomes	**Hospital treatment** Reattendance to emergency department within 7 days following discharge; N (%): I (n = 37) = 10 (27.0)

	C (n = 31) = 8 (25.8) Test of difference: p= 0.270 Repeat inpatient/outpatient treatment within 7 days following discharge; N (%): I (n = 37) = 9 (24.3) C (n = 31) = 8 (25.8) Test of difference: p= 0.243 Effect size*: RD (95% CI) =-0.01 (-0.22 to 0.19); p= 0.89; RR (95% CI) = 0.94 (0.41 to 2.15); p= 0.89 **Health-related quality of life** Well-being rating, (from 0= 'feeling absolutely awful, the worst I've ever felt', to 10= 'feeling absolutely wonderful, the best I've ever felt'), improvement from presentation; Mean (SD): - 24 hours post presentation I (n = 39) = −3.0 (2.3) C (n = 32) = −3.9 (2.3) Test of difference: p= 0.120 Effect size*: MD (95% CI) = 0.90 (-0.18 to 1.98), p = 0.10 - 48 hours post presentation I (n = 38) = −4.6 (2.4) C (n = 32) = −5.5 (2.9) Test of difference: p= 0.174 - 7 days post discharge I (n = 36) = −4.7 (2.9) C (n = 31) = −4.7 (3.0) Test of difference: p= 0.983 **Babies born small-for-gestational-age (SGA)** NA

	Babies born preterm NA
Reported adverse events (overall)	One adverse incidence occurred with suspected oculogyric crisis following administration of intravenous cyclizine prior to discharge
Comments **Risk of bias**	 Moderate

Author	Nelson-Piercy
Year	2001
Country	United Kingdom
Ref #	[14]
Study design	RCT
Setting	Inpatient gynaecology wards in eight collaborating centres in London
Recruitment	Among women with severe or prolonged HG, admitted to inpatient care between April 1995 and December 1996
Population	**Mean age (SD)**: not stated **Severity of symptoms**: No. vomiting ≥5 times per day, I = 6, C = 6 **Duration of symptoms**: not stated **Gestational week (SD)**: I = 10.6 (2.1), C = 8.3 (1.9) **Weight, mean (SD)**: I = 68.9 (19.8) kg, C = 61.8 (15.2) kg **Singleton pregnancies**: I = 100%, C = 92% **Psychosocial health/socioeconomic status**: not stated **Ethnicity (%)**: not stated
Inclusion criteria	onset of nausea and vomiting before 12 weeks of gestation, dependent on intravenous fluids for at least one week (first admission for hyperemesis) or 24 hours (second or subsequent admission for hyperemesis), receiving regular treatment with at

	least one anti-emetic, ketonuria on admission, mid-stream urine specimen that did not indicate infection, normal random 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, and receiving regular treatment with oral thiamine or a single dose of parenteral thiamine **Exclusion**: treatment with oral steroids in the previous two months, proven peptic ulceration requiring treatment in the previous five years, nonviable pregnancy, overt clinical features of thyrotoxicosis
Follow up	- after 72 hours (not fully reported in the article, thus not reported here) - after 1 week
Intervention	Prednisolone 40 mg daily in two divided oral doses (4 x 5 mg tablets 12 hourly), if still vomiting after three days, change to equivalent intravenous alternative (hydrocortisone 100 mg twice daily)
Participants (n)	12
Drop-outs, n (%)	0 (0%)
Comparison	Placebo 40 mg daily in two divided oral doses (4 x 5 mg tablets 12 hourly), if still vomiting after three days, change to equivalent intravenous alternative (normal saline injections twice daily)
Participants (n)	13
Drop-outs, n (%)	1 (8%)
Primary outcomes	**Nausea** Improvement in nausea score (min = 0, max = 10); Median (range): I (n = 12) = 6.5 (2.0 - 10.0) C (n = 12) = 4.0 (-5.0 to 9.0) Test of difference: p= 0.10 **Vomiting**

	Number of women still vomiting at 1 week, N (%): I (n = 12) = 5 (42%) C (n = 12) = 7 (58%) Test of difference: RR (95%CI) =1.4 (0.6-3.2) **Inability to tolerate oral fluids or food** Number of women on intravenous infusion at 1 week; N (%): I (n = 12) = 3 (25%) C (n = 12) = 3 (25%) Test of difference: RR (95%CI) = 1.0 (0.2-4.0) Improvement in food intake (min = NA, max = NA); Median (range): I (n = 12) = 2.0 (1.0 - 4.0) C (n = 12) = 1.5 (-2.0 to 4.0) Test of difference: p = 0.039
Secondary outcomes	**Hospital treatment** Length of hospital stay after randomisation (days); Median (range): I (n = 12) = 7.0 (2.0 - 21.0) C (n = 12) = 7.0 (2.0 - 26.0) Test of difference: p = 0.84 Number readmitted for hyperemesis; N (%): I (n=12) = 5 (42%) C (n=12) = 8 (67%) Effect size*: RD (95% CI) = -0.25 (-0.64 to 0.14), p = 0.20; RR (95% CI) = 0.36 (0.07 to 1.88); p = 0.22 **Health-related quality of life** Improvement in wellbeing rating (min = 0, max = 10); Median (range): I (n = 12) = 6.5 (1.0 - 10.0)

	C (n = 12) = 3.5 (-2.0 to 8.0) Test of difference: p = 0.021 **Babies born small-for-gestational-age (SGA)** Number of birthweights < 5th centile; N (%): I (n = 12) = 1 (8%) C (n = 12) = 1 (8%) Test of difference: NA Effect size*: RD (95% CI) = 0.00 (-0.22 to 0.22), p =1.00; RR (95% CI) = 1.00 (0.07 to 14.21), p = 1.00 **Babies born preterm** Number of deliveries < 37 weeks; N (%): I (n = 11) = 2 (18%) C (n = 11) = 4 (36%) Test of difference: NA Effect size*: RD (95% CI) = -0.18 (-0.55 to 0.18), p =0.33; RR (95% CI) = 0.50 (0.11 to 2.19), p = 0.36
Reported adverse events (overall)	Termination of pregnancy, stillbirth, neonatal deaths (chorioamnionitis)
Comments **Risk of bias**	Mean gestational age at trial entry higher in the steroid group (10.6 weeks) than in the placebo group (8.3 weeks), open label after completion of one-week assessment Moderate

Author	Robson
Year	2021
Country	United Kingdom
Ref #	[15]

Study design	RCT (data from internal pilot phase only)
Setting	Secondary care setting (inpatient and/or outpatient)
Recruitment	Among patients who attended 12 secondary care centers between April 2018 and August 2019
Population	**Age, median (range), overall**: 27 (18 to 38) years **Severity of symptoms, overall**: median PUQE-score (range) at baseline = 13 (7 to 15) **Duration of symptoms**: not stated **Gestational week, median (range), overall**: 8 (5 to 16) weeks **BMI or weight**: not stated **Multiple birth, overall:** 3 (9%) **Psychosocial health/socioeconomic status**: Employment status, overall (%) Full-time = 37% Part time = 15% Unemployed = 36% Self-employed = 6% Student = 6% **Ethnicity (%)**: White British, overall = 79% Other, overall = 21%
Inclusion criteria	Pregnant women suffering from severe nausea and vomiting in pregnancy, gestation of < 17 weeks, had previously taken first-line antiemetic treatment (cyclizine, chlorpromazine, promethazine, prochlorperazine or doxylamine/pyridoxine) as prescribed, that is over a minimum of 24 hours with no sustained improvement in symptoms, age ≥ 18 years, able to give informed consent, able to read/understand written English. **Exclusion**: allergy/hypersensitivity to study drug(s), prior exposure to study drug(s) intravenously or orally >72 hours, pre-existing diagnosis of a medical condition (listed in article), moderate renal impairment, severe liver

	impairment, severe diarrhea, hypokalemia, known hypomagnesaemia, vomiting caused by another underlying condition/infection, concomitant use of apomorphine or serotonergic drugs, confirmed diagnosis of severe lactose intolerance
Follow up	At day 2 At day 5 (PUQE and VAS for nausea not reported here) At day 10 (PUQE and VAS for nausea not reported here) 20 weeks' gestation (not reported here) Post birth (not reported here)
Intervention 1	Metoclopramide (and dummy ondansetron) Metoclopramide (10 mg three times daily) and dummy (three times daily); in all arms, trial medication was, in addition to i.v. rehydration, initially given intravenously and then continued orally once women were able to tolerate oral fluids for a maximum of 10 days.
Participants (n)	8
Drop-outs, n (%)	8-6= 2 (25%); outcome NVPQoL: 8-3= 5 (63%)
Intervention 2	Ondansetron (and dummy metoclopramide) Ondansetron (4 mg three times daily) and dummy (three times daily)
Participants (n)	8
Drop-outs, n (%)	outcome readmission: 0 (0%); outcome PUQE: 8-6= 2 (25%); outcome NVPQoL: 8-4= 4 (50%)
Intervention 3	Metoclopramide and ondansetron Metoclopramide (10 mg three times daily) and ondansetron (4 mg three times daily)
Participants (n)	9
Drop-outs, n (%)	outcome readmission: 0 (0%); outcome PUQE: 9-7= 2 (22%); outcome NVPQoL: 9-5= 4 (44%)
Comparison	Placebo (dummy metoclopramide and dummy ondansetron)

	Double dummy (three times daily)
Participants (n)	8
Drop-outs, n (%)	outcome readmission: 0 (0%); outcome PUQE: 8-5= 3 (38%); outcome NVPQoL: 8-5= 3 (38%)
Primary outcomes	**Nausea/ Vomiting/Retching** Nausea, vomiting and retching over the past 24h (PUQE score) (min = 3; max = 15; higher= worse), at day 2; median (minimum; maximum): I1 (n = 6) = 9 (3; 13) I2 (n = 6) = 5 (3; 13) I3 (n = 7) = 7 (3; 11) C (n = 5) = 8 (3; 12) Test of difference: NA **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** Number of readmissions within 10 days; median (minimum; maximum): I1 (n = 6) = 0 (0; 3)* I2 (n = 8) = 0 (0; 2)* I3 (n = 9) = 0 (0; 1)* C (n = 8) = 0 (0; 1)* Test of difference: NA **Health-related quality of life** Health-related nausea and vomiting during pregnancy quality-of-life (NVPQoL) (min = NA; max = 210; higher= worse), at day 10; median (minimum; maximum): I1 (n = 3) = 148 (88, 175) I2 (n = 4) = 160 (88, 196)

	I3 (n = 5) = 155 (40, 170) C (n = 2) = 105 (81, 128) Test of difference: NA **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** NA
Reported adverse events (overall)	Termination for fetal abnormality, termination for other reasons, right calf deep-vein thrombosis, incidental paronychia
Comments **Risk of bias**	 Moderate

Author	Safari
Year	1998
Country	USA
Ref #	[16]
Study design	RCT
Setting	Inpatient care 2 days, thereafter outpatient care
Recruitment	Among women with HG admitted to the hospital for rehydration between July 1996 and April 1997
Population	**Mean age (SD)**: I = 27 (5.8) years; C = 24.8 (5.8) years **Severity of symptoms**: loss of >5% body weight, I = 40%, C = 50% **Duration of symptoms, median (range)**: I = 14 (6 to 64) days; C = 28 (5 to 75) days (longer in C, p=.03) **Gestational week (SD)**: I = 9.8 (2.1); C = 9.5 (2.7) **BMI or weight**: not stated

	Singleton/twin pregnancies: not stated **Psychosocial health/socioeconomic status**: not stated **Ethnicity (%)**: not stated
Inclusion criteria	patients with an intrauterine normal-appearing pregnancy of ≤16 weeks' gestation with the diagnosis of HG (persistent vomiting, large ketonuria, and weight loss) for whom nausea and vomiting did not resolve after intravenous hydration in an outpatient triage area, or for whom this was the second admission for hyperemesis **Exclusion**: molar gestation, medical complications contraindicating or requiring steroid use, unclear etiology of nausea and vomiting
Follow up	-at 2 days -at 2 weeks after discharge -at delivery (data not reported here due to high risk of bias)
Intervention	Methylprednisolone after initial intravenous rehydration, methylprednisolone 16 mg orally 3 times a day for 3 days, followed by a tapering regimen (halving of dose every 3 days) to none for 2 weeks; patients with response to therapy were discharged on the second hospital day and were instructed to continue the remainder of their assigned medication
Participants (n)	20
Drop-outs, n (%)	-at 2 days: 0 -at 2 weeks after discharge: 20-17=3 (15%) -at delivery: 20-12=8 (40%)
Comparison	Promethazine (Phenergan) after initial intravenous rehydration, promethazine 25 mg tablets 3 times a day for a total period of 2 weeks; as for the intervention group, patients with response to therapy were discharged on the second hospital day with assigned medication
Participants (n)	20
Drop-outs, n (%)	-at 2 days: 0

	-at 2 weeks after discharge: 20-17=3 (15%) -at delivery: 20-11=9 (45%)
Primary outcomes	**Nausea/Vomiting/Inability to tolerate oral fluids or food** Number of patients with treatment failure in 2 days (persistent vomiting >5 times per day, inability to tolerate liquids by mouth, or the patient's impression that she was not better); N (%): I (n = 20) = 3 (15%) C (n = 20) = 2 (10%) Test of difference: p= 0.0001 **Nausea** NA **Vomiting** NA **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** Number of patients readmitted to hospital after 2 weeks for recurrence of vomiting; N (%): I (n = 17) = 0 (0%) C (n = 17) = 5 (29%) Test of difference: p= 0.0001 **Health-related quality of life** NA **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** NA

Reported adverse events (overall)	Termination of pregnancy, Neonatal death (Smith-Lemli-Opitz syndrome)
Comments	Patients in the promethazine group had significantly longer duration of symptoms at baseline. If therapy failure after 2 days, the patient's study participation ended, and the alternative study drug was offered.
Risk of bias	Moderate for outcomes at 2 days and at 2 weeks

Author	Sahakian
Year	1991
Country	USA
Ref #	[17]
Study design	RCT
Setting	Outpatient care
Recruitment	By care-providing physicians and nurses between July 1989 and August 1990
Population	**Mean age (SD)**: All nausea patients: I = 29.4 (5.6) years, C = 28.1 (5.3) years **Severity of symptoms**: In subgroup with severe nausea patients (nausea score >7): Nausea score (mean, SD), I = 8.2 (0.8), C = 8.7 (0.9) Vomiting at baseline (%), I = 58%, C =60% **Duration of symptoms**: not stated **Gestational week (mean, range)**: All nausea patients: I = 9.3 (6.0 to 15.5), C = 9.7 (6.0 to 19.0) **BMI or weight**: not stated **Singleton/twin pregnancies**: not stated **Psychosocial health/socioeconomic status**: not stated **Ethnicity (%)**: not stated

Inclusion criteria	not stated, included women with nausea and vomiting and viable pregnancy **Exclusion**: other medical condition that might manifest itself with nausea and vomiting, requirement of hospitalization
Follow up	at 72 hours (3 days)
Intervention	Vitamin B6 (pyridoxine hydrochloride) 25 mg tablets orally every 8 hours for 3 days, advice to divide meals into frequent small ones rich in carbohydrates and low in fat
Participants (n)	31 in total; 12 with severe nausea
Drop-outs, n (%)	NA; in total: 74-59=15 (20%)
Comparison	Placebo 25 mg tablets orally every 8 hours for 3 days, same advice regarding meals as the intervention group
Participants (n)	28 in total; 10 with severe nausea
Drop-outs, n (%)	NA; in total: 74-59=15 (20%)
Primary outcomes	**Nausea** (severe nausea-patients only) Difference from baseline in severity of nausea on a visual analogue scale (min = 0; max = 10; higher= worse); Mean (SD): I (n = 12) = -4.3 (2.1) C (n = 10) = -1.8 (2.2) Test of difference: $p < 0.01$ Effect size*: MD (95% CI) = -2.50 (-4.31to -0.69), p = 0.007 **Vomiting** (severe nausea-patients only) Number of patients with vomiting; N (%): I (n = 12) = 3 (25%) C (n = 10) = 7 (70%)

	Test of difference: p > 0.05 Effect size*: RD (95% CI) = -0.45 (-0.83 to -0.07), p= 0.02; RR (95% CI) = 0.36 (0.12 to 1.03), p = 0.06 **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** NA **Health-related quality of life** NA **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** NA
Reported adverse events (overall)	NA
Comments **Risk of bias**	 Moderate

Author	Shin
Year	2007
Country	South Korea
Ref #	[18]
Study design	RCT
Setting	Inpatient care
Recruitment	Among women admitted to two hospitals between April 2003 and April 2004
Population	**Mean age**: I = 29.4 years; C1 = 29.5 years; C2 = 28.4 years

	Severity of symptoms: mean daily degree of nausea and vomiting at admission, revised version of RINVR (min = 6; max = 30; higher = worse) I = 26.26; C1 = 26.24; C2 = 25.86 **Duration of symptoms**: not stated **Gestational week**: (in days) 35 to 49 days: I = 21.7%; C1 = 33.3%; C2 = 18.2% 50 to 60 days: I = 21.7%; C1 = 19.0%; C2 = 36.4% 61 to 72 days: I = 26.1%; C1 = 28.6%; C2 = 27.3% 73 days: I = 30.4%; C1 = 19.0%; C2 = 18.2% **BMI or weight**: not stated **Singleton/twin pregnancies**: not stated **Psychosocial health/socioeconomic status**: not stated **Ethnicity (%)**: not stated
Inclusion criteria	women diagnosed with HG (defined as consistent nausea and vomiting, electrolyte imbalance, more than 5% loss of weight, dehydration, positive ketonuria and increased urine specific gravity), aged 20 to 40 years, between 5 and 30 weeks of gestational stage, receiving only conventional intravenous fluid therapy **Exclusion**: complications of pregnancy such as anaemia (haemoglobin less than 10 g/dL), pyelonephritis, thyroid disorder, pregnancy-induced hypertension or diabetes, hydatidiform mole, cervical incompetence and other chronic diseases, for example: cardiac, renal, or pulmonary diseases
Follow up	-at 24 hours after treatment -at 48 hours after treatment -at discharge
Intervention	Acupressure (P6) From the second day of hospitalization up to the day before discharge, 7-second acupressure applied to Nei-Guan point (using a thumb) with 2-second pauses, three times daily before meals; each session lasted 10 mins; in addition, conventional IV fluid therapy (SBU's interpretation of text in the Research intervention section, p 513)

Participants (n) **Drop-outs, n (%)**	23 0
Comparison 1 **Participants (n)** **Drop-outs, n (%)**	Placebo Applied with the thumb for 7 seconds with 2-second pauses to a bony part around the radial pulse at the wrist, three times daily before meals for 10 mins; in addition, conventional IV fluid therapy (SBU's interpretation of text in the Research intervention section, p 513) 21 0
Comparison 2 **Participants (n)** **Drop-outs, n (%)**	Control Received conventional IV fluid therapy (standard care) 22 0
Primary outcomes	**Nausea/ Vomiting** Index of Nausea, Vomiting and Retching, INVR; (min = 6; max = 30; higher= worse); Mean (SD): -at 24 hours after treatment I (n = 23) = 17.57 (NA) C1 (n = 21) = 22.05 (NA) C2 (n = 22) = 21.59 (NA) Test of difference (between all 3 groups): ANOVA post hoc contrast: F = 4.55, p=0.014 -at 48 hours after treatment I (n = 23) = 12.48 (NA)

	C1 (n = 21) = 19.38 (NA) C2 (n = 22) = 17.91 (NA) Test of difference (between all 3 groups): ANOVA post hoc contrast: F = 12.40, p < 0.001 -at discharge I (n = 23) = 9.22 (NA) C1 (n = 21) = 14.67 (NA) C2 (n = 22) = 13.05 (NA) Test of difference (between all 3 groups): ANOVA post hoc contrast: F = 12.28, p < 0.001 **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** NA **Health-related quality of life** NA **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** NA
Reported adverse events (overall)	NA
Comments **Risk of bias**	Study inclusion criteria of gestational stage 5 to 30 weeks exceeds our inclusion limit of 20 weeks gestation, but none of the included participants had more than 73 days of gestation (about 10.5 weeks) Moderate

Author	Sullivan
Year	1996
Country	USA
Ref #	[19]
Study design	RCT
Setting	Inpatient care
Recruitment	Among women admitted with severe HG between July 1993 and November 1994
Population	**Mean age (SD)**: I = 20.8 (3.4) years; C = 23.0 (5.0) years **Severity of symptoms**: I = 6.45*; C = 6.38* **Duration of symptoms**: not stated **Gestational week (SD)**: I = 11.0 (2.7); C = 10.2 (3.8) **Weight (mean, SD)**: I = 64.0 (19.5) kg; C = 74.4 (24.0) kg **Singleton/twin pregnancies**: singleton only **Psychosocial health/socioeconomic status**: not stated **Ethnicity (%)**: 29 black women and 1 white woman
Inclusion criteria	severe HG during the first and early second trimesters of pregnancy that had not been previously treated by IV medication or hospitalization; criteria indicative of severity requiring hospitalization included at least two of the following: (1) at least a 2.25 kg weight loss compared to the initial prenatal visit or a previous outpatient record, (2) ketonuria >80 mg/dl in a random urine specimen, (3) hypokalemia (potassium <3.0 mEq/dl) or hyponatremia (sodium <134 mEq/dl) requiring IV replacement, (4) positive test result for serum acetone, or (5) more than two visits to the obstetric emergency department for HG, which required IV hydration or promethazine suppositories as outpatient treatment **Exclusion**: not severe HG, preexisting medical condition, eating disorder, or psychiatric disease, or a multiple or molar gestation that would preclude the diagnosis
Follow up	-every 8 hours days 1 to 5 (averaged into a daily nausea score) -48 hours (cut-off for treatment failure)

	-until discharge
Intervention **Participants (n)** **Drop-outs, n (%)**	Ondansetron After initiated intravenous rehydration, ondansetron 10 mg intravenously infused over 30 mins, first dose mandatory, thereafter all doses given on as needed basis every 8 hours until the patient was ingesting a bland diet 15 15-13=2 (13%) treatment failures at 48 hours
Comparison **Participants (n)** **Drop-outs, n (%)**	Promethazine After initiated intravenous rehydration, promethazine 50 mg intravenously, following the same protocol as the intervention group 15 15-12=3 (20%) treatment failures at 48 hours
Primary outcomes	**Nausea/Vomiting** Number of participants with treatment failure (no change in nausea or emesis after 48 hours of medication and hydration); N (%): I (n = 15) = 2 (13%) C (n = 15) = 3 (20%) Test of difference: p = 1.00 (Data on nausea also possible to extract from figure, not tabulated here) **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** Length of hospital stay, days; Mean (SD): I (n = 13) = 4.47 (2.3) C (n = 12) = 4.47 (1.5) Test of difference: p = 1.00

	Health-related quality of life NA **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** NA
Reported adverse events (overall)	Sedation
Comments **Risk of bias**	If no change in nausea or emesis after 48 hours, the patient was considered a treatment failure and excluded from further data collection Low for primary outcome (nausea/vomiting) Moderate for secondary outcome (hospital treatment)

Author	Tan
Year	2009
Country	Malaysia
Ref #	[20]
Study design	RCT
Setting	Inpatient care
Recruitment	Among women first-time admitted to the ward between June 2006 and March 2007
Population	**Mean age (SD)**: I = 27.7 (4.2) years; C = 28.5 (4.7) years **Severity of symptoms**: Median (IQR) nausea score (0 – 10) at recruitment, I = 7 (5), C = 7 (4) **Duration of symptoms**: not stated **Gestational week (SD)**: I = 10.5 (3.1), C =9.6 (2.8) **Weight (kg, SD)**: I = 55.2 (11.9), C = 53.5 (9.5)

	Singleton pregnancies: only singleton pregnancies (one exclusion in control group due to twins) **Psychosocial health/socioeconomic status**: not stated **Ethnicity (%)**: Malay, I = 87.5%, C = 84.8% Chinese, I = 2.1%, C = 2.2% Indian, I = 8.3%, C = 1.9% Others, I = 2.1%, C = 2.2%
Inclusion criteria	presumed HG (severe nausea and vomiting during pregnancy with clinical features warranting hospitalization), gestation of less than 20 weeks, first hospital admission and enrolment within 12 h of admission **Exclusion**: multiple pregnancies, prior outpatient pyridoxine use, and other concurrent illnesses, which might exacerbate the symptoms of nausea and vomiting, or which could have delayed recovery
Follow up	- at hospital discharge - week 1 - week 2
Intervention	Vitamin B6 (pyridoxine) 20 mg orally three times per day in conjunction with standard therapy of intravenous rehydration, metoclopramide, and oral thiamine, continued for 2 weeks after discharge; any anti-emetic started before ward admission was stopped; treatment regimen was often altered by providers at second admission
Participants (n)	48
Drop-outs, n (%)	- at hospital discharge: 48-47=1 (2%)
Comparison	Placebo (tic tac) Given with the same regimen, and in conjunction with the same standard therapy as the intervention group

Participants (n) **Drop-outs, n (%)**	46 - at hospital discharge: 46-45=1 (2%)
Primary outcomes	**Nausea** - at hospital discharge Nausea on a visual analogue scale (min = 0; max = 10; higher= worse); Median (interquartile ranges): I (n = 47) = 2 (4) C (n = 45) = 2(3) Test of difference: p= 0.38 **Vomiting** - at hospital discharge Number of women with any vomiting in the last 24h; N (%): I (n = 47) = 19 (40%) C (n = 45) = 13 (29%) Test of difference: RR (95% CI) = 1.4 (0.8–2.5), p= 0.28 Effect size*: RD (95% CI) = 0.12 (-0.08 to 0.31), p = 0.83; RR (95% CI) = 1.4 (0.79 to 2.49), p = 0.25 **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** Hospital stay, days; Mean (SD): I (n = 47) = 3.9 (2.3) C (n = 45) = 3.1 (1.0) Test of difference: p=0.112 Effect size*: MD (95% CI) = 0.80 (0.08 to 1.52), p = 0.03 **Health-related quality of life**

	Overall wellbeing on a visual analogue scale, week 1 (min=0, max=10; higher= better); Median (IQR): I (n = 33) = 8 (3) C (n = 33) = 8 (3) Test of difference: p=0.81 Overall wellbeing on a visual analogue scale, week 2 (min=0, max=10; higher= better); Median (IQR): I (n = 24) = 8 (1) C (n = 28) = 9 (1) Test of difference: p=0.73 **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** NA
Reported adverse events (overall)	Dizziness, headaches, diarrhoea, palpitations, dry mouth.
Comments **Risk of bias**	Low at discharge (moderate later follow-ups, due to dropout)

Author **Year** **Country** **Ref #**	Tan 2010 Malaysia [21]
Study design **Setting**	RCT Inpatient care

Recruitment	Among women with HG and need of intravenous antiemetic therapy, first time admitted to the gynecology ward between November 2008 and August 2009
Population	**Mean age (SD)**: I = 27.8 (3.5) years; C = 27.8 (4.2) years **Severity of symptoms**: mean (range) nausea score on VNRS (min = 1; max = 10; more = worse), I = 5 (2.75 to 7); C =5 (1.5 to 7) **Duration of symptoms**: not stated **Gestational week (SD)**: I = 9.2 (2.3); C = 9.3 (2.6) **BMI**: I = 23.0 (3.5); C = 22.5 (4.2) **Singleton/twin pregnancies**: only singleton (multiple gestation was an exclusion criteria) **Psychosocial health/socioeconomic status**: not stated **Ethnicity (%)**: Malay, I =74.0%); C = 81.6% Indian, I = 17.8%; C = 13.2% Chinese, I = 4.1%; C = 2.6% Other, I = 4.1%; C = 2.6%
Inclusion criteria	clinical HG with dehydration and detectable ketonuria by urine dipstick at a gestation of 16 weeks or less **Exclusion**: multiple gestation, established nonviable pregnancy, preexisting medical condition that can cause nausea and vomiting (eg, culture-proven symptomatic urinary tract infection or dengue fever), gastrointestinal causes of vomiting (eg, gastroenteritis), medical causes of vomiting (eg, diabetic ketoacidosis), and known allergy to metoclopramide or promethazine
Follow up	-at 8 hours -at 16 hours -at 24 hours
Intervention	Metoclopramide 10 mg metoclopramide administered by slow injection intravenously just after randomization and thereafter every 8 hours for 24 hours (in total 4 doses); in

	addition to intravenous antiemetic, standard care included intravenous rehydration with saline (with the addition of potassium chloride as required if hypokalemic), and oral thiamine 10 mg daily
Participants (n)	79
Drop-outs, n (%)	79-73=6 (7.6%), excluded for criteria infringements
Comparison	Promethazine 25 mg promethazine administered according to the same protocol as the intervention group
Participants (n)	80
Drop-outs, n (%)	80-76=4 (5.0%), excluded for criteria infringements
Primary outcomes	**Nausea** Nausea, visual numerical rating scale (min = 1; max = 10; higher= worse); Median (interquartile range): - at 8 h (n= 143) I (n = NA) = 4 (1.5 to 5) C (n = NA) = 4 (1.75 to 6) Test of difference: p= 0.54 - at 16 h (n= 137) I (n=NA) = 3 (1 to 5) C (n= NA) = 3 (1 to 5) Test of difference: p= 0.80 - at 24 h (n=126) I (n=NA) = 2 (1 to 5) C (n= NA) = 2 (1 to 4) Test of difference: p= 0.99 **Vomiting**

	Number of vomiting episodes in the first 24 hours; Median (interquartile range): total n= 144 I (n = NA) = 1 (0 to 5) C (n = NA) = 2 (0 to 3) Test of difference: .81 **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** Hospital stay, days; Median (interquartile range): I (n=73) = 1.8 (1.5 to 2.5) C (n= 76) = 1.7 (1.5 to 2.4) Test of difference: p= 0.71 **Health-related quality of life** Well-being at 24 hours, visual numerical rating scale (min = 1; max = 10; higher= better); Mean (SD): total n= 142 I (n = NA) = 7.6 (2.2) C (n = NA) = 7.1 (2.3) Test of difference: p= 0.24 **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** NA
Reported adverse events (overall)	felt drowsy, unable to sleep, dry mouth, felt dizzy, diarrhoea, headache, palpitations, involuntary muscle movement, skin rash

Comments	
Risk of bias	Low

Author	Tan
Year	2013
Country	Malaysia
Ref #	[22]
Study design	RCT
Setting	Inpatient care
Recruitment	Among women with HG and need of intravenous antiemetic therapy, first time admitted to the gynecology ward no more than 2 hours ago between November 2010 and February 2012
Population	**Mean age (SD)**: I = 28.5 (4.6) years; C = 29.3 (4.6) years **Severity of symptoms**: mean (range) nausea score on VNRS (min = 1; max = 10; more = worse), I = 9 (7 to 10); C = 9 (7 to 10) **Duration of symptoms**: not stated **Gestational week (SD)**: I = 9.8 (2.8); C = 9.8 (2.5) **BMI**: I = 24.0 (4.5); C = 23.7 (4.5) **Singleton/twin pregnancies**: singleton only (multiple gestation was excluded) **Psychosocial health/socioeconomic status**: education (%) Primary, I = 5.4%; C = 1.8% Secondary, I = 40.5%; C = 45.9% Tertiary, I = 54.1%; C = 52.3% **Ethnicity (%)**: Malay, I = 76.6%; C = 76.6% Indian, I = 9.9%; C = 15.3%

	Other, I = 13.5%; C = 8.1%
Inclusion criteria	first hospitalization for HG (intractable nausea and vomiting of pregnancy with dehydration and starvation clinically judged to require hospitalization for IV rehydration and antiemetic drug administration), age 18 years or older, ketonuria by urine dipstick of at least 1+, gestation 16 weeks or less, plasma glucose 110 mg/dL or less, and sodium 125 mmol/L or greater **Exclusion**: multiple gestation, established nonviable pregnancy, pre-existing medical conditions that can cause nausea and vomiting (eg, culture-proven symptomatic urinary tract infection, dengue fever), gastrointestinal causes of vomiting (eg, gastroenteritis, gastritis, peptic ulcer), medical causes of vomiting (eg, diabetic ketoacidosis), and women with underlying medical problems (eg, established gestational hypertension, diabetes, heart disease, renal disease, and thyroid disorder)
Follow up	-at 8 hours -at 16 hours -at 24 hours -at medical decision to discharge
Intervention	Dextrose saline rehydration In addition to 250 mg thiamine and an antiemetic intravenously (typically 10 mg metoclopramide 8 hourly for 24 hours or until significant symptom relief), 5% dextrose-0.9% saline by intravenous infusion at a rate of 125 mL/h over 24 hours, thereby providing 150 g of glucose (equivalent to 600 calories) over 24 hours; potassium chloride added as required; oral intake allowed as tolerated
Participants (n)	111
Drop-outs, n (%)	111-102=9 (8%)
Comparison	Normal saline rehydration In addition to 250 mg thiamine and an antiemetic intravenously as in the intervention group, 0.9% saline by intravenous infusion at a rate of 125 mL/h over 24 hours; potassium chloride added as required; oral intake allowed as tolerated
Participants (n)	111

Drop-outs, n (%)	111-101=10 (9%)
Primary outcomes	**Nausea** Nausea, visual numerical rating scale (min = 1; max = 10; higher= worse); Median (interquartile range): - at 8h I (n = 102) = 6 (4 to 7) C (n = 101) = 7 (5 to 8) Test of difference: p< 0.01 - at 16 h I (n = 102) = 4 (2 to 5) C (n = 101) = 5 (3 to 6) Test of difference: p= 0.03 - at 24 h I (n = 102) = 2 (1 to 4) C (n = 101) = 2 (2 to 4) Test of difference: p= 0.39 **Vomiting** Vomiting episodes, at the end of the 24-hour study period; Median (interquartile range): I (n = 102) = 0 (0 to 2) C (n = 101) = 0 (0 to 2) Test of difference: p= 0.66 **Inability to tolerate oral fluids or food** Recording of first oral intake, h after recruitment; Mean (SD) I (n = 101) = 11.2 (5.7) C (n = 99) = 13.2 (6.0)

	Test of difference: p= 0.022 Oral intake of any quantity of solids or fluids; n (%): - at 8h I (n = 101) = 40 (40%) C (n = 99) = 24 (24%) Test of difference: RR (95%CI) = 2.0 (1.1–3.8); p= 0.023 - at 16h I (n = 101) = 84 (83%) C (n = 99) = 78 (79%) Test of difference: RR (95%CI) = 1.3 (0.7–2.7); p= 0.47 - at 24h I (n = 101) = 98 (97.0) C (n = 99) = 93 (93.9) Test of difference: RR (95%CI) = 2.1 (0.5–8.7); p= 0.33
Secondary outcomes	**Hospital treatment** Hospital stay (h); Mean (SD): I (n = 102) = 43 (21) C (n = 101) = 48 (21) Test of difference: p= 0.14 **Health-related quality of life** Well-being score at 24 h, VNRS (min = 1; max = 10; higher= better); Mean (SD): I (n = 102) = 8.5 (1.6) C (n = 101) = 8.4 (1.5) Test of difference: p= 0.75 **Babies born small-for-gestational-age (SGA)**

	NA **Babies born preterm** NA
Reported adverse events (overall)	NA
Comments **Risk of bias**	After the 24-hour main study period, open-label intravenous fluid was started if still required Low

Author **Year** **Country** **Ref #**	Tan 2020 Malaysia [23]
Study design **Setting** **Recruitment** **Population**	RCT Inpatient care Among women with HG, first time admitted to the gynecology ward no more than 2 hours ago between April 2016 and April 2017 **Mean age (SD)**: I = 29.0 (4.5) years; C = 29.8 (5.1) years **Severity of symptoms**: mean (range) nausea score on VNRS (min = 0; max = 10; more = worse), I = 5 (3 to 8); C = 6 (5 to 8) **Duration of symptoms**: not stated **Gestational week (SD)**: I = 9.8 (2.7); C = 9.2 (2.6) **BMI**: I = 22.9 (4.6); C = 24.2 (5.1) **Singleton/twin pregnancies**: singleton only (multi-gestation was excluded) **Psychosocial health/socioeconomic status**: occupation (%) Unemployment, I = 30%; C =21%

	Ethnicity (%): Malay, I = 66%; C = 5% Chinese, I = 5%; C = 5% Indian, I = 20%; C = 5% Others, I = 9%; C = 5%
Inclusion criteria	women ≥18 years of age at ≤16 weeks of gestation hospitalized for HG (defined as when nausea and vomiting are of a severity to cause dehydration and starvation with hospitalisation) for the first time in the pregnancy who had ≥2+ urinary ketones by dipstick; severe weight loss, electrolyte imbalance or severe dehydration were not specifically required for study eligibility **Exclusion**: known multi-gestation, molar or non-viable pregnancy and a medical condition that contraindicates oral feeding or fasting
Follow up	-at 8 hours -at 16 hours -at 24 hours -at discharge
Intervention	Delayed oral feeding First 12 hours, encouraged to fast during standard inpatient care, which comprised intravenous rehydration with normal saline solution (with potassium chloride added if required for hypokalaemia), intravenous anti-emetic drug (first-line 10 mg metoclopramide 8-hourly) and supplementation with oral thiamine 1 mg daily; after 12 hours, food packages (containing an assortment of sweet biscuits and apple or orange juices) for resumption of feeding at own pace
Participants (n)	80
Drop-outs, n (%)	0
Comparison	Early oral feeding Identical food package handed over at recruitment, encouraged to resume oral intake of both fluid and solid as soon as, as much as, and as often as could be tolerated, while receiving same standard inpatient care as the intervention group

Participants (n) **Drop-outs, n (%)**	80 0
Primary outcomes	**Nausea** Nausea score, VNRS (min = 0; max = 10; higher= worse); Median (interquartile range): - at 8 h I (n = 80) = 3 (1 to 5) C (n = 80) = 5 (2 to 6) Test of difference: p= 0.046 - at 16 h I (n = 80) = 2 (0 to 5) C (n = 80) = 2 (0 to 4) Test of difference: p= 0.26 - at 24 h I (n = 80) = 0 (0 to 4) C (n = 80) = 1 (0 to 4) Test of difference: p= 0.34 **Vomiting** Vomiting frequency in first 24 hours; Median (interquartile range): I (n = 80) = 1 (0 to 4) C (n = 80) = 1 (0 to 5) Test of difference: p= 0.24 **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment**

	Duration of hospitalisation (days); Median (interquartile range): I (n = 80) = 2 (1 to 2) C (n = 80) = 2 (1 to 2) Test of difference: p= 0.57 **Health-related quality of life** NA **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** NA
Reported adverse events (overall)	Felt drowsy, unable to sleep, dry mouth, felt dizzy, headache, experienced palpitation, experienced tremors, experienced extreme hunger. No major harms of aspiration, Mallory-Weiss tear or intensive care admission were encountered.
Comments **Risk of bias**	 Moderate

Author	Ylikorkala
Year	1979
Country	Finland
Ref #	[24]
Study design	RCT
Setting	Inpatient care
Recruitment	Among women with HG for whom vomiting did not stop or decrease significantly during the first two days in hospital
Population	**Mean age (SD)**: I = 25.3 (2.8) years; C = 25.8 (4.3) years **Severity of symptoms**: mean (SD) study-specific hyperemesis severity score (min = 6; max = 20; higher = worse), I = 9.7 (2.2); C = 11.1 (3.3)

	Duration of symptoms: not stated **Gestational week (SD)**: I = 10.3 (2.8); C = 10.6 (2.8) **BMI or weight**: not stated **Singleton/twin pregnancies**: not stated **Psychosocial health/socioeconomic status**: not stated **Ethnicity (%)**: not stated
Inclusion criteria	women with HG for whom vomiting did not stop or decrease significantly during the first two days in hospital **Exclusion**: not stated
Follow up	During six days after initial injection Birth outcomes were also followed
Intervention	ACTH (tetracosactid) 0.5 mg given intramuscularly for 4 days, in addition to intravenous fluids and electrolytes as medically indicated
Participants (n)	16
Drop-outs, n (%)	0
Comparison	Placebo Given intramuscularly for 4 days, in addition to intravenous fluids and electrolytes as medically indicated
Participants (n)	16
Drop-outs, n (%)	0
Primary outcomes	**Nausea** NA **Vomiting** Vomiting stopped during hospitalization; N (%)

	I (n = 16) = 16 (100%) C (n = 16) = 16 (100%) Test of difference: NA **Nausea /Vomiting/Inability to tolerate oral fluids or food** Relief score (Vomiting/Weight change/Acetonuria/Readmission/Patient's opinion); (min = -13; max = 15; higher= better); Mean (SD): I (n = 16) = 9.4 (3.4) C (n = 16) = 8.8 (3.1) Test of difference: p > 0.05 **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** Readmission; n(%): I (n = 16) = 2 (13%) C (n = 16) = 2 (13%) Test of difference: NA **Health-related quality of life** NA **Babies born small-for-gestational-age (SGA)** NA **Babies born preterm** Premature labor (36th week); N (%) I (n = 13) = 1 (8%) C (n = 12) = 0 (0%) Test of difference: NA
Reported adverse	spontaneous abortion

events (overall)	
Comments **Risk of bias**	Moderate

Author	Yost
Year	2003
Country	USA
Ref #	[25]
Study design	RCT
Setting	Inpatient care
Recruitment	Among women presenting to the hospital between July 1998 and August 2001
Population	**Mean age (SD)**: I = 22.9 (4.9) years, C = 22.3 (4.6) years **Severity of symptoms**: not detailed per group (see inclusion criteria) **Duration of symptoms**: days (SD) of HG before randomization, I = 20 (21.7), C = 19.5 (23.6) **Gestational week (SD)**: I =11.0 (2.7), C = 10.8 (2.7) **BMI or weight**: not stated **Singleton pregnancies**: I = 98%, C = 98% **Psychosocial health/socioeconomic status**: not stated **Ethnicity (%)**: Hispanic, I =57%, C = 57% African American, I = 38%, C = 39% White, I = 2%, C = 4% Other, I = 4%, C = 0%
Inclusion criteria	previously not responding to the standard outpatient therapy, demonstrating 3+ or 4+ dipstick urinary ketones as evidence of severe dehydration

	Exclusion: molar pregnancy, non-viable fetus
Follow up	Post birth
Intervention	Methylprednisolone 125 mg intravenously, followed by an oral prednisolone taper (40 mg for 1 day, 20 mg for 3 days, 10 mg for 3 days, 5 mg for 7 days); at day 2, an additional 80 mg methylprednisolone dose, if needed; all women also received intravenous hydration until ketonuria cleared (first liter included thiamine 100 mg), promethazine 25 mg and metoclopramide 10 mg intravenously every 6 hours for 24 hours, followed by the same regimen orally as needed until discharge; identical study drug assignment in case of subsequent admission(s)
Participants (n)	64
Drop-outs, n (%)	64-56=8 (13%)
Comparison	Placebo Identical-appearing placebo regimen, plus intravenous hydration with thiamine, promethazine, and metoclopramide as the intervention group
Participants (n)	62
Drop-outs, n (%)	62-54= 8 (13%)
Primary outcomes	**Nausea** NA **Vomiting** NA **Inability to tolerate oral fluids or food** NA
Secondary outcomes	**Hospital treatment** Number of emergency room visits after randomisation; Mean (SD): I (n = 56) = 0.7 (1.2) C (n = 54) = 0.5 (1.0)

	Test of difference: p = 0.44 Number of admissions after randomisation; Mean (SD): I (n = 56) = 1.9 (1.8) C (n = 54) = 1.6 (1.0) Test of difference: p= 0.32 Number of women re-hospitalized; N (%): I (n = 56) = 19 (34%) C (n = 54) = 19 (35%) Test of difference: p= 0.89 Effect size*: RD (95% CI) = -0.01 (-0.19 to 0.17), p=0.89; RR (95% CI) = 0.96 (0.58 to 1.61); p=0.89 Total hospital days, all admissions; Mean (SD): I (n = 56) = 7.6 (18.0) C (n = 54) = 4.3 (4.3) Test of difference: p= 0.18 **Health-related quality of life** NA **Babies born small-for-gestational-age (SGA); N (%):** I (n=56) =7 (13%) C (n=54) = 10 (19%) Test of difference: p= 0.36 Effect size*: RD (95% CI) = -0.06 (-0.20 to 0.07), p=0.38; RR (95% CI) = 0.68 (0.28 to 1.64); p=0.39 **Babies born preterm** Number of deliveries ≤ 36; N (%) I (n=56) =7 (13%) C (n=51) = 4 (8%)

	Test of difference: p=0.37 Effect size*: RD (95% CI) = 0.05 (-0.06 to 0.17), p= 0.39; RR (95% CI) = 1.65 (0.51 to 5.31), p= 0.40
Reported adverse events (overall)	stillbirth, major anomaly, spontaneous abortion, gestational diabetes, pregnancy hypertention
Comments **Risk of bias**	 Low

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