Effect of acustimulation on morning sickness or hyperemesis in pregnancy: a systematic review of Western and Chinese literature

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Effect of acustimulation on morning sickness or hyperemesis in pregnancy: a systematic review of Western and Chinese literature.

Abstract (English)

Context: Nausea and vomiting in pregnancy (NVP) or hyperemesis gravidarum (HG) has a significant impact on quality of life. Many remedies for NVP have been suggested. Pregnant women and their caregivers have been concerned about the teratogenic effect, side effects and the poor efficacy of pharmaceutical medications to completely relieve the symptoms during pregnancy.

Research question: Is there clinical evidence for the efficacy of acustimulation in the treatment of NVP or HG? If yes, what is the most appropriate treatment modality?

Method: A systematic review of randomized controlled trials (RCTs), including both English and Chinese databases, has been conducted to assess the efficacy of different techniques of acustimulation for NVP and HG. The methodological quality of the studies was assessed using the Cochrane's risks of bias tool. Revised STRICTA (2010) criteria were used to appraise the acustimulation procedures. Pooled relative risks (RRp) and standard mean deviations (SMD) with 95% confidence intervals (CI) were calculated from the data provided by the investigators of the original trials.

Results: Twenty-nine trials including 3519 patients met the inclusion criteria. Twenty trials could be included in statistical pooling. The overall effect of different acustimulation techniques shows a significant reduction for the combined outcome for nausea, vomiting or ketones in case of HG (RRp 1.73, 95% CI 1.43 to 2.08). The overall analysis of studies with continuous outcome measures for nausea, vomiting and the combined effect did not show evidence for relieving symptoms of NVP and HG (SMD -0.12, 95% CI -0.35 to 0.12).

Conclusions: The effect of acustimulation on nausea and vomiting or hyperemesis in pregnancy is still unclear. Future clinical trials with a rigorous design and large sample sizes should be conducted to evaluate the efficacy and safety of these interventions for NVP and HG.

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Effect van acustimulatie op misselijkheid en braken of hyperemesis in de zwangerschap: een systematische review van de westerse en Chinese literatuur.

Abstract (Nederlands)

Context: Misselijkheid en braken tijdens de zwangerschap (NVP) of hyperemesis gravidarum (HG), waarvoor reeds vele remedies werden voorgesteld, hebben een belangrijke impact op de kwaliteit van het leven. Zwangere vrouwen en hun verzorgers zijn bezorgd over het teratogeen effect, bijwerkingen en de slechte werkzaamheid van farmaceutische medicijnen om de symptomen volledig te verlichten.
Onderzoeksvraag: Is er klinisch evidentie voor de werkzaamheid van acustimulatie in de behandeling van NVP of HG? Zo ja, wat is de meest geschikte behandelingsvorm?
Methode: Een systematische review van gerandomiseerde gecontroleerde trials (RCT's), inclusief zowel Engelse als Chinese databanken, werd uitgevoerd om de werkzaamheid van de verschillende technieken van acustimulatie voor NPV en HG te beoordelen. De methodologische kwaliteit van de studies werd geëvalueerd met behulp van de Cochrane's risks of bias tool. Gereviseerde STRICTA (2010) criteria werden gebruikt om de acustimulatie procedures te beoordelen. Pooled relatief risico (RRp) en de gestandaardiseerde verschilscore (SMD) met 95% betrouwbaarheidsintervallen (CI) werden berekend uit de resultaten van de oorspronkelijke studies.
Resultaten: Negenentwintig studies met 3519 patiënten voldeden aan de inclusiecriteria. Twintig studies werden opgenomen in statistische pooling. De totale analyse van verschillende acustimulatie technieken toonde een significante reductie van het gecombineerde effect van misselijkheid, braken of ketonen in geval van HG (RRp 1.73, 95% CI 1.43 tot 2.08). De globale analyse van het gemiddelde van misselijkheid, braken en het gecombineerde effect toonden geen evidentie voor het verlichten van symptomen NVP en HG (SMD -0.12, 95% CI -0.35 to 0.12).
Conclusies: Het effect van acustimulatie op misselijkheid en braken of hyperemesis in de zwangerschap is nog onduidelijk. Klinische studies met een strikt design en een groot aantal deelnemers moeten worden uitgevoerd om de werkzaamheid en veiligheid van deze interventies voor NVP en HG te evalueren.
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Key words

Nausea, vomiting, hyperemesis gravidarum, pregnancy, acupressure, acupuncture, acustimulation, ear acupressure, moxibustion, systematic review.

Introduction

Nausea and vomiting are commonly experienced by women in early pregnancy, mostly between 6 and 12 weeks. This can continue to 20 weeks and persist after this time for up to 20% of women[1]. Prevalence of nausea ranges from 50% to 80%, of vomiting and retching around 50%. Persistent and severe nausea and vomiting may lead to malnutrition and the development of hyperemesis gravidarum (HG), which is a disorder that may cause the loss of >5% of original body weight, dehydration, electrolyte imbalance, acidosis or ketosis during pregnancy[2]. HG is less common, affecting between 0.3% and 3% of pregnant women[1]. In China prevalence rates for HG from 0.35% to 0.47% have been reported[3].

Nausea and vomiting in pregnancy (NVP) has a significant impact on quality of life for pregnant women and their families[4]. It causes discomfort, disability and suffering and results in absence from work and social activities[5]. Furthermore, almost 50% of women reported that their NVP negatively affected the relationship with their partner and their partner's daily live[4]. Therefore, it is important to treat this condition[6].

Many pharmaceutical and non-pharmaceutical[1] remedies for nausea and vomiting in early pregnancy have been suggested. Pharmaceutical treatments include anticholinergics, antihistamines, dopamine antagonists, vitamins (B6 and B12), H3 antagonists[1], corticosteroids and metoclopramide. After the thalidomide tragedy in the 1960s, pregnant women and their caregivers have been concerned about the use of pharmaceutical interventions to control or relieve symptoms during pregnancy. Besides the possible teratogen effect, side effects like drowsiness, sedation, heartburn or arrhythmia[1, 7], the poor efficacy of pharmaceutical medications to completely relieve the symptoms[8] used in the past have left a therapeutic gap in the treatment of nausea and vomiting during pregnancy[9]. Women are commonly offered psychological support[5], dietary advice and advice about the (usually) self-limiting nature of the condition[1].

In recent years the use of complementary and alternative therapies, has become popular in many Western countries[10]. They include herbal remedies (ginger, chamomile, peppermint, raspberry leaf), homeopathic remedies (Nux vomica, Pulsatilla), acupressure, acustimulation

bands, acupuncture[1, 6, 7] and moxibustion[11-13]. They may be perceived as "natural" and therefore safe.

In China, acupuncture has been used to treat morning sickness for thousands of years[5]. A number of studies of various acupuncture modalities have been conducted assessing their efficacy for treating NVP and HG[14]. The latest Cochrane review[1] considered studies of acupressure randomized against sham acupuncture or other controls. The overall conclusion of the authors was that the evidence regarding the effectiveness of acustimulation of the P6 point and auricular acupressure was limited. Acupuncture showed no significant benefit to women in pregnancy. Festin (2014)[15] reported that acupressure may be more effective than sham acupressure at reducing nausea and vomiting. However, evidence was weak, and interventions and outcomes varied between trials. They reported that it is unknown whether acupuncture is more effective than sham acupuncture in reducing nausea and vomiting and whether acupressure and acupuncture are effective in treating HG.

Although a number of systematic reviews on the effect of acustimulation for NVP have recently been performed[1, 15-18], these reviews did only include 1 article published in Chinese. Moreover, moxibustion was only included in one previous review[1]. Given the fact that many studies of acupuncture and moxibustion for NVP and HG have been published in non-Western scientific literature and have not been reviewed, the literatures identified by previous reviews may not be comprehensive enough to cover all current evidence. Therefore, we made a comprehensive systematic review on randomized controlled trials of acustimulation for NVP and HG that were published in both Chinese and Western language literature. This review aimed to find out if acupressure, acupuncture or moxibustion, together called acustimulation, were more effective than sham or placebo acupuncture or other conventional treatments in the treatment of NVP and HG[19].

Methods

Search strategies

A comprehensive electronic search was performed in the following databases from their inception to August 2014: Cochrane Database of Systematic Reviews, The Cochrane Central Register of Controlled Trials (CENTRAL), Medline (National Library of Medicine), Embase

and Science Direct (Elsevier), Latin American and Caribbean Health Sciences (LILACS), Allied and Complementary Medicine Database (AMED), Database of abstracts of reviews of effects (DARE), Trip Database, Web of science core collection database, Cumulative Index to Nursing and Allied Health Literature (Cinahl), Physiotherapy Evidence Database (Pedro), BJI Best Practise OvidSP, BMJ Clinical evidence and National Institute for Health and Care Excellence (NICE). An additional search for articles in Chinese language was made in the Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), VIP database (Chinese Scientific Journals database), WanFang database, Index to Chinese Periodicals of Hong Kong (HKInChiP), Chinese Clinical Trial Register (ChiCTR), and ProQuest Digital Dissertations (PQDD), the latter focusing on "gray literature", such as unpublished studies, dissertations and conference reports.

The following terms were used in the search strategies: (acupuncture or acupressure or needle or auricular acupuncture or acupoint stimulation or moxibustion) and (pregnan*) and (nausea or vomiting or morning sickness or hyperemesis). Mesh terms were used as much as possible. Equivalent Chinese terms were used in searching the Chinese language databases.

Criteria for including studies for this review:

Selection of studies

One author, fluent in both English and Chinese, searched the databases and assessed potentially relevant articles against the inclusion criteria. Any doubt regarding the eligibility of a study was discussed within the team.

Types of studies and subjects

Inclusion of studies was restricted to randomized controlled clinical trials (RCT) or quasi-randomized clinical trials (qRCT) with at least 20 participants per arm, studying women suffering from nausea or vomiting or HG in normal pregnancy in which acupressure, acupuncture, auricular stimulation or moxibustion was used as treatment. We used no restriction for age of the pregnant women or gestational age. Nausea and vomiting as a result of pregnancy complications like partum hemorrhage, hypertension, pre-eclampsia, diabetes in pregnancy or cesarean section were excluded from this review. We did not include observational studies (cohort, case control, case study), studies reported in abstracts only and studies with a cross-over design without a wash-out period of at least one week because of the time effect reported in some previous studies [20, 21].

Language

Studies in Arabian or Farsi were excluded from this analysis. There were no other language restrictions.

Types of interventions

According to the principles of traditional Chinese medicine (TCM), the relief of nausea and vomiting is accomplished by the stimulation of meridian points to restore the balance of "Qi" flow affecting digestive functions.

Acupuncture

Acupuncture is defined as the stimulation of the acupoint with a needle, including auricular acupuncture and electro-acupuncture that employed needle penetration. Other variants of acupuncture, such as acupoint injection, laser acupuncture, acupotomy (small needle-scalpel), and transcutaneous electrical nerve stimulation (TENS) were excluded.

Acupressure

Acupressure is a gentle, noninvasive form of stimulation achieved by applying pressure to the acupuncture points[4, 22]. Traditional Asian systems use a number of acupuncture points for anti-emetic treatments. The P6 or NeiGuan point is a major site for the relief of nausea and vomiting. It is located on the volar side of the wrist approximately 3 cm above the wrist crease, between 2 easily palpated tendons. Pressure can be applied manually (using fingers or thumbs) or with wristband devices that provide steady pressure from a small button or disc on the site. The SeaBand is one commercial type of such devices[14]. Studies using other points for acupressure or auricular acupressure are also included in the review.

Moxibustion

Moxibustion is defined as the stimulation of acupoints with heat generated by burning of moxa (Artemisia Vulgaris). Usually a moxa cigar is kept about 2-3 cm above the skin.
We also included studies of combining acupuncture and moxibustion treatment (acupuncture and moxibustion combined, AMC), which is usually done by placing a moxa block on the handle of the acupuncture needle.

Studies using acustimulation in combination with other treatments, such as medication,

massage, physiotherapy, traditional Chinese herbs, or injection were excluded, just like cupping.

Types of control interventions

As control interventions, we included studies that used sham or placebo acupuncture, IV fluid therapy, oral Western medication, Chinese herbal medicine or no treatment.

Sham acupuncture consists of applying needles or pressure to sites that are considered to be non-therapeutic[14] and is often used for comparison when studying the effect of acupuncture. Placebo acupuncture mimics the acupuncture process without actually applying stimulation to any site[14]. Unlike sham acupuncture, placebo acupuncture offers a presumably almost physiologically inert placebo[23].

We also included studies that compared the same intervention with different combination of acupoints, although acupoint specificity was not the focus of this review.

Types of outcome measures:

In most studies the severity of nausea and vomiting episodes was measured by commonly used, validated instruments such as the Rhodes Index score or a visual analogue scale (VAS). The Rhodes index consists of three subscales: nausea, vomiting (both with a range of 0 to 12) and retching (range 0 to 8)[1]. The visual analogue scale (VAS) includes a 10 cm ruler with a beginning and an end and a clear range where patients indicate their health condition. Zero represents the best condition (lack of nausea) and ten represents the worst possible degree of nausea[22].

In other studies, outcome was reported as a reduction or cessation in nausea, vomiting, retching, ketonuria, electrolyte abnormalities, or rate of food intake. We limited our analyses to primary outcomes in this review.

Adverse outcomes

When they were available, data on side-effects of the interventions were extracted.

Data extraction

One author (EH) extracted the data and two other assessors (SHX and HVH) checked the extracted data. Discrepancies were resolved through discussion or, if required, we consulted a second review author. If information regarding any of the above was unclear, we attempted to

contact authors of the original reports to provide further details.
For each study, the following variables were extracted: study design, number of arms, population, gestational age, outcome measures, interventions and details of the interventions.

Quality assessment:

The reporting of interventions in controlled trials of acupuncture
We used the "Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): Extending the CONSORT Statement" criteria. The items of the checklist comprised by STRICTA are acupuncture rationale, details of needling, treatment regime, other components of treatment, practitioner background and control intervention[(24)].

Assessment of risk of bias
The methodological quality of identified studies was independently assessed by three people. One author (EH) assessed risk of bias for each study while two other persons (SHX and HVH) respectively assessed the Chinese and English studies using the Cochrane's risks of bias tool criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We resolved any disagreement by discussion or by involving a fourth assessor.
Cochrane's risks of bias assessment has the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias. Each domain was rated as "low", "high", or "unclear".
Given the impossibility of blinding the acupuncturist, we only assessed the blinding of participants and personnel from knowledge of which intervention a participant received. We assessed the methods as low risk of bias for single blinding, due to the nature of the intervention. Blinding was assessed as high risk in following cases: no blinding; more than two active intervention arms and the type of treatment were blinded but the control condition (no intervention) was not. Incomplete outcome data (attrition bias) were assessed as low risk when no outcome data were missing or when outcome data were missing in less than 20% in each arm of the study, and reasons for missing data were reported and balanced across groups.

Statistical analysis

For measuring treatment effects, results for dichotomous outcomes were presented as a relative risk (RR), continuous outcomes as the mean outcome on the last intervention day,

both with a 95% confidence interval (CI). Heterogeneity tests were performed for both the main analyses and subgroup analyses when calculating summary statistics. For pooling of studies with continuous outcomes we only included studies that reported at least a mean and its SD or SE from each group. A random-effect analysis has been performed in view of the high level of heterogeneity of the results. If there were more arms in the study, we used the control group which permitted the most optimal degree of blinding. All statistical analyses were performed using STATA version13 (reference: StataCorp. Stata Statistical Software: Release 13, College Station, TX: StataCorp LP. 2013.)

Results

Selection of studies

The search identified 1052 potentially relevant citations for review. After removal of duplicates, 741 citations were left. There were 507 papers excluded for reasons of irrelevance. There were 171 full-text articles retrieved for further assessment. From these, 29 studies met the inclusion criteria and were included in this review. Nine studies were excluded from pooling because of insufficient information. Finally, 20 studies were included in quantitative analyses (Fig 1).

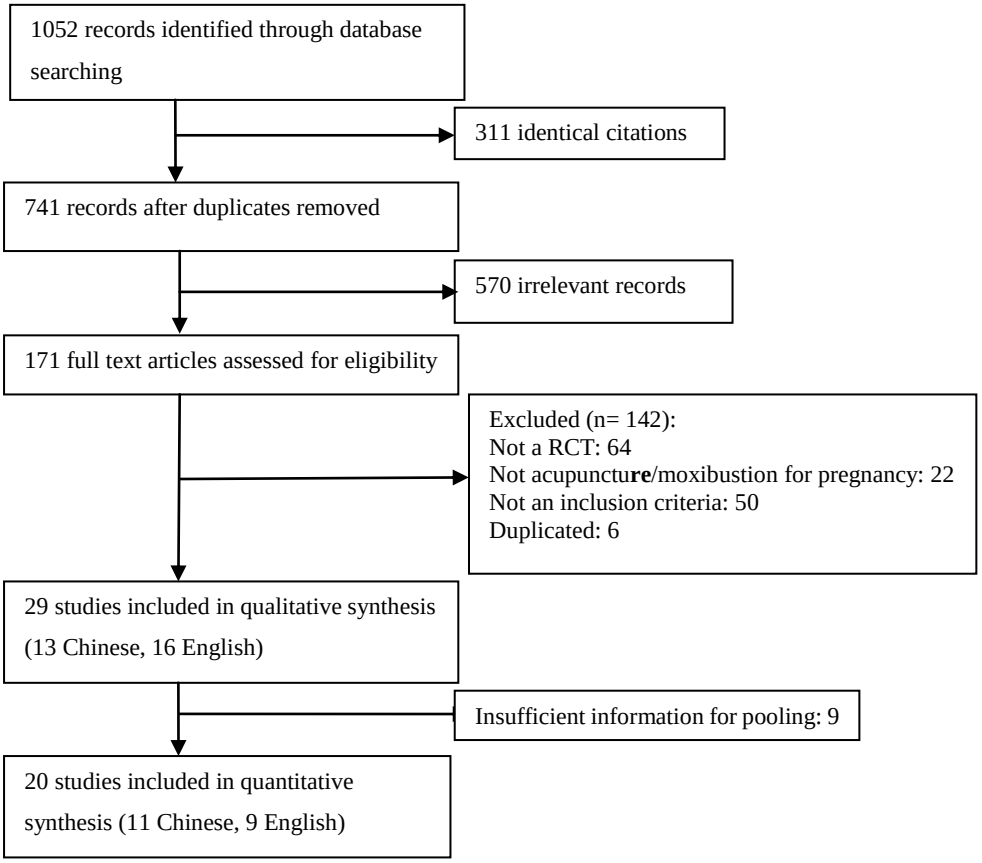


Figure 1: Flowchart of study selection

Description of included studies

Of the 29 studies, 16 were published in English and 13 were conducted in China and published in Chinese. All studies were full length journal reports. All of the studies recruited pregnant woman with symptoms of nausea with or without vomiting. There were 15 studies on nausea and vomiting alone (13 English, two Chinese). HG was considered in 14 studies (three English, 11 Chinese). Nine studies[2, 3, 12, 25-30] were performed in the hospital, one study[31] involved in- and outpatients and in two studies[13, 32] it was not clearly reported whether patients were hospitalized or not. In the remaining 17 studies all subjects were outpatients. Together these studies involved 3519 subjects with 1431 being in the treatment arm and 2088 in the control arm. Eighteen trials used a two-armed parallel group design, 10 studies a three-armed and one study[10] a four-armed parallel group design.

The sample size of the included studies ranged from 55[33] to 593[10] subjects. The stage of pregnancy at which women were recruited to the studies varied, but was mainly in the first

trimester of pregnancy (less than 12 weeks gestation). Three studies recruited women up to 30 weeks[2, 9, 20] and in one study[11] women with a gestational age of more than two months were included, but the upper limit was not specified[1].
The included studies examined acupressure, acupuncture, auricular acupressure and moxibustion. The duration of the studies varied from four to ten days in 25 studies. There were four studies that lasted two to four weeks[5, 8, 10, 33]. The frequency of treatments varied from once a day to once every week and the duration of each treatment session lasted between five and twenty minutes for acupuncture or moxibustion and up to eight - 24 hours continuously for acupressure. Table 1 presents the characteristics of all included studies.

The effectiveness of acupressure was examined in 13 studies. Eight studies[2, 5, 9, 20, 22, 25, 34, 35] compared acupressure against sham acupressure, two studies[36, 37] used a placebo control group, and four studies compared with no treatment[5, 6, 9, 20]. One study[38] compared acupressure to vitamin B6 50 mg. In this study women in both groups also received a placebo intervention. One study made a comparison to ginger caps[6]. One study [36]only presented the number per group in percentage in the results tables. Based on another study [4] we used n = 48/49.
All these studies examined the result of an intervention with the acupoint P6 (Nei Guan) using finger or wristband, except for two studies[3, 22]. From these, one trial[3] compared the P6 point in combination with auricular acupressure, and one trial[22] compared acupressure on the KID21 (You Men) point on the abdomen with sham acupressure on the abdomen. In that study all women had also taken 40 mg vitamin B6 twice daily. Patients suffering from HG also received IV fluid therapy in both arms of two studies[2, 3].

Nine trials[8, 10, 26-28, 31-33, 39] examined the effectiveness of acupuncture. They examined the result of an intervention using a variety of different acupoints according to TCM, except for two studies[8, 26]. From these, one trial[8] added acupressure on the P6 point between acupuncture sessions in the treatment group and one trial combined the needling with moxibustion[26]. Two trials compared acupuncture with sham acupuncture[10, 33]; in one of these[10], separate groups received traditional, P6, sham acupuncture or no treatment. Acupuncture was compared to conventional or herbal interventions in three trials[8, 26, 31], to IV fluid therapy in three studies[27, 28, 32] and to moxibustion in one study[39].

Four studies[7, 29, 30, 40] compared auricular acupressure to Chinese herbs[40], no treatment[7] and

IV fluid therapy [29, 30]. One study with IV fluid therapy [29] combined the ear acupressure with acupuncture needling and also had one arm comparing with P6 acupressure. In the study[7] comparing ear acupressure to no treatment, patients were allowed to take anti-emetic drugs when needed. The authors reported that the results appeared to favor the treatment group, although scores were lower in this group at baseline so results are difficult to interpret[1].

There were three studies on moxibustion[11-13], comparing moxa to Chinese herbal medicine[11], IV fluid therapy[12] and one study with moxa in the treatment group as only difference between the two intervention groups.

The studies for acupuncture and moxibustion were mainly conducted in Chinese for the treatment of HG using a combination of the following five points Zu San Li (ST36), Nei Guan (PC6), Zhong Wan (CV12), Gong Sun (SP4) and San Yin Jiao (SP6). Studies using the P6 point alone for acupressure were mainly in English.

Standards for reporting interventions in clinical trials of acupuncture (STRICTA) in the included studies

Table 2 presents the appraisal of the standards for reporting acupuncture treatment in all the included studies using the revised STRICTA criteria (2010)[24]. None of the included studies reported the acustimulation procedure sufficient detailed to satisfy the STRICTA criteria. Although treatment regimen and control interventions were always reported, details of needling or acupressure and other components of treatment were often insufficiently described. The background of the TCM practitioner was only reported in one study[22].

Assessment of risk of bias in the included studies

Table 3 presents the results of the risk of bias assessment. The methodological quality of the included studies was mixed. Most of the studies had at least one or two items scoring unclear or high except for one study[33] that had a low score for all items. With regard to selection bias, three studies[27, 29, 34] were rated at high risk of bias for random sequence generation and more than 80 % of the studies did not describe allocation concealment. The amount of missing outcome data in most of the studies was generally low with attrition levels below 20% and the reasons for attrition and missing data well reported. Almost 60 % of the studies had a high risk with respect to blinding of participants and personnel, especially in the Chinese

studies.

Effects of interventions

Outcomes in most Chinese studies[3, 11-13, 26-32, 39, 40] and three English studies[8, 34, 41] were mainly classified into the following categories: cured, improved or ineffective. "Cured" referred to a complete relief of nausea and vomiting and disappearing of ketones in case of HG at the end of the treatment period or during follow-up. "Improved" indicated a general relief of nausea and vomiting and disappearing of ketones for HG, but with occasional reoccurrence of symptoms and "ineffective" refers to no improvement. Because the "cured" category appeared to be the only category consistent across these studies in assessing treatment efficiency, we analyzed the cured rate as yes or no in this review.
Most studies on NVP used only subjective outcome measures such as the Rhodes Index score or Visual Analogue Scale (VAS) questionnaire to assess severity of nausea and vomiting. Objective outcome measurements using ketones for HG were used in five studies[2, 27, 29, 31, 40]. Table 4 shows the data for dichotomous outcomes (cured rate and RR) and table 5 those of continuous outcomes on the last day of the intervention (mean + SD) from studies included in the pooling.

There were nine studies of which we could not enter data into the meta-analyses because of insufficient information. Six of these studies[2, 20, 22, 29, 30, 37] reported a significant difference of the treatment group compared to their control group. Table 6 shows more detailed information of the excluded studies, reasons for exclusion and significance according to the author. Finally 20 studies met the inclusion criteria for pooling.

1. Analyses for dichotomous data
The overall analysis for dichotomous data from 14 studies using acupressure[3, 34, 36, 40], acupuncture[8, 26-28, 31, 32, 39] or moxa[11-13] shows a beneficial reduction in the incidence of the combined outcome for nausea, vomiting and ketones in case of HG with a pooled RR of 1.73 (95% CI 1.43 to 2.08, I squared 61%) (Figure 2), indicating 73% less patients with symptoms at outcomes measured in the treatment group compared to the control group. Subgroup analyses of the different acustimulation techniques each show significant improvements with similar pooled RRs as the combined analysis.

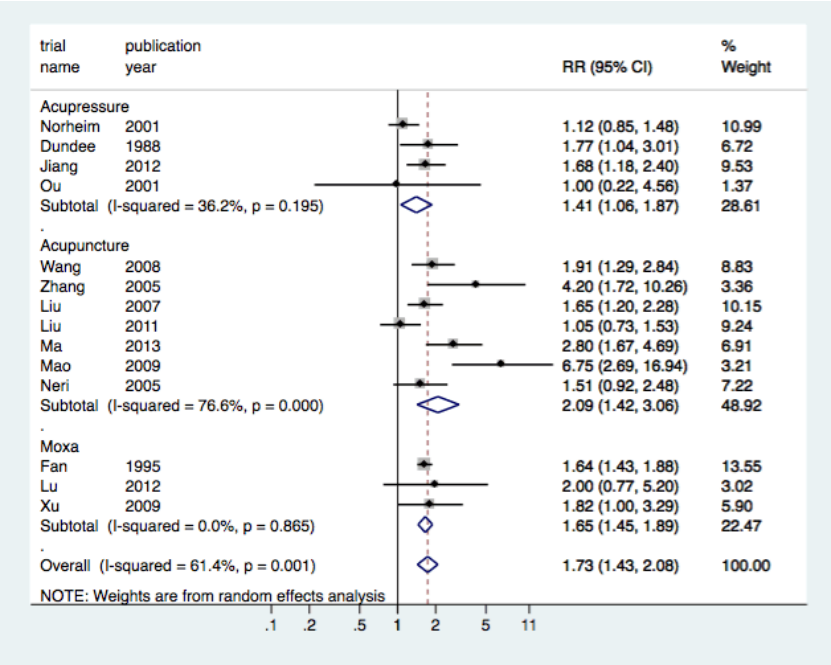


Figure 2: Improvement in nausea and vomiting during pregnancy per technique of acustimulation (relative risk (RR), 95% CI)

2. Analyses for continuous data

Figure 3 shows the analyses for continuous data using data from seven studies[5-7, 10, 35, 38, 40]. The results are presented per outcome measurements for nausea, vomiting or combined. We did not include the results for retching, ketones and acupuncture against P6 acupuncture. Analysis of the mean from four studies[5, 6, 10, 35] does not show evidence of an effect on nausea (pooled SMD -0.18, 95% CI -0.52 to 0.16, I squared 62%), nor does a similar analysis for vomiting from four studies[6, 10, 35, 40] (pooled SMD 0.13, 95% CI -0.46 to 0.72, I squared 88%). The analysis for the effect on the combined outcome for nausea and vomiting from five studies[6, 7, 35, 38, 40] does not show a significant effect of the treatment either (pooled SMD -0.23, 95% CI -0.62 to 0.15, I squared 71.4%). The overall SMD for all outcomes, resulting for studies with continuous outcome measures, was -0.12 (95% CI -0.35 to 0.12, I-squared 76%). There was no difference between studies that were blinded or not-blinded.

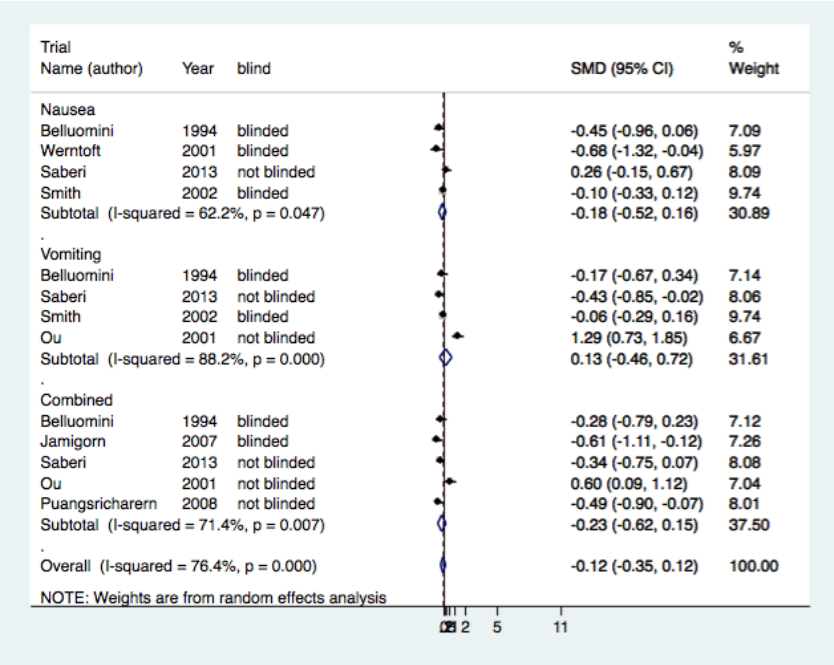


Figure 3: Efficacy per outcome measurement for studies with continuous outcome measures (Standard mean difference (SMD), 95% CI)

Adverse events reporting

Four studies[5, 33, 36, 38] reported on adverse events: increased sickness and local pain of the wrist due to tightness of the wristband, and sleep disturbance, altered taste, bruising, pressure in nose, headache and one case of increased sickness for acupuncture. There were no adverse effects reported in studies for auricular acupuncture or moxibustion.

Discussion

The present study reviewed randomized controlled trials on the efficacy of different techniques of acupoint stimulation for the treatment of nausea and vomiting or HG in early pregnancy. To our knowledge, this is the first systematic review that also systematically included studies in Chinese for NVP or HG. The different acustimulation techniques examined here were acupressure finger or wristband, auricular acupressure, traditional acupuncture and moxibustion. Most studies in the trials with acupressure were in English and examined the result of the stimulation of one point (P6 or Neiguan) in studies for NVP. The studies for acupuncture and moxibustion were mainly conducted in Chinese for the treatment of HG using a combination of the following five points Zu San Li (ST36), Nei Guan (PC6), Zhong Wan (CV12), Gong Sun (SP4) and San Yin Jiao (SP6).

Our meta-analysis included data from 20 trials. The analyses of the means for nausea, vomiting and the combined effect from studies with continuous outcome measures did not show any evidence for relieving symptoms of NVP and HG. Excluding control groups with Chinese herbal medicine in a sensitivity analysis, the effect on the combined outcome of nausea and vomiting compared to sham- or placebo-controlled intervention groups became significant (SMD -0.43, 95% CI -0.65 to -0.2, I squared 0%). The overall analyses for dichotomous data shows a beneficial reduction in the incidence of the combined outcome for nausea, vomiting and ketones in case of HG. We could not perform analyses by blinding because of the poor or unclear blinding of most Chinese studies. Two additional sensitivity analyses have been carried out, one excluding control groups with Chinese herbal medicine or conventional treatment[8, 11, 26, 31] and one restricting the pooling to Chinese studies alone. The results showed no differences with the general results.

Nevertheless, results obtained in this meta-analysis must be interpreted with caution. A major limitation in this study was that we faced a considerable amount of statistical heterogeneity between the trials. This might be due to combining data from trials on different interventions, comparison groups, and a lack of standardization of primary outcomes measured or reported. Moreover, the methodological quality of the included studies assessed by the Cochrane's risk of bias tool was mixed. Some studies had high rates of attrition, poor allocation concealment and other methodological problems, which put them at high risk of bias. Another major limitation of the studies was blinding, especially in the Chinese studies. Although many of the included studies were described as being double-blind or keeping women blind to group allocation, lack of effective blinding may also have introduced bias. Some of the trials that investigated the effectiveness of blinding provided some evidence that women may have had some idea of group allocation[10, 33, 36]. The lack of blinding or unconvincing blinding may be particularly relevant where the main outcome is women's subjective, self-reported symptoms.

According to the revised STRICTA criteria, some essential details of the acupuncture treatment protocol were often insufficiently described. This is not unexpected given the fact that STRICTA was introduced in 2010. The precise description of these components of the acupuncture procedures will enable other researchers to replicate the reported treatment protocol accurately and reliably in both research and clinic setting and allow others to appraise the findings critically[19].

Very few studies in the current review reported adverse events for the treatment with acupressure and acupuncture. No serious adverse events were reported and none for auricular acupressure and moxibustion. Although it may not be safe to assume that because negative

outcomes were not reported, they did not occur, a systematic review about adverse events following acupuncture[41] suggested that most adverse events can easily be avoided by standardizing teaching and clinical practices.

A previous meta-analysis[4] and 2 recent reviews[1, 17] on acustimulation effects for NVP showed limited evidence for the effects of P6 acupressure or acupuncture for reducing NVP. No trials of treatments for HG showed any evidence of benefit. In contrast with the latest Cochrane review[1] that tried to present findings for a time point approximately three days after the start of treatment, we opted to choose the last day of the intervention for outcome measurement. Therefore, we sometimes obtained a different result for some outcomes in this study.

Although there is some limited evidence for the effect of the stimulation of one point, a combination of acupoints according to TCM diagnoses shows to have a better result in the treatment outcomes for more severe nausea and vomiting (HG).

Conclusion

Findings from moderate quality studies show that overall different acustimulation techniques significantly reduce the combined outcome for nausea, vomiting and ketones in case of HG, excluding control groups with either Western or Chinese pharmacological treatments. We found no evidence for an increase of adverse effects.

Taking into account the moderate quality of the studies, especially with regard to the blinding, it is too early to definitely conclude on the beneficial effects of acustimulation for the treatment of NVP. Future clinical trials with rigorous design and large sample sizes should be conducted.

Conflict of interest

The authors declare that they have no competing financial or non-financial interest from the funders.

Author's contributions

EH designed the study and searched the databases. EH, HVH and SHX assessed risk of bias. EH initially acquired data and drafted the manuscript. FB and MG performed further statistical analysis. FB, MG and EH read and approved the final version of the manuscript.

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Tables

Table 1: Baseline characteristics of the studies

1st author, year	Design, number of arms	Population (n) , gestational age	Outcomes	Participants (n), intervention		dose, frequency, treatment duration
				Treatment group	Placebo control group	
acupressure finger						
Dundee 1988 (34)	qRCT, 3	350, 6-14 w	NVP	119, P6	112, sham, dummy point near right elbow 119, control: no treatment	5 min every 4 hours, 4days
Belluomini 1994 (35)	RCT, 2	60, ≤ 12 w	NVP	30, P6	30, sham, placebo point	10 min, 4x/d, for 7 days
Shin 2007 (2)	qRCT, 3	66, 5-30 w	HG	23, P6 + IV fluid therapy	21, sham control, a bony part around the radial pulse + IV fluid therapy 22, control, only conventional IV fluid therapy	10 min, 3x/d before meal from day 2 - day of discharge (mean 5-7 days)

Rad 2012 (22)	RCT, 2	80, first trimester	NVP	40, pressure thumb of researcher on the two symmetrical KID21 points + Vit B 6 40 mg	40, pressure thumb of researcher on a false point + Vit B 6 40 mg	20 min/d for 4 days + Vit B 6 40 mg
Jiang 2012 (3)	RCT, 2	130, 5-10, 7 w	HG	65, P6 + IV fluid therapy + ear acupressure stomach, spleen, duodenum, liver, shen men, heart	65, IV fluid therapy	10 min, 3x/d before meal of nausea for 7 days Control: 3-7 days
acupressure band						
O'Brien 1996 (9)	RCT, 3	161, 4.6-23.6 w	NVP	54, P6	53, sham: acupressure band inappropriately placed 54, control: no treatment	Band applied for 5 days, removed morning of day 6
Norheim 2001* (36)	RCT, 2	97, 8-12 w	NVP	48, P6	49, placebo, wristband with felt patch, no button P6	24h/d, 4 day run-in, 4 day intervention, 4 day follow-up, 12d
Steele 2001 (37)	qRCT, 2	110, ≤ 13 w	NVP	68, P6	42, placebo, P6 without acupressure buttons	Continuously on both wrists for 4 days, remove only when bathing

Werntoft 2001 (5)	RCT, 3	60, mean 10 w	NVP	20, P6	20, sham: button on upper side of wrist 20, control: no treatment	On for 24 hours, only not when showering, for 14 days
Heazell 2006 (25)	RCT, 2	80, 5- 14 w	HG	40, P6	40, sham: a site on the dorsal aspect of the forearm	8 hours a day, from 9 AM to 5 PM, length of inpatient stay (mean 3.4)
Jamigorn 2007 (38)	RCT, 2	66, 6-12 w	NVP	33, P6 + placebo tablets	33, sham: wristband on dummy-point + 50 mg tablets of Vit B6	Bands: continuously for 5 days Tablets: every 12 h for 5 days
Can Gurkan 2008 (20)	QRCT, 3	75, 5-20 w	NVP	26, P6	24, sham: upper side wrist 25, control: no treatment	Daytime, taken off at night; no bands day 1-3, bands on day 4-6, no bands day 7-9, for 9 days
Saberi 2013 (6)	RCT, 3	143, ≤ 16 w	NVP	48, P6	50, ginger caps 45, control: no treatment	Nothing on day 1-3, treatment on day 4-7 P6: continuously bilateral Ginger caps: 3x/day
Acupuncture						
Knight 2001 (33)	RCT, 2	55, 6-10 w	NVP	28, needling P6, St 36, Ren 12, SP4, St 44	27, cocktail sticks on bony regions near acupoint	Needles left during 15 min, 2x in first week,

						then 1x/ week for 2weeks
Smith 2002 (10)	RCT, 4	593, ≤ 14 w	NVP	148, maximum 6 various points based on TCM diagnosis	148, P6 148, sham: close to acupoints 149, control: no treatment	Needles left during 20 min, 2x in first week, then weekly, for 4 weeks.
Neri 2005 (8)	RCT, 2	81, ≤ 12 w	HG	43, needling PC6, CV12, ST 36, + acupressure PC6	38, metoclopramide infusion + Vit B12 complex(30 mg/day)	Acupuncture: 20 min, 2x/ week + acupressure for 6-8 h/day, for 2 weeks. Metoclopramide: infusion 2x/week + vit. B12, for 2 weeks.
Zhang 2005 (26)	RCT, 3	150, 6-12 w	HG	50, needling + moxibustion CV12, PC6, ST36, SP9	50, Chinese drug group: Suye Huanglian decoction 50, Western medicine: IV fluid therapy + phenobarbital	Acup: 10-15 min, 2x/d, for 7days Chinese drug: 2x/d, 7d Western drug: daily, 7d
Liu 2007 (27)	RCT, 2	94, early pregnancy	HG	47, needling: scalp, stomach area, CV12, PC6, ST36 + IV fluid therapy	47, control: IV fluid therapy	1x/d for 10 days

Wang 2008 (32)	RCT, 2	95, early pregnancy	HG	53, CV17, CV12, SP6, PC6, ST36	42, control: IV fluid therapy	Acupuncture: 30 min, 1x/d, 6d Control: 1x/d, 6d
Mao 2009 (31)	RCT, 3	90, 6-12 w	HG	30, IV fluid therapy + needling BL11, ST37, PC6, SP4, CV12, ST36	30, Western medicine: IV fluid therapy + luminal 30 mg 30, Chinese drug group: IV fluid therapy + Chinese herbal decoction	Each group IV fluid therapy Acup: 25 min, 2x/d for 7days Western medicine: 3x/d for 7 days Chinese drug group: 3x/d for 7 days
Liu 2011 (39)	RCT, 2	60, early pregnancy	HG	30, needling CV12, PC6, ST36	30, moxibustion ST36, CV12, PC6, SP4	15-20 min, 1x/d for 10 days
Ma 2013 (28)	RCT, 2	60, early pregnancy	HG	30, CV12, BL21 + IV fluid therapy	30, IV fluid therapy	Acupuncture: 20 min, 1x/d for 5 days IV fluid therapy: 1x/d , for 5 days
auricular acupressure						
Ou 2001 (40)	RCT, 3	90, early pregnancy	NVP	Group 1: 30, ear acupressure: diaphragm (bilateral), shen men, kidney +	30, group 2: ear acupressure: diaphragm (bilateral), shen men, kidney	Group 1: acupressure: 10 min, 3x/d + herbs 3x/d, for 7 days Group 2: acupressure: 10

				Chinese herbal medicine	30, group 3: Chinese herbal medicine	min, 3x/d, for 7days Group 3: herbs: 3x/d for 7 days
Puangsricharern 2008 (7)	RCT, 2	91, ≤ 14 w	NVP	45, magnet pellets, placed at both auricles	46, no treatment, 6d	30 seconds, 4x/day before meals and at bedtime, day 3-day 6
Li 2010 (29)	RCT, 3	141, 5-30 w	HG	47, ear acupoints: stomach, spleen, duodenum, liver, shen men, heart,+ needling CV 12, PC6, ST36	47, P6 acupressure 47, IV fluid therapy	Ear acupressure: 3x/d before meals or in case of nausea Acupuncture: 30 min, 1x/d for 10 days P6 acupressure: 10 min, 3x/d before meals or nausea, for 10 days
Liu 2012 (30)	RCT, 2	54, mean 8 w	HG	27, pylorus, stomach, spleen, esophagus, duodenum, liver, heart, subcortex , shen men, jiao gan.	27, fasting for 2-3 d, rest, IV fluid therapy	Bilateral, 2 min, 15 min before meal, 3x/d for 7days
Moxa						
Fan 1995	RCT, 2	302, >2m	NVP	151, moxa SP6, CV4	151, chinese herbal	5-10 min, 1x/d for 7days

(11)				ST36, Li3	decoction	Herbs:1x/d for 7days
Xu 2009 (12)	RCT, 2	51, early pregnancy	HG	26, IV fluid therapy + moxa ST36, CV12, PC6, SP4	25, IV fluid therapy	Moxa: 15-20 min, 1-2x/d IV fluid 1x/d, for 10 days
Lu 2012 (13)	RCT, 2	64, 38-80 d	HG	32, IV fluid therapy + citicoline 500 mg + moxa ST36, CV12, PC6	32, IV fluid therapy + citicoline 500 mg	IV fluid: 1x/d Moxa: 20 min, 2x/d for 5 days

NVP, Nausea and vomiting during pregnancy; HG, Hyperemesis gravidarum; *Based on the review van Helmreich[4]: n = 48/49.

Table 2: Appraisal of acupuncture, acupressure and moxibustion procedure based on the Revised STRICTA (2010)

1st Author, Year	**Acu-puncture rationale**	**Details of needling or acupressure**							**Treat-ment regim en**	**Other components of treatment**		**Prac-titio-ner back-ground**	**Control or compara -tor inter-ventions**
		No. of needle inser-tions	Points used	Depth of insertion	Responses sought	Needle stimuli-tion	Needle/ pressure retention time	Needle or wrist-band type		Other inter-ventions administered to the acupuncture	Setting and context		

									group				
acupressure finger													
Dundee 1988	TCM	NA	R	NA	NR	NA	R	NA	R	NR	NR	NR	R
Belluomini 1994	TCM	NA	R	NA	NR	NA	R	NA	R	NR	NR	NR	R
Shin2007	TCM	NA	R	NA	NR	NA	R	NA	R	R	R	NR	R
Rad 2012	TCM	NA	R*	NA	R	NA	R	NA	R	R	R	R	R
Jiang 2012	TCM	NA	R*	NA	R	NA	R	NA	R	R	R	NR	R
acupressure band													
O'Brien 1996	TCM	NA	R*	NA	NR	NA	R	R	R	NR	NR	NR	R
Norheim 2001	TCM	NA	R*	NA	NR	NA	R	R	R	NR	NR	NR	R
Steele 2001	TCM	NA	R*	NA	NR	NA	R	R	R	NR	NR	NR	R
Werntoft 2001	TCM	NA	R	NA	NR	NA	R	R	R	NR	NR	NR	R
Heazell 2006	TCM	NA	R*	NA	NR	NA	R	R	R	R	R	NR	R
Jamigorn 2007	TCM	NA	R	NA	NR	NA	R	R	R	R	R	NR	R
Can Gurkan 2008	TCM	NA	R*	NA	NR	NA	R	R	R	NR	NR	NR	R
Saberi 2013	TCM	NA	R*	NA	NR	NA	R	R	R	R	R	NR	R
Acupuncture													
Knight 2001	TCM	R	R*	R	R	R	R	R	R	NR	NR	NR	R
Smith 2002	TCM	R	R	R	R	R	R	R	R	NR	NR	NR	R
Neri 2005	TCM	R	R	R	R	R	R	R	R	R	R	NR	R
Zhang 2005	TCM	R	R	NR	R	R	R	R	R	R	R	NR	R
Liu 2007	TCM	R	R	NR	NR	NR	NR	NR	R	R	R	NR	R
Wang 2008	TCM	R	R	R	R	R	R	R	R	NR	NR	NR	R
Mao 2009	TCM	R	R	R	R	R	R	R	R	R	R	NR	R

Liu 2011	TCM	R	R	NR	R	NR	R	R	R	NR	NR	NR	R
Ma 2013	TCM	R	R	R	NR	NR	R	R	R	R	R	NR	R
auricular acupressure													
Ou 2001	TCM	NA	R	NA	NR	NR	NR	NA	R	NR	NR	NR	R
Puangsricharern 2008	TCM	NA	R*	NA	NR	NR	R	R	R	R	NR	NR	R
Li 2010	TCM	R	R	NR	NR	NR	R	R	R	R	R	NR	R
Liu 2012	TCM	NA	R*	NA	R	NA	R	R	R	R	NR	NR	R
Moxa													
Fan 1995	TCM	NA	R	NA	R	NR	R	NR	R	NR	NR	NR	R
Xu 2009	TCM	NA	R	NA	R	NR	R	NR	R	R	R	NR	R
Lu 2012	TCM	NA	R	NA	NR	NR	R	NR	R	R	R	NR	R

TCM, acupoint selection based on Traditional Chinese Medicine Theory; NA, not applicable; R, reported; NR, not reported; R* reported and mentioned if unilateral or bilateral.

MacPherson H, Altman DG, Hammerschlag R, Youping L, Taixiang W, White A, Moher D; STRICTA Revision Group. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. PLoS Med. 2010 Jun 8;7(6):e1000261

Tabel 3: Cochrane's Risk of Bias Assessment

1st Author (Year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Acupressure finger							

Dundee 1988	High	Unclear	High	Low	High	Low	Unclear
Belluomini 1994	Low	Unclear	Low	Low	High	High	Low
Shin2007	Low	Unclear	Low	Low	Low	Low	Low
Rad 2012	Unclear	Unclear	Low	Low	Low	Unclear	Low
Jiang 2012	Unclear	Unclear	High	Low	Low	Unclear	unclear
acupressure band							
O'Brien 1996	Low	Low	Low	Low	Low	Unclear	Low
Norheim 2001	Low	Unclear	Low	Low	Low	Unclear	Low
Steele 2001	Low	Low	Low	Low	Low	Unclear	Low
Werntoft 2001	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Heazell 2006	Unclear	Unclear	Low	Low	Low	Low	Unclear
Jamigorn 2007	Low	Low	Low	Low	Low	Unclear	Unclear
Can Gurkan 2008	Unclear	Unclear	Low	Low	Low	Unclear	Low
Saberi 2013	Low	Unclear	High	Low	Low	Low	Low
Acupuncture							
Knight 2001	Low	Low	Low	Low	Low	Low	Low
Smith 2002	Low	Low	Low	Low	High	Unclear	Unclear
Neri 2005	Low	Unclear	High	Unclear	Low	Unclear	Unclear
Zhang 2005	Low	Unclear	High	Low	Low	Low	Low
Liu 2007	High	Unclear	High	Low	Low	Low	Unclear
Wang 2008	Low	Unclear	High	Low	Low	Low	Unclear
Mao 2009	Low	Unclear	High	Low	Low	Low	Low
Liu 2011	Low	Unclear	High	Low	Low	High	Unclear

Ma 2013	Unclear	Unclear	High	Unclear	Low	High	Unclear
auricular acupressure							
Ou 2001	Low	Unclear	High	Low	Low	Low	Low
Puangsricharern 2008	Low	Unclear	High	Low	Low	Low	Unclear
Li 2010	High	Unclear	High	Low	Low	Low	Low
Liu 2012	Unclear	Unclear	High	Unclear	High	High	Unclear
Moxa							
Fan 1995	Unclear	Unclear	High	Unclear	Low	Low	Unclear
Xu 2009	Unclear	Unclear	High	Low	Low	Low	Unclear
Lu 2012	Unclear	Unclear	High	Low	Low	Unclear	Unclear

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (Updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Table 4: Dichotomous outcomes from original studies (*included in pooling).

Studies (Author, Year)	**Number of subjects, intervention**		**Outcome measurement**	**Outcomes Cured rate n/N (%)**		**Included in pooling**
	Treatment group	Comparator		Treatment group	Comparator	
Dundee 1988	Acupressure P6 N = 119	Sham acupressure N= 112	Emetic symptoms: cured rate based on subjective report	32/119 (26.89 %)	17/112 (15.18%)	*
Dundee	Acupressure P6	No treatment	Emetic symptoms: cured	32/119 (26.89 %)	15/119 (12.60 %)	

1988	N = 119	N = 119	rate based on subjective report			
Jiang 2012	Acupressure P6 + ear acupressure N = 65	Conventional IV fluid therapy N = 65	Nausea, vomiting, rate of food intake, ketonuria: Cured rate	42/65 (64.6%)	25/65 (38.5%)	*
Norheim 2001	Acupressure P6 N = 48	Placebo acupressure N=49	Intensity of symptoms: VAS. Improved rate.	34/48 (71 %)	31/49 (63 %)	*
Neri 2005	Acupuncture + P6 acupressure N = 43	Metoclopramide infusion + Vit B 12 complex N = 38	Vomiting episodes: improved rate after session 3	24/43 (55.81 %)	14/38 (36.84 %)	*
Zhang 2005	Acupuncture + moxibustion (AMC) N = 50	Chinese herbal medicine N = 50	NVP, ketones, electrolytes, rate of food intake: cured rate	21/50 (42 %)	9/50 (15.25 %)	
Zhang 2005	Acupuncture + moxibustion (AMC) N = 50	IV fluid therapy + conventional therapy N = 50	NVP, ketones, electrolytes, rate of food intake: cured rate	21/50 (42 %)	5/50 (9.09 %)	*
Liu 2007	Acupuncture + IV therapy	IV fluid therapy N = 47	Treatment effect: Nausea, vomiting, food	38/47 (80.85 %)	23/47 (48.93 %)	*

	N = 47		intake			
Wang 2008	Acupuncture + IV therapy N = 53	IV fluid therapy N = 42	Nausea, vomiting, electrolytes	41/53 (77.35 %)	17/42 (0.47 %)	*
Mao 2009	Acupuncture + IV therapy N = 30	IV fluid therapy + Chinese herbal medicine N = 30	Total treatment effect: electrolytes and vomiting rate: cured rate	27/30 (90 %)	3/30 (10 %)	
Mao 2009	Acupuncture + IV therapy N = 30	IV fluid therapy + conventional therapy N = 30	Ketones: cured rate	27/30 (90 %)	4/30 (13.33 %)	*
Liu 2011	TCM Acupuncture N = 30	TCM Moxibustion N = 30	Nausea and vomiting, ketones, rate of food intake: cured rate	20/30 (66.67 %)	19/30 (63.33 %)	*
Ma 2013	Acupuncture + IV therapy N = 30	IV fluid therapy N = 30	Total treatment effect: ketones, vomiting rate: cured rate	28/30 (93.3 %)	10/30 (33.33 %)	*
Ou 2001	Ear acupressure N = 30	Chinese herbal medicine N = 30	Total treatment effect: electrolytes, nausea and vomiting rate: cured rate	3/30 (10.0 %)	3/30 (10.0 %)	*
Fan 1995	TCM moxa N = 151	Chinese herbal decoction	Nausea and vomiting Total: Cured rate	146/151 (96.7%)	89/151 (58.9%)	*

		N= 151				
Xu 2009	TCM moxa N = 26	IV fluid therapy N = 25	Nausea and vomiting, ketones, rate of food intake: Cured rate	17/26 (65.38 %)	9/25 (36.0 %)	*
Lu 2012	TCM Moxa + IV fluid + conventional therapy N = 32	IV fluid therapy + conventional therapy N = 32	Nausea and vomiting, ketones, rate of food intake: Cured rate	10/32 (31.25 %)	5/32 (15.62 %)	*

Table 5: Continuous outcomes on last day of treatment from original studies (*included in pooling).

Studies (Author, Year)	**Number of subjects, intervention**		**Outcome measurement**	**Outcomes (mean + SD)**		**Included in pooling**
	Treatment group	Comparator		Treatment group	Comparator	
Belluomini 1994	Acupressure P6 N=30	Sham acupressure point N = 30	Rhodes Index scores Nausea scores:	5.80 ± 2.9	7.04 ± 2.6	*
Belluomini 1994	Acupressure P6 N=30	Sham acupressure point N = 30	Rhodes Index scores Emesis scores:	1.28 ± 1.9	1.63 ± 2.3	*

Belluomini 1994	Acupressure P6 N=30	Sham acupressure point N = 30	Total	8.69 ± 5.0	10.03 ± 4.6	*
Werntoft 2001	Acupressure P6 N = 20	Sham acupressure N = 20	VAS Degree of nausea	4.2 ± 2.6	5.9± 2.4	*
Werntoft 2001	Acupressure P6 N = 20	No treatment N = 20	VAS Mean degree of nausea	4.2 ± 2.6	6.5 ± 2.2	
Jamigorn 2007	Acupressure P6 + placebo tablets N = 33	Sham acupressure + Vit B6 N = 33	Rhodes index score, Improvement in nausea, vomiting and retching	4.1 ± 1.8	5.3 ± 2.1	*
Saberi 2013	Acupressure P6 N = 48	No treatment N=45	Rhodes Index scores Vomiting	4.25 ± 3.38	5.66 ± 3.10	*
			Nausea	8.03 ± 4.11	7.08 ± 3.0	*
			Retching	3.66 ± 2.47	4.48 ± 2.25	
			Total	14.56 ± 8.66	17.23 ±6.91	*
Smith 2002	Traditional acupuncture N = 148	Sham Acupuncture N = 148	Nausea	3.4 ± 3.0	3.7 ± 2.8	*
			Dry retching	0.8 ± 1.4	0.9 ± 1.4	

			Vomiting	0.9 ± 1.5	1.0 ± 1.6	*
Smith 2002	TCM Acupuncture N = 148	Acupressure P6 N = 148	Rhodes Index scores: Nausea	3.4 ± 3.0	4.0 ± 3.3	
			Dry retching	0.8 ± 1.4	0.9 ± 1.3	
			Vomting	0.9 ± 1.5	0.9 ± 1.8	
Smith 2002	Traditional acupuncture N = 148	No treatment N = 149	Rhodes Index scores Nausea	3.4 ± 3.0	5.0 ± 3.0	
			Dry Retching	0.8 ± 1.4	1.6 ± 1.7	
			Vomiting	0.9 ± 1.5	1.4 ± 2.0	
Mao 2009	Acupuncture + IV therapy N = 30	IV fluid therapy + Chinese herbal medicine N = 30	Ketones	1.20 ± 0.41	1.53 ± 0.68	
Mao 2009	Acupuncture + IV therapy N = 30	IV fluid therapy + conventional therapy N = 30	Ketones	1.20 ± 0.41	1.60 ± 0.72	
Ou 2001	Ear acupressure N = 30	Chinese herbal medicine N = 30	Vomiting	3.53 ± 1.72	1.33 ± 1.69	*
			Ketones	1.47 ± 1.66	0.67 ± 1.32	

			Main symptoms	18.4 ± 11.02	12.13 ±9.67	*
Puangsricharern 2008	Auricular acupressure N = 45	No treatment N = 46	Mean Rhodes index Nausea and vomiting scores	7.7 ± 4.9	11.3 ± 9.2	*

Tabel 6: Studies excluded from analyzes because of insufficient information.

Reason for exclusion	Study	Significance for treatment group according to author
No measure of variability	Shin 2007	- significant for degree of nausea and vomiting - significant reduction for ketonuria levels over time by women with HG.
	Li 2010	- significant difference (P <0.05) for the severity and frequency of nausea and vomitingi). - ketone bodies disappeared in the 2 acupressure groups significantly faster (p < 0.05) than in the group with IV fluid therapy.
	Liu 2012	- a statistically significant difference (P <0.05) for the severity and frequency of nausea and vomiting compared to IV fluid therapy.
Data reported in Mean and interquartile range (IQR)	Rad 2012	- statistically significant difference favouring Youmen acupressure over sham acupressure
	Heazell	- no difference between length of stay, amount of medication, or fluid required between the acupressure and placebo groups - acupressure reduced the number of patients who stayed more than four nights in the hospital.
	Knight	- no statistically significant difference between the control and intervention groups.

Data reported in Mean rank	Steele	- The treatment group had significantly less frequency and severity of nausea and vomiting of pregnancy than the placebo group
	Can Gurkan	- Acupressure would appear to be effective in symptom control, and alleviation and placebo effects in reducing the symptoms of nausea and vomiting during pregnancy.
Data reported only means of error bar plots	O'Brien 1996	- No benefit of acupressure for symptom relief compared with either sham acupressure or no treatment