National Institute for Health and Care Excellence

Draft for consultation

Antenatal care

[S] Management of heartburn in pregnancy

NICE guideline <number>

Evidence reviews underpinning recommendations 1.4.5 to 1.4.6

February 2021

Draft for consultation

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

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN:

Contents

Management of heartburn during pregnancy

Review question

What interventions are effective in treating heartburn during pregnancy?

Introduction

Many women experience heartburn during pregnancy. It can be extremely uncomfortable and can negatively affect women's experience of pregnancy and their quality of life. The aim of this review is to evaluate the effectiveness of interventions for heartburn in pregnancy.

Summary of the protocol

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

Table 1: Summary of the protocol (PICO table)

Population	Pregnant woman with new or pre-existing heartburn or acid reflux (a burning sensation or discomfort felt behind the sternum or throat or both)
Intervention	• Acupuncture • Alginate reflux suppressants • Antacids (for example Maalox® plus suspension or tablets) • Dietary modifications (for example eating a smaller meal, avoiding acidic foods) • Histamine 2 receptor antagonists • Proton pump inhibitors (PPIs)
Comparison	• Any other intervention (including combinations of listed interventions) • Placebo, sham treatment or no treatment (compared to single interventions) Note: Combinations of interventions will be compared with one of the component interventions alone but not to no treatment nor placebo
Outcome	**Critical** • Relief of heartburn during pregnancy • Fetal death at any stage of pregnancy **Important** • Gastrointestinal side-effects of interventions whilst receiving treatment • Preterm birth (birth before 37^{+0} weeks) • Quality of life • Women's experience and satisfaction of care during or after treatment for heart burn • Small for gestational age (SGA)

PPI: proton-pump inhibitor; SGA: small for gestational age.

For further details, see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A.

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

Clinical evidence

Included studies

Four randomised controlled trials (RCTs) (Da Silva 2009, Lang 1989, Meteerattanapipat 2017, Reisfield 1971) and 1 retrospective cohort study (Matok 2012) on pregnant women with new or existing heartburn were included in this review.

The included studies are summarised in Table 2.

One RCT compared acupuncture versus no acupuncture (Da Silva 2009) for the treatment of symptomatic dyspepsia. Both arms also received counselling on lifestyle behaviour modifications, and the use of antacids was permitted. Two RCTs compared an alginate-based reflux suppressant to an antacid (Lang 1989; Meteerattanapipat 2017): the former compared Algicon® oral suspension (containing sodium alginate and potassium bicarbonate) to a magnesium trisilicate mixture BP (containing magnesium carbonate light, magnesium trisilicate, and sodium hydrogen carbonate), whilst the latter compared Liquid Gaviscon® (containing sodium alginate, sodium bicarbonate and calcium carbonate) to Maalox® (containing magnesium hydroxide and aluminium hydroxide). One RCT compared an antacid (a combination of magnesium hydroxide, aluminium hydroxide and simethicone liquid or tablet) to a placebo liquid or tablet as appropriate (Reisfield 1971). One retrospective cohort study compared pregnant women who took PPIs in the first trimester for the treatment of acid reflux to those not exposed to PPIs (Matok 2012).

One study was conducted in Brazil (Da Silva 2009); 1 study was conducted in Israel (Matok 2012); 1 study was conducted in Thailand (Meteerattanapipat 2017); 1 study was conducted in the UK (Lang 1989); 1 study was conducted in the US (Reisfield 1971).

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

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of clinical studies included in the evidence review

A summary of the studies that were included in this review is presented in **Error! Reference source not found.**.

Table 2: Summary table of included studies

Study Study design Country	Population	Intervention	Comparison	Outcomes
da Silva 2009 RCT Brazil	N=36 pregnant women aged 15 to 39 years, with new onset dyspepsia symptoms at 15-30 weeks of pregnancy	Acupuncture (n=21; once or twice per week for 8 weeks, total 8-12 sessions)[1]	No acupuncture (n=21)[1]	• Relief of heartburn • Quality of life
Lang 1989 RCT UK	N=157 women at <38 weeks gestation with recent onset of symptoms of reflux dyspepsia of pregnancy	Alginate-based reflux suppressant (n=79; Algicon® suspension 10 ml for 2 weeks)[2]	Antacid (n=78; Magnesium trisilicate mixture BP 10 ml for 2 weeks)[3]	• Relief of heartburn • Gastrointestinal side-effects of interventions whilst receiving treatment
Matok 2012 Retrospective cohort study Israel	N=110783 women aged 15 to 49 years who had given birth to singletons	PPI exposure in the first trimester of pregnancy (n=1186)[4]	No exposure to PPI in first trimester of pregnancy (n=109,597)	• Fetal death • Preterm birth • SGA
Meteerattana-pipat 2017 RCT Thailand	N=100 pregnant women aged 18 to 40 years with a diagnosis of heartburn and <36 weeks of gestation.	Alginate-based reflux suppressant (n=50; Liquid Gaviscon® 15 ml, 4 times a day for 2 weeks)[5]	Antacid (n=50; Maalox® 15ml, 4 times a day for 2 weeks)[6]	• Relief of heartburn • Gastrointestinal side effects of interventions whilst receiving treatment • Quality of life • Women's experience and satisfaction of care during or after treatment for heartburn
Reisfield 1971 RCT US	N=156 pregnant women who complained of heartburn	Antacid (n=83; Mylanta® liquid or tablets)[7,8]	Placebo liquid or placebo tablet (n=73)[8]	• Relief of heartburn • Gastrointestinal side effects of interventions whilst receiving treatment

PPI: proton pump inhibitor; RCT: randomised controlled trial; SGA: small for gestational age.
1. All participants received information about lifestyle and dietary modifications that may reduce or stop dyspepsia and were permitted to take antacids during the duration of the trial.
2. 5 ml of Algicon oral suspension contains 500 mg sodium alginate and 100 mg potassium bicarbonate.
3. ml of Magnesium trisilicate mixture BP contains 250 mg of magnesium carbonate light, 250 mg magnesium trisilicate, and 250 mg sodium hydrogen carbonate.
4. PPI exposure included defined daily dose of 20 mg omeprazole, 30 mg lansoprazole, or 40 mg pantoprazole.

5. 10 ml of Liquid Gaviscon® contains 500 mg sodium alginate, 267 mg sodium bicarbonate and 160 mg calcium carbonate.
6. 5ml of Maalox contains 120 mg magnesium hydroxide and 220 mg aluminium hydroxide.
7. 5ml of Mylanta® contains 200 mg magnesium hydroxide, 200 mg of aluminium hydroxide and 20 mg simethicone.
8. 19 patients in this trial also received oral iron therapy, group assignment not specified.

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. See supplementary material 2 for details.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of studies included in the economic evidence review

No economic studies were identified which were applicable to this review question.

Economic model

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

Clinical evidence statements

Comparison 1. Acupuncture versus no acupuncture

Critical outcomes

Relief of heartburn during pregnancy

- Very low quality evidence from 1 RCT (N=36) showed that there is a clinically important difference favouring traditional acupuncture over no acupuncture on change after 8 weeks treatment from baseline in severity and frequency as assessed by a numerical rating scale (range 0-10) in pregnant women who experience heartburn: MD -4.20 (95% CI -6.36 to -2.04).
- Fetal death at any stage of the pregnancy
- No evidence was identified to inform this outcome.

Important outcomes

Gastrointestinal side-effects of interventions whilst receiving treatment

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Quality of life

- Very low quality evidence from 1 RCT (N=36) showed that there is a clinically important difference favouring traditional acupuncture over no acupuncture on the ability to sleep after 8 weeks of treatment in pregnant women who experience heartburn: RR 2.80 (95% CI 1.14 to 6.86).
- Very low quality evidence from 1 RCT (N=36) showed that there is a clinically important difference favouring traditional acupuncture over no acupuncture on the ability to eat after 8 weeks of treatment in pregnant women who experience heartburn: RR 2.40 (95% CI 1.11 to 5.18).

Women's experience and satisfaction of care during or after treatment for heartburn

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 2. Alginate-based reflux suppressant versus antacid

Critical outcomes

Relief of heartburn during pregnancy

Improvement of heartburn frequency

- Moderate quality evidence from 1 RCT (N=100) showed no clinically important difference between alginate-based reflux suppressant (Liquid Gaviscon®) and antacid (Maalox®) on the number of pregnant women whose heartburn frequency improves after 2 weeks of treatment: RR 0.91 (95% CI 0.77 to 1.08).

Improvement of heartburn intensity

- High quality evidence from 1 RCT (N=100) showed no clinically important difference between alginate-based reflux suppressant (Liquid Gaviscon®) and antacid (Maalox®) on the number of pregnant women whose heartburn intensity improves after 2 weeks of treatment: RR 1.00 (95% CI 0.89 to 1.12).

Cured/improved during day

- Very low quality evidence from 1 RCT (N=97) showed no clinically important difference between alginate-based reflux suppressant (Algicon®) and antacid (Magnesium trisilicate mixture BP) on the number of pregnant women whose heartburn is cured or improved during the day after 2 weeks of treatment: RR 0.89 (95% CI 0.71 to 1.11).

Cured/improved during night

- Very low quality evidence from 1 RCT (N=97) showed no clinically important difference between alginate-based reflux suppressant (Algicon®) and antacid (Magnesium trisilicate mixture BP) on the number of pregnant women whose heartburn is cured or improved during the night after 2 weeks treatment: RR 1.07 (95% CI 0.87 to 1.31).

50% reduction of frequency in daily heartburn

- Low quality evidence from 1 RCT (N=100) showed no clinically important difference between alginate-based reflux suppressant (Liquid Gaviscon®) and antacid (Maalox®) on the number of pregnant women who experience a 50% or greater reduction in the frequency of heartburn after 2 weeks treatment: RR 1.08 (95% CI 0.75 to 1.55).

50% reduction of heartburn intensity

- Moderate quality evidence from one RCT (N=100) showed no clinically important difference between antacid (Maalox®) and alginate-based reflux suppressant (Liquid Gaviscon®) on the number of pregnant women who experience a 50% or greater reduction in the intensity of heartburn after 2 weeks treatment, although there is some uncertainty: RR 0.80 (95% CI 0.62 to 1.03).

Fetal death

No evidence was identified to inform this outcome.

Important outcomes

Gastrointestinal side-effects of interventions whilst receiving treatment

Anorectic symptoms

- Very low quality evidence from 1 RCT (N=97) showed no clinically important difference between alginate-based reflux suppressant (Algicon®) and antacid (Magnesium trisilicate mixture BP) on the number of pregnant women with heartburn who exhibit anorectic symptoms after 2 weeks treatment: RR 2.82 (95% CI 0.12 to 67.64).

Loss of appetite

- Very low quality evidence from 1 RCT (N=97) showed no clinically important difference between alginate-based reflux suppressant (Algicon®) and antacid (Magnesium trisilicate mixture BP) on the number of pregnant women with heartburn who experience loss of appetite after 2 weeks treatment: RR 2.82 (95% CI 0.12 to 67.64).

Bloating

- Low quality evidence from 1 RCT (N=100) showed no clinically important difference between alginate-based reflux suppressant (Liquid Gaviscon®) and antacid (Maalox®) on the number of pregnant women with heartburn who experience bloating after 2 weeks treatment: RR 1.75 (95% CI 0.55 to 5.61).

Chalk-like taste

- Low quality evidence from 1 RCT (N=100) showed no clinically important difference between alginate-based reflux suppressant (Liquid Gaviscon®) and antacid (Maalox®) on the number of pregnant women with heartburn who experience a chalk-like taste after 2 weeks treatment: RR 1.57 (95% CI 0.66 to 3.72).

Constipation

- Low quality evidence from the 2 RCTs (N=197) showed no clinically important difference between alginate-based reflux suppressant and antacid on the number of pregnant women with heartburn who experience constipation after 2 weeks treatment: RR 0.85 (95% CI 0.42 to 1.71).
    - Very low quality evidence from 1 RCT conducted in a high-income World Bank country (N=97) showed no clinically important difference between alginate-based reflux suppressant (Algicon®) and antacid (Magnesium trisilicate mixture BP) on the number of pregnant women with heartburn who experience constipation after 2 weeks treatment: RR: 2.82 (95% CI 0.12 to 67.64).

- Low quality evidence from 1 RCT conducted in a low- or middle-income World Bank country (N=100) showed no clinically important difference between alginate-based reflux suppressant (Liquid Gaviscon®) and antacid (Maalox®) on the number of pregnant women with heartburn who experience constipation after 2 weeks treatment: RR: 0.77 (95% CI 0.37 to 1.59).

Diarrhoea

- Very low quality evidence from 2 RCTs combined (N=197) showed no clinically important difference between alginate-based reflux suppressant and antacid on the number of pregnant women with heartburn who experience diarrhoea after 2 weeks treatment: RR 0.39 (95% CI 0.12 to 1.31).
  - Very low quality evidence from 1 RCT conducted in a high-income World Bank (N=97) showed no clinically important difference between alginate-based reflux suppressant (Algicon®) and antacid (Magnesium trisilicate mixture BP) on the number of pregnant women with heartburn who experience diarrhoea after 2 weeks treatment: RR: 0.47 (95% CI 0.12 to 1.77).
  - Low quality evidence from 1 RCT conducted in a low- and middle-income World Bank country (N=100) showed no clinically important difference between alginate-based reflux suppressant (Liquid Gaviscon®) and antacid (Maalox®) on the number of pregnant women with heartburn who experience diarrhoea after 2 weeks treatment: RR: 0.20 (95% CI 0.01 to 4.06).

Nausea

- Very low quality evidence from the 2 RCTs (N=197) showed no clinically important difference between alginate-based reflux suppressant and antacid on the number of pregnant women with heartburn who experience nausea after 2 weeks treatment: RR 2.29 (95% CI 0.85 to 6.20).
  - Very low quality evidence from 1 RCT conducted in a high-income World Bank (N=97) showed no clinically important difference between alginate-based reflux suppressant (Algicon®) and antacid (Magnesium trisilicate mixture BP) on the number of pregnant women with heartburn who experience nausea after 2 weeks treatment: RR: 1.88 (95% CI 0.61 to 5.83).
  - Low quality evidence from 1 RCT conducted in a low- or middle-income World Bank country (N=100) showed no clinically important difference between alginate-based reflux suppressant (Liquid Gaviscon®) and antacid (Maalox®) on the number of pregnant women with heartburn who experience nausea after 2 weeks treatment: RR: 4.00 (95% CI 0.46 to 34.54).

Vomiting

- Very low quality evidence from 1 RCT (N=100) showed no clinically important difference between alginate-based reflux suppressant (Liquid Gaviscon®) and antacid (Maalox®) on the number of pregnant women with heartburn who experience vomiting after 2 weeks treatment: RR 0.70 (95% CI 0.26 to 1.88).

Preterm birth

No evidence was identified to inform this outcome.

Quality of life

- Low quality evidence from 1 RCT (N=100) showed no clinically important difference between alginate-based reflux suppressant (Liquid Gaviscon®) and antacid (Maalox®) on change in quality of life in pregnant women with heartburn after 2 weeks treatment as assessed by the physical health composite scores of the Short Form 12 (version 2) health survey: difference in medians 0.1, (p=0.82)

- Low quality evidence from 1 RCT (N=100) showed no clinically important difference between alginate-based reflux suppressant (Liquid Gaviscon®) and antacid (Maalox®) on change in quality of life in pregnant women with heartburn after 2 weeks treatment as assessed by the mental health composite scores of the Short Form 12 (version 2) health survey: difference in medians 4.6, (p=0.35)

Women's experience and satisfaction of care during or after treatment for heartburn

- High quality evidence from 1 RCT (N=100) showed no clinically important difference between alginate-based reflux suppressant (Liquid Gaviscon®) and antacid (Maalox®) on the number of pregnant women with heartburn who were satisfied or very satisfied after 2 weeks treatment: RR 1.00 (95% CI 0.82 to 1.22).

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 3. Antacid versus placebo

Critical outcomes

Relief of heartburn during pregnancy

Complete relief of heartburn during pregnancy

- Very low quality evidence from 1 RCT (N=156) showed a clinically important difference favouring antacid (magnesium hydroxide, aluminium hydroxide, and simethicone liquid or tablet) over placebo liquid or tablet on the number of pregnant women with heartburn who experience complete relief: RR 2.04 (95% CI 1.44 to 2.89).

No relief of heartburn during pregnancy

- Very low quality evidence from 1 RCT (N=156) showed a clinically important difference favouring antacid (magnesium and aluminium hydroxide and simethicone liquid or tablet) over placebo on the number of pregnant women with heartburn who did not experience any relief: RR 0.21 (95% CI 0.09 to 0.49).

Fetal death

No evidence was identified to inform this outcome.

Important outcomes

Gastrointestinal side-effects of interventions whilst receiving treatment

Upsetting taste

- Very low quality evidence from 1 RCT (N=156) showed no clinically important difference between antacid (magnesium hydroxide, aluminium hydroxide and simethicone liquid or tablet) and placebo on the number of pregnant women with heartburn who experience an upsetting taste: RR 0.29 (95% CI 0.04 to 1.92).

Constipation

- Very low quality evidence from 1 RCT (N=156) showed no clinically important difference between antacid (magnesium hydroxide, aluminium hydroxide and simethicone liquid or tablet) and placebo on the number of pregnant women with heartburn who experience constipation: RR 0.44 (95% CI 0.06 to 3.24).

Preterm birth

No evidence was identified to inform this outcome.

Quality of life

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during treatment for heartburn

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

Comparison 4. Proton-pump inhibitor exposure (PPIs) versus no PPI exposure

Critical outcomes

Relief of heartburn during pregnancy

No evidence was identified to inform this outcome.

Fetal death at any stage of pregnancy

Perinatal mortality during the third trimester of pregnancy

- Very low quality evidence from 1 retrospective cohort study (N=109,544) showed that there is no statistically significant difference between the number of pregnant women with heartburn who were exposed to PPIs (omeprazole, lansoprazole, pantoprazole) in the first trimester and the number of women who were not exposed to PPIs on the number of fetal deaths during the third trimester: Adjusted OR 0.32 (95% CI 0.08 to 1.31).

Important outcomes

Gastrointestinal side-effects of interventions whilst receiving treatment

No evidence was identified to inform this outcome.

Pre-term birth

- Very low quality evidence from 1 retrospective cohort study (N=109,544) showed that there is no clinically important difference between the number of pregnant women with heartburn who were exposed to PPIs (omeprazole, lansoprazole, pantoprazole) in the first trimester and the number of women who were not exposed to PPIs on the number of babies who are born preterm during the third trimester: Adjusted OR 0.86 (95% CI 0.62 to 1.19).

Quality of life

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care during or after treatment for heartburn

No evidence was identified to inform this outcome.

Small for gestational age

- Very low quality evidence from 1 retrospective cohort study (N=109,544) showed that there is no clinically important difference between the number of pregnant women with heartburn who were exposed to PPIs (omeprazole, lansoprazole, pantoprazole) in the first trimester and the number of women who were not exposed to PPIs on the number of babies who are born small for gestational age during the third trimester: Adjusted OR 0.7 (95% CI 0.48 to 1.03).

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that heartburn relief during pregnancy and fetal death at any stage of pregnancy were critical outcomes for the woman and baby respectively, and that gastrointestinal side-effects of interventions whilst receiving treatment, quality of life, women's experience and satisfaction of care during treatment, small for gestational age and preterm birth were important outcomes.

The quality of the evidence

The quality of the evidence ranged from very low to high, with most of the evidence of low or very low quality and only 2 outcomes rated as high.

The quality of evidence for the comparison of acupuncture versus no acupuncture was very low for the outcomes of relief of heartburn, and quality of life with respect to the ability to eat and sleep mainly due to very serious risk of bias of the one included study, indirectness of population, and imprecision in the effect estimates. No evidence was identified on the outcomes of gastro-intestinal side-effects of interventions whilst receiving treatment, women's experience and satisfaction of care during or after treatment, fetal death, small for gestational age and preterm birth.

The quality of evidence for the comparison of alginate-based reflux suppressants versus antacids was high to very low for various measures of relief of heartburn, various gastrointestinal side-effects of interventions whilst receiving treatment, women's experience and satisfaction of care during or after treatment, and quality of life. This was mainly due to one study which overall was at very serious risk of bias and imprecision in the effect estimates. No evidence was identified on the outcomes of fetal death, small for gestational age, and preterm birth.

The quality of evidence for the comparison of antacids versus placebo was very low to low on the outcomes of relief of heartburn and gastrointestinal side-effects of interventions whilst receiving treatment due to serious risk of bias in the one included study, serious indirectness, and imprecision in the effect estimates. No evidence was identified on the outcomes of quality of life, women's experience and satisfaction of care during or after treatment, fetal death and small for gestational age.

The quality of evidence for the comparison of proton-pump inhibitor versus no proton-pump inhibitor was very low for the outcomes of fetal death, small for gestational age, and preterm birth due to very serious risk of bias in the included cohort study and serious indirectness. Imprecision was not assessable as the effect estimates were adjusted odds ratio. No evidence was identified on the outcomes of relief of heartburn, gastro-intestinal side effects of interventions whilst receiving treatment, quality of life and women's experience and satisfaction of care during treatment.

There was no RCT nor non-RCT evidence identified on the use of dietary modifications or histamine 2-receptor antagonists to treat heartburn in pregnancy.

Benefits and harms

Information about changes to lifestyle and diet

The committee agreed with the recommendation from the 2008 NICE guideline on antenatal care for uncomplicated pregnancies (CG62) that pregnant women with new or pre-existing heartburn or acid reflux should be provided with information about potential lifestyle and/or

dietary changes, which may help to reduce or stop heartburn. The NICE guideline on gastro-oesophageal reflux disease and dyspepsia in adults includes recommendations about dietary and lifestyle advice so the committee made a cross reference to this guideline.

Antacids and alginate-based reflux suppressants

The committee recommended that antacids and alginate-based reflux suppressants should be considered for the treatment of heartburn during pregnancy because there was evidence that antacids were effective on alleviating heartburn compared to placebo with no increases in gastrointestinal side effects and evidence that both antacids and alginate-based reflux suppressants were as equally effective as each other in alleviating heartburn.

In the evidence comparing antacids and alginate-based reflux suppressants various measures of heartburn relief during treatment were reported in the two studies. While one variant in one study (50% reduction of heartburn intensity) may have marginally favoured antacids (with a borderline important point estimate and confidence intervals approaching significance), in the majority of outcomes there was no difference between the two interventions.

There were no differences between intervention groups on quality of life or any reported gastrointestinal side effect during treatment. Data for three side effects – constipation, diarrhoea, and nausea – were reported in both of the two studies.

The committee noted that overall there was a lack of evidence regarding the effects of using antacids and alginate-based reflux suppressants on the baby (fetal death, small for gestational age) and therefore could not rule out these hypothetical risks.

Generally, the committee noted that there was a lack of evidence about whether using pharmacological interventions to alleviate heartburn can have harmful effect on the baby. The committee noted that while the types of studies included in this review were the best available to answer the question on its effectiveness, they would not necessarily be the only study designs that report on adverse effects associated with treatments. More information about side effects, adverse effects, warnings or contraindications is provided by the British National Formulary (BNF) and Medicines and Healthcare products Regulatory Agency Medicines (MHRA).

Other interventions

Although there was some evidence that acupuncture was effective compared to no acupuncture, and that exposure to PPIs is not harmful to the baby, the committee decided that it was not sufficient to merit recommending their use. For the use of acupuncture to treat heartburn during pregnancy, one small RCT of 36 pregnant women with symptoms of dyspepsia conducted in Brazil, an upper-middle income country, was identified. All women in the study were permitted to take antacids and received standard treatment, which consisted of information about potential lifestyle and dietary modifications that may reduce or stop dyspepsia. There were clinically important differences between the acupuncture and no acupuncture (standard treatment) groups favouring acupuncture on heartburn relief and quality of life related outcomes: women in the acupuncture group experienced a significant reduction from baseline in the severity and frequency of heartburn and were more likely to experience a 50% or greater improvement in the ability to eat and a similar improvement in the ability to sleep. However overall the committee agreed that the single small study with very low quality evidence was insufficient evidence on which to base a recommendation which would reflect a change in practice.

One large retrospective cohort study conducted in Israel, including almost 110,000 women, compared pregnant women who had been exposed to proton-pump inhibitors (omeprazole, lansoprazole, or pantoprazole) in the first trimester to those who had not been exposed to

them. When confounding factors (including gestational and maternal age and smoking status) were adjusted for this study found no significant differences between PPI exposure and no PPI exposure on the third trimester outcomes of fetal death, preterm birth and small for gestational age. No other harms or benefits of interest in this review were reported in the study. The committee therefore agreed that although the use of PPIs after antacids is common practice, no recommendation in favour of their use should be made in lieu of evidence for their effectiveness.

Cost effectiveness and resource use

No economic evidence was identified which was relevant to this review question.

These recommendations reflect current practice and will not lead to any change in resource use.

References

da Silva 2009

da Silva, J.B., Nakamura, M.U., Cordeiro, J.A., Kulay, L.J., Saidah, R. Acupuncture for dyspepsia in pregnancy: a prospective, randomised, controlled study, Acupuncture in Medicine, 27(2), 50–3, 2009

Lang 1989

Lang, G. D., Dougall, A., Comparative study of Algicon suspension and magnesium trisilicate mixture in the treatment of reflux dyspepsia of pregnancy, British Journal of Clinical Practice, 43, 48-51, 1989

Matok 2012

Matok, I., Levy, A., Wiznitzer, A., Uziel, E., Koren, G., Gorodischer, R. The safety of fetal exposure to proton-pump inhibitors during pregnancy, Digestive Diseases and Sciences, 57, 699-705, 2012

Meteerattanapipat 2017

Meteerattanapipat, P., Phupong,V. Efficacy of alginate-based reflux suppressant and magnesium-aluminium antacid gel for treatment of heartburn in pregnancy: a randomized double-blind controlled trial, Scientific Reports, 7, 44830, 2017

Reisfield 1971

Reisfield, D.R. Pyrosis and pregnancy, Current Therapeutic Research, Clinical & Experimental, 13(11), 680–4, 1971

Appendices

Appendix A – Review protocols

Review protocol for review question: What interventions are effective in treating heartburn during pregnancy?

Table 3: Review protocol

Field (based on PRISMA-P)	Content
Review question	What interventions are effective in treating heartburn during pregnancy? Note: the safety of pharmacological interventions to treat heartburn during pregnancy will not be covered in this review. For information on the safety of any pharmacological interventions, please consult the BNF/MHRA.
Type of review question	Intervention
Objective of the review	The aim of this review is to evaluate the pregnancy outcomes of different treatment interventions for heartburn during pregnancy and to establish whether there are any harms for the mother or baby associated with them.
Eligibility criteria – population	Pregnant woman with new or pre-existing heartburn or acid reflux (a burning sensation or discomfort felt behind the sternum or throat or both).
Eligibility criteria – intervention(s)	• Acupuncture • Alginate reflux suppressants • Antacids (for example Maalox® plus suspension or tablets) • Dietary modifications (for example eating a smaller meal, avoiding acidic foods) • Histamine 2-receptor antagonists • Proton pump inhibitors
Eligibility criteria – comparator(s)	• Any other intervention (including combinations of listed interventions) • Placebo, sham treatment (for example sham acupuncture) or no treatment (compared to single interventions) Note: Combinations of interventions will be compared with one of the component interventions alone (e.g. acupuncture or diet modification + medication versus medication alone) but combination interventions will not be compared with 'no treatment' or placebo.
Outcomes and prioritisation	**Critical** • Relief of heartburn during pregnancy • Fetal death at any stage of pregnancy **Important** • Gastrointestinal side-effects of interventions whilst receiving treatment

Field (based on PRISMA-P)	Content
	• Preterm birth (birth before 37+0 weeks) • Quality of life • Women's experience and satisfaction of care during or after treatment for heartburn • Small for gestational age (SGA) Note: SGA is defined as having a birth weight below the 10th centile. Some studies will report this as Low Birth Weight (LBW) adjusted for Gestational Age (GA) rather than as SGA.
Eligibility criteria – study design	INCLUDE: • Systematic reviews • Randomised or quasi-randomised controlled trials (individual or cluster) If no evidence of these types is found for a listed class of intervention, the following types of non-randomised studies in order of priority will be considered: • Non-randomised controlled trials • Prospective cohort studies • Retrospective cohort studies Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
Other inclusion exclusion criteria	**Exclusion** POPULATION: • Studies exclusively on multiple pregnancies • Pregnancy with known or pre-existing congenital anomalies STUDY DESIGN: • Case-control studies • Cross-over studies • Cross-sectional studies • Epidemiological reviews or reviews on associations • Non-comparative studies PUBLICATION STATUS: • Conference abstract LANGUAGE: • Non-English **Inclusion** COUNTRY:

Field (based on PRISMA-P)	Content
	• No restriction
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroup analysis according to World Bank status (High-income countries; Low and middle-income countries) will be conducted (see https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups for classification of countries). Note that the use of the World Bank definitions of low-, middle- and high-income countries in this guideline is consistent with its use in the Postnatal care up to 8 weeks after birth (update) NICE guideline CG37. In the presence of heterogeneity, the following subgroup analyses will also be conducted: • Gestational age at presentation (by trimester) This subgroup factor will be used as a confounding factor to assess risk of bias of any included cohort studies using the relevant checklist. Other confounding factors that will be considered in the risk of bias evaluation when including cohort studies are: • BMI or body weight of woman • Smoking/Alcohol/substance misuse during pregnancy Statistical heterogeneity will be assessed by visually examining the forest plots and by calculating the I2 inconsistency statistic (with an I2 value≥50% indicating serious heterogeneity, and ≥80% indicating very serious heterogeneity).
Selection process – duplicate screening/selection/analysis	Studies included in the 2008 NICE guideline on antenatal care for uncomplicated pregnancies (CG62) that satisfy the review protocol will be included in this review. Review questions selected as high priorities for health economic analysis (and those selected as medium priorities and where health economic analysis could influence recommendations) will be subject to dual weeding and study selection; any discrepancies above 10% of the dual weeded resources will be resolved through discussion between the first and second reviewers or by reference to a third person. All data extraction will quality assured by a senior reviewer. Draft excluded studies and evidence tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.
Data management (software)	NGA STAR software will be used to generate bibliographies/citations, and conduct study sifting and data extraction. Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5). For details please see the methods chapter of the full guideline. 'GRADEpro' will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase. Limits (e.g. date, study design): • Date limit: 2006 (date of last search for CG62) • Apply standard animal/non-English language exclusion • Limit to RCTs and systematic reviews in first instance but download all results.
Identify if an update	This antenatal care update will replace the 2008 NICE guideline on antenatal care for uncomplicated pregnancies (CG62), which will be taken down in due course. The following relevant recommendations in the 2008 NICE guideline on antenatal care for uncomplicated pregnancies (CG62) on treatment of heartburn were made: 1.4.2.1 Women who present with symptoms of heartburn in pregnancy should be offered information regarding lifestyle and diet modification. 1.4.2.2 Antacids may be offered to women whose heartburn remains troublesome despite lifestyle and diet modification.
Author contacts	Developer: National Guideline Alliance.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.

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

CCTR: Cochrane Controlled Trials Register; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; NIHR: National Institute for Health Research; RCT(s): randomised controlled trial(s); RoB: risk of bias; ROBIS: Risk Of Bias In Systematic reviews tool; ROBINS-I: Risk Of Bias In Non-randomized studies – of Interventions tool.

Appendix B – Literature search strategies

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

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

#	Searches
1	Pregnancy/ use ppez
2	Pregnant Women/ use ppez
3	pregnancy/ use emczd
4	pregnant woman/ use emczd
5	pregnan$.tw.
6	1 or 2 or 3 or 4 or 5
7	Heartburn/ use ppez
8	Dyspepsia/ use ppez
9	Gastroesophageal Reflux/ use ppez
10	heartburn/ use emczd
11	dyspepsia/ use emczd
12	gastroesophageal reflux/ use emczd
13	(heart burn$ or heartburn$ or dyspeps$ or indigestion$ or pyrosis$).tw.
14	((acid$ or gastro?esophag$ or gastro-oesophag$ or gastro-esophag$ or gastric) adj reflux$).tw.
15	(reflux$ adj disease$).tw.
16	(GERD or GORD).tw.
17	Esophagitis, Peptic/ use ppez
18	reflux esophagitis/ use emczd
19	((reflux or eosinophilic or erosive or ulcerative or peptic) adj (oesophagitis or esophagitis)).tw.
20	acid$ sup?ress$.tw.
21	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	6 and 21
23	limit 22 to english language
24	letter/
25	editorial/
26	news/
27	exp historical article/
28	Anecdotes as Topic/
29	comment/
30	case report/
31	(letter or comment*).ti.
32	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33	randomized controlled trial/ or random*.ti,ab.
34	32 not 33
35	animals/ not humans/
36	exp Animals, Laboratory/
37	exp Animal Experimentation/
38	exp Models, Animal/
39	exp Rodentia/
40	(rat or rats or mouse or mice).ti.
41	34 or 35 or 36 or 37 or 38 or 39 or 40
42	letter.pt. or letter/
43	note.pt.
44	editorial.pt.
45	case report/ or case study/
46	(letter or comment*).ti.
47	42 or 43 or 44 or 45 or 46
48	randomized controlled trial/ or random*.ti,ab.
49	47 not 48
50	animal/ not human/
51	nonhuman/

#	Searches
52	exp Animal Experiment/
53	exp Experimental Animal/
54	animal model/
55	exp Rodent/
56	(rat or rats or mouse or mice).ti.
57	49 or 50 or 51 or 52 or 53 or 54 or 55 or 56
58	41 use ppez
59	57 use emczd
60	58 or 59
61	23 and 60
62	23 not 61

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

#	Searches
#1	MeSH descriptor: [Pregnancy] this term only
#2	MeSH descriptor: [Pregnant Women] this term only
#3	(pregnan*):ti,ab,kw
#4	#1 OR #2 OR #3
#5	MeSH descriptor: [Heartburn] this term only
#6	MeSH descriptor: [Dyspepsia] this term only
#7	MeSH descriptor: [Gastroesophageal Reflux] this term only
#8	(heart NEXT burn* or heartburn* or dyspeps* or indigestion* or pyrosis*):ti,ab,kw
#9	((acid* or gastro?esophag* or gastro-oesophag* or gastro-esophag* or gastric) NEXT reflux*):ti,ab,kw
#10	(reflux* NEXT disease*):ti,ab,kw
#11	(GERD or GORD):ti,ab,kw
#12	MeSH descriptor: [Esophagitis, Peptic] this term only
#13	((reflux or eosinophilic or erosive or ulcerative or peptic) NEXT (oesophagitis or esophagitis)):ti,ab,kw
#14	(acid* NEXT sup?ress*):ti,ab,kw
#15	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16	#4 AND #15

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

#	Searches
1	MeSH DESCRIPTOR Pregnancy EXPLODE ALL TREES IN DARE,HTA
2	MeSH DESCRIPTOR Pregnant Women EXPLODE ALL TREES IN DARE,HTA
3	(pregnan*) IN DARE, HTA
4	#1 OR #2 OR #3
5	MeSH DESCRIPTOR Heartburn EXPLODE ALL TREES IN DARE,HTA
6	MeSH DESCRIPTOR Dyspepsia EXPLODE ALL TREES IN DARE,HTA
7	MeSH DESCRIPTOR Gastroesophageal Reflux EXPLODE ALL TREES IN DARE,HTA
8	((heart NEAR burn* or heartburn* or dyspeps* or indigestion* or pyrosis*)) IN DARE, HTA
9	(((acid* or gastroesophag* or gastrooesophag* or gastro-oesophag* or gastro-esophag* or gastric) NEAR reflux*)) IN DARE, HTA
10	((reflux* NEAR disease*)) IN DARE, HTA
11	((GERD or GORD)) IN DARE, HTA
12	MeSH DESCRIPTOR Esophagitis, Peptic EXPLODE ALL TREES IN DARE,HTA
13	(((reflux or eosinophilic or erosive or ulcerative or peptic) NEAR (oesophagitis or esophagitis))) IN DARE, HTA
14	((acid* NEAR (supress* or suppress*))) IN DARE, HTA
15	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
16	#4 AND #15

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

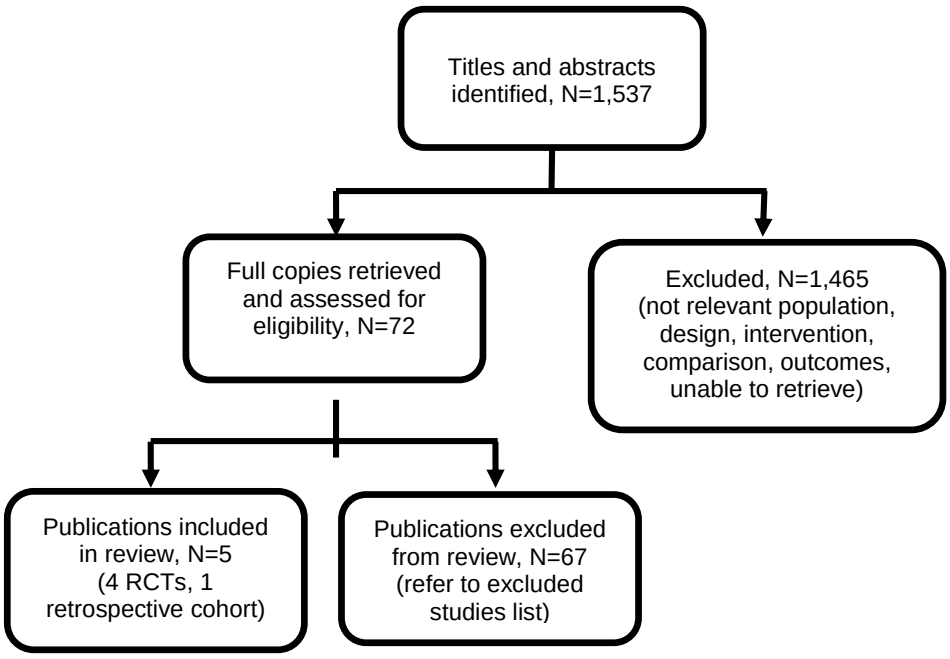
#	Query
S17	S15 NOT S16 Limiters - English Language
S16	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website
S15	S4 AND S14

#	Query
S14	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S13	TI (((reflux or eosinophilic or erosive or ulcerative or peptic) N1 (oesophagitis or esophagitis))) OR AB (((reflux or eosinophilic or erosive or ulcerative or peptic) N1 (oesophagitis or esophagitis)))
S12	(MH "Gastroesophageal Reflux")
S11	TI ((GERD or GORD)) OR AB ((GERD or GORD))
S10	TI (reflux* N1 disease*) OR AB (reflux* N1 disease*)
S9	TI (((acid* or gastro?esophag* or gastro-oesophag* or gastro-esophag* or gastric) N1 reflux*)) OR AB (((acid* or gastro?esophag* or gastro-oesophag* or gastro-esophag* or gastric) N1 reflux*))
S8	TI ((heart burn* or heartburn* or dyspeps* or indigestion* or pyrosis*)) OR AB ((heart burn* or heartburn* or dyspeps* or indigestion* or pyrosis*))
S7	(MH "Gastroesophageal Reflux")
S6	(MH "Dyspepsia")
S5	(MH "Heartburn")
S4	S1 OR S2 OR S3
S3	TI pregnan* OR AB pregnan*
S2	(MH "Expectant Mothers")
S1	(MH "Pregnancy")

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What interventions are effective in treating heartburn during pregnancy?

Figure 1: PRISMA flow chart for review question:



Appendix D – Clinical evidence tables

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

Table 4: Clinical evidence table

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation da Silva, J. B., Nakamura, M. U., Cordeiro, J. A., Kulay Jr, L., Saidah, R., Acupuncture for dyspepsia in pregnancy: a prospective, randomised, controlled study, Acupuncture in medicine : journal of the British Medical Acupuncture Society, 27, 50-53, 2009 **Ref Id** 897312 **Country/ies where the study was carried out** Brazil **Study type** RCT **Aim of the study** To assess the effectiveness of acupuncture compared to conventional treatment alone on symptomatic dyspepsia during pregnancy. **Study dates**	**Sample size** N=36 Intervention: N=20 Control: N=16 **Characteristics** Maternal age (years) - mean ±SD Intervention: 28.0 (6.3) Control: 24.8 (5.5) Current weight (kg) - mean ±SD Intervention: 65.8 (11.0) Control: 61.9 (11.2) Body mass index for gestational age - mean ±SD Intervention: 24.6 (3.5) Control: 23.8 (4.3) **Inclusion criteria**	**Interventions** Intervention: acupuncture once per week, occasionally twice when deemed necessary, during eight weeks (minimum of eight and maximum of 12 sessions) Control: No treatment.	**Details** Intervention: traditional acupuncture using on average 12 needles left in place for approximately 25 minutes. Neither electro-stimulation nor ear acupuncture were used. Both treatment groups were counselled by a group of nurses regarding lifestyle behaviour modifications, including dietary changes, to alleviate dyspepsia. Participants were permitted to take antacids. **Power analysis** Not reported. **Statistical analyses**	**Results** Outcomes for woman Relief of heartburn during pregnancy Change from baseline in severity and frequency of heartburn (numerical rating scale; NRS) - mean ±SD Intervention: -5.1 (3.7) Control: -0.9 (2.9); p=0.001 Quality of life Improvement of at least 50% in eating - number/total number (n/N) (%) Intervention: 15/20 (75%) Control: 5/16 (31%); p=0.008	**Limitations** Cochrane risk of bias tool V2: Randomisation process: Some concerns. (No details on random sequence generation. Research nurse selected from a box closed pieces of paper with a treatment order written on it.) Deviations from intended interventions: Low risk. (Blinding of personnel not possible; not possible to blind participants given design of study). Measurement of the outcome: Some concerns. (Research assistant collected data but no further details provided). Missing outcome data: Low risk. (19% dropout rate, 1 in acupuncture and 5 in acupuncture group).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
January to December 2003. **Source of funding** State-funded.	Pregnant women aged from 15 to 39 years. At 15 to 30 weeks of pregnancy. Dyspepsia symptoms. Participants had no underlying disease as a possible cause of the symptoms or history of similar symptoms prior to pregnancy. **Exclusion criteria** Women in high-risk pregnancy group. Received acupuncture in the preceding year.		Fisher test used to analyse changes over time in the numerical rating scale (NRS) for severity and frequency of heartburn. Two-sample t-test used to analyse differences between initial and final treatment sessions. **Intention-to-treat (ITT) analysis** Not reported.	Improvement of at least 50% in sleeping - n/N (%) Intervention: 14/20 (70%) Control: 4/16 (25%); p=0.009	Selective reporting: Some concerns. (no protocol available) Other sources of bias: Some concerns. (Participants also received lifestyle and dietary modification advice and antacid use was permitted. Seven participants in each group reported antacid use with those in the acupuncture groups reducing, and those in the control group increasing, their use of antacids). Overall: High risk
Full citation Lang, G. D., Dougall, A., Comparative study of Algicon suspension and magnesium trisilicate mixture in the treatment of reflux dyspepsia of pregnancy, British Journal of Clinical Practice, 43, 48-51, 1989 **Ref Id** 897055	**Sample size** N=157 Intervention: n=79 Control: n=78 **Characteristics** Maternal age (years) - mean Intervention: 27.3 Control: 25.7	**Interventions** Intervention: Algicon suspension 10 ml Control: Magnesium trisilicate mixture BP Both interventions to be taken after meals and at bedtime for two weeks.	**Details** **Power analysis** Not reported. **Statistical analyses** Not reported. **Intention-to-treat (ITT) analysis** Not reported.	**Results** Outcomes for the woman Relief of heartburn during pregnancy Cured/improved (daytime) at 2 weeks Intervention (n=50): 36	**Limitations** Cochrane risk of bias tool V2: Randomisation process: Some concerns. (Insufficient information). Deviations from intended interventions (assignment): Some concerns. (Medication distributed by pharmacy, but no

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out UK **Study type** Randomised trial. **Aim of the study** To assess the effectiveness of Algicon suspension compared to magnesium trisilicate mixture in the treatment of in pregnant women with reflux dyspepsia. **Study dates** Not reported. **Source of funding** Not reported.	Symptom history (weeks) - mean Intervention: 9.3 Control: 10.7 **Inclusion criteria** Women at <38 weeks gestation; Symptoms of reflux dyspepsia of pregnancy of recent onset. **Exclusion criteria** Symptoms or signs of pre-eclampsia; History of dyspepsia; Suspected peptic ulcer prior to pregnancy; Use of anticonvulsants and metoclopramide.			Control (n=47): 38 Cured/improved (night-time) at 2 weeks Intervention (n=50): 41 Control (n=47): 36 Gastrointestinal side-effects of interventions whilst receiving treatment Anorexia - number Intervention (n=50): 1 Control (n=47): 0 Appetite - number Intervention (n=50): 1 Control (n=47): 0 Constipation - number Intervention (n=50): 1 Control (n=47): 0 Diarrhoea - number Intervention (n=50): 3 Control (n=47): 6	further details provided. Insufficient information provided on blinding). Missing outcome data: High risk. (38% of sample were lost to follow-up after 2 weeks treatment). Measurement of the outcome: Some concerns. (No protocol available). Other sources of bias: Low risk (no other serious concerns) Overall: High risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Nausea - number Intervention (n=50): 8 Control (n=47): 4 Vomiting - number Intervention (n=50): 6 Control (n=47): 8	
Full citation Matok,I., Levy,A., Wiznitzer,A., Uziel,E., Koren,G., Gorodischer,R., The safety of fetal exposure to proton-pump inhibitors during pregnancy, Digestive Diseases and Sciences, 57, 699-705, 2012 **Ref Id** 250304 **Country/ies where the study was carried out** Israel **Study type** Retrospective cohort study. **Aim of the study** To assess the safety of proton-pump inhibitors (PPIs) on the fetus during pregnancy. **Study dates**	**Sample size** Intervention: N=1,186 (1,159 infants and 27 abortuses) exposed to PPIs (omeprazole n=955; lansoprazole n=233; pantoprazole n=17) Control: N=109,597 **Characteristics** Maternal age (years) - mean ±SD Intervention: 29.6 (6.1) Control: 28.6 (6.0) Maternal smoking - number (%) Intervention: 13 (0.6)	**Interventions** Intervention: PPIs (Omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg). Control: pregnant women not taking PPIs.	**Details** PPIs (omeprazole, lansoprazole, and pantoprazole) were dispensed during the first trimester of pregnancy (at 13 weeks of gestation or earlier). Statistical analyses Continuous outcome data were analysed using Student's t-test. Multivariate logistic-regressions models were developed to identify independent risk factors associated with adverse fetal outcomes. Spearman correlation was performed between infants' weight and	**Results** Outcomes for the woman - during the third trimesters of pregnancy Preterm delivery (<37 weeks) - number (%) Intervention (n=666): 38 (5.7) Control (n=108,878): 7,105 (6.5); adjusted p=0.357 Adjusted OR (95% CI)*: 0.86 (0.62 to 1.19) Outcomes for the baby - during the third trimesters of pregnancy Fetal death - number (%)	**Limitations** ROBINS-I: Confounding bias: Serious risk of bias (although appropriate methods used to control for potential confounders, i.e. regression analyses, unclear what conditions were present in control group participants - participants identified from medical codes, i.e. inference that presence of code to presence of condition). Selection of participant's bias: Serious risk of bias (retrospective study). Classification of interventions bias: Serious risk of bias (control group not clearly defined and information not

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
January 1998 to December 2009. **Source of funding** Not reported.	Control: 1,146 (1.1) Maternal diabetes - number (%) Intervention: 100 (8.4) Control: 61,896 (5.6) Peripartum fever - number (%) Intervention: 7 (0.6) Control: 1,152 (1.1) **Inclusion criteria** 1] Females aged 15 to 49 years. 2] Registered on the Clalit database and living in the southern district of Israel. 3] Given birth to singletons at the Soroka Medical Centre. **Exclusion criteria** Not reported.		number of infants exposed to PPIs during the third trimester. Categorical multivariate logistic-regression model developed to determine whether there was an association between greater exposure in terms of defined daily doses of PPIs and increased risk of major congenital malformations. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. For the analysis of outcomes other than congenital malformations, two additional groups were defined: exposure to PPIs during the second (weeks 14 to 26) and third (week 27 and above) trimesters. Subgroup analysis was conducted on all major heart defects. The following potential	Intervention (n=666): 2 (0.3) Control (n=108,878): 1,348 (1.2); adjusted p=0.114 Adjusted OR (95% CI)*: 0.32 (0.08 to 1.31) [data includes some early neonatal deaths] Small for gestational age (SGA) Low birth weight (<2,500 g) - number (%) Intervention (n=666): 40 (6.0) Control (n=108,878): 8,988 (8.3); adjusted p=0.052 Adjusted OR (95% CI)*: 0.70 (0.48 to 1.03)	recorded at start of intervention as a retrospective study). Deviations from intended interventions bias: No information. Missing data bias: Serious risk of bias (>20% missing data on adverse pregnancy outcomes). Measurement of outcomes bias: Low risk of bias (risk of bias expected to be low due to outcome measures and comparable outcome assessments across intervention groups). Selection of the reported results bias: Low risk of bias (all outcomes reported). Overall bias: Serious risk of bias Other information Outcomes reported separately in the publication for exposure to omeprazole and lansoprazole. *Models controlled for year of birth, maternal age, population group, maternal diabetes, maternal smoking, peripartum

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			confounders were included in statistical analysis: maternal age, parity, self-reported smoking status during pregnancy, maternal diabetes mellitus, year of birth, and population group. For pregnancy outcomes other than congenital malformations, peripartum fever (temperature of ≥38ºC) and pregnancy duration in days were added to the covariates.		fever, duration of pregnancy in days, and parity.
Full citation Meteerattanapipat, P., Phupong, V., Efficacy of alginate-based reflux suppressant and magnesium-aluminium antacid gel for treatment of heartburn in pregnancy: a randomized double-blind controlled trial, Scientific ReportsSci, 7, 44830, 2017 **Ref Id** 896884 **Country/ies where the study was carried out**	**Sample size** N=100 Intervention: N=50 Control: N=50 **Characteristics** Maternal age (years) - mean ±SD Intervention: 29.0 (5.5) Control: 30.9 (5.4) Gestational age when heartburn	**Interventions** Intervention: 15 ml oral alginate-based reflux suppressant three times per day after meals and before bedtime for two weeks. Control: 15 ml magnesium-aluminium antacid gel three times per day after meals and before bedtime for two weeks.	**Details** Participants were advised to modify lifestyle behaviours (including reducing risk factors of heartburn symptoms, e.g. tobacco and alcohol abstinence, avoiding post-prandial recumbent and trigger foods). At 1-week follow-up, participants with persistent or worsened symptoms	**Results** Outcomes for the woman Relief of heartburn during pregnancy Improvement of heartburn frequency - number (%) Intervention: 40 (80%) Control: 44 (88%); p=0.275	**Limitations** Cochrane risk of bias tool V2: Randomisation process: Low risk of bias (random number table using a block-of-four technique, allocation sequence generated prior to study by an investigator who had no contact with participants. Primary investigator assigned participants to treatment groups with interventions prepared in

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Thailand **Study type** RCT **Aim of the study** To assess the effectiveness of alginate-based reflux suppressant compared with magnesium-aluminum antacid gel on the reduction of heartburn frequency in pregnancy. **Study dates** June 2015 to July 2016. **Source of funding** Supported by the Ratchadapiseksompotch Fund, Chulalongkorn University.	present (weeks) - mean ±SD Intervention: 26.9 (8.0) Control: 23.6 (9.2) Pre-pregnancy body mass index (BMI; kg/m2) - mean ±SD Intervention: 22.4 (4.7) Control: 21.9 (3.5) History of heartburn before pregnancy - number (%) Intervention: 30 (60%) Control: 23 (46%) Frequency of heartburn (times per week) - median (interquartile range; IQR) Intervention: 13 (5 to 20.2) Control: 12 (7 to 21) Intensity of heartburn - median (IQR) Intervention: 42.5 (31 to 60) Control: 43.5 (28.8 to 60)		(i.e. heartburn frequency at least two times per week) were included in the study. **Power analysis** Adjusting for a 10% rate of participant withdrawals, a minimum of 50 women in each treatment group was required to detect statistical difference. **Statistical analyses** Chi-square and Fisher-exact tests were used for categorical outcome data. Continuous outcome data were analysed using independent t-test. Non-parametric data were analysed, where appropriate, using Mann-Whitney U test. **Intention-to-treat (ITT) analysis** Analysis based on ITT.	50% reduction of frequency in all-day of heartburn - number (%) Intervention: 28 (56%) Control: 26 (52%); p=0.688 Improvement of heartburn intensity (visual analogue scale; VAS) - number (%) Intervention: 46 (92%) Control: 46 (92%); p=1.000 50% reduction in pain score for heartburn intensity (VAS): - number (%) Intervention: 32 (68%) Control: 40 (80%); p=0.075 Gastrointestinal side effects Constipation - number (%) Intervention: 10 (20) Control: 13 (26)	sequentially numbered opaque bags). Deviations from intended interventions (assignment): Low risk. (Healthcare providers and participants masked to treatment assignment). Missing outcome data: Low risk. (No participants lost to follow-up). Measurement of the outcome: Low risk. (All outcomes in protocol reported plus some others not specified). Other sources of bias: Low risk (no other serious concerns). Overall: Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria Pregnant women aged 18 to 40 years. <36 weeks of gestation. Presenting to the University antenatal care clinic with a diagnosis of heartburn. **Exclusion criteria** Pregnant women with medical diseases. Contraindications to study drug and allergies to alginate-based reflux suppressant and magnesium-aluminium antacid gel.			Chalk-like taste - number (%) Intervention: 11 (22) Control: 7 (14) Diarrhoea - number (%) Intervention: 0 (0) Control: 2 (4) Bloating - number (%) Intervention: 7 (14) Control: 4 (8) Nausea - number (%) Intervention: 4 (8) Control: 1 (2) Quality of life SF-12v2 change on physical health composite score (PCS) - median (IQR) Intervention: 7.7 (0 to 15.3) Control: 7.6 (0 to 15.9); p=0.82 SF-12v2 mental health change on composite score	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(MCS) - median (IQR) Intervention: 11.4 (0.9 to 21.7) Control: 6.8 (0.5 to 18.1); p=0.352 Women's experience and satisfaction of care during or after treatment - Satisfied or very satisfied with treatment - number (%) Intervention: 40 (80%) Control: 40 (80%); p=1.000	
Full citation Reisfield, D. R., Pyrosis and pregnancy, Current therapeutic research, clinical and experimental, 13, 680-684, 1971 **Ref Id** 896947 **Country/ies where the study was carried out** USA **Study type** Double-blind RCT **Aim of the study**	**Sample size** N=156 Intervention: n=83 (67 on active tablets, 16 on active liquid) Control: n=73 (65 on placebo tablets, 8 on placebo liquid) **Characteristics** Maternal age (years) - range* The majority of patients (n=97) were aged between	**Interventions** Intervention group: magnesium and aluminium hydroxides plus simethicone liquid and tablet (Mylanta®). Comparison group: identical appearing placebo liquid (titanium dioxide, sweeteners, preservatives, and artificial flavours) and tablet (calcium sulfate, lactose, sweeteners, artificial flavours, and colouring).	**Details** Oral iron therapy was prescribed to 19 patients (not reported separately for treatment groups). **Power analysis** Not reported. **Statistical analyses** Chi-square tests were conducted and tests having a probability of <1.10 were considered to be non-significant.	**Results** Outcomes for the woman Relief of heartburn during pregnancy Complete relief of heartburn - number Intervention (active tablets): 46 Intervention (active liquid): 12 Control (placebo tablets): 22	**Limitations** Cochrane risk of bias tool V2: Randomisation process: Some concerns. (Insufficient information of randomisation process. There was prior coding of identical tablets or liquid). Deviations of intended interventions (assignment): Low risk. (Study personnel and participants blinded to treatment assignment.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To assess the effectiveness of an antacid in reducing gastric distress in pregnant women with pyrosis. **Study dates** Not reported. **Source of funding** Not stated.	20 and 29 years, with 36 patients aged 30 to 39 years. Degree of heartburn - number Mild Intervention (active tablets): 4 Intervention (active liquid): 3 Control (placebo tablets): 6 Control (placebo liquid): 0 Moderate Intervention (active tablets): 19 Intervention (active liquid): 4 Control (placebo tablets): 20 Control (placebo liquid): 2 Severe Intervention (active tablets): 43 Intervention (active liquid): 9 Control (placebo tablets): 38 Control (placebo liquid): 6		**Intention-to-treat (ITT) analysis** Not reported.	Control (placebo liquid): 3 Partial relief of heartburn - number Intervention (active tablets): 16 Intervention (active liquid): 3 Control (placebo tablets): 22 Control (placebo liquid): 1 Side effects Upsetting taste - number Intervention: 1 Control: 3 Constipation - number Intervention: 1 Control: 2	Assessors blinded to group assignment). Missing outcome data: Low risk. (4% dropout before end of treatment). Measurement of the outcome: Some concerns. (No protocol available). Other sources of bias: Some concerns. (19 participants also received iron therapy, group assignment not specified. Treatment length not specified). Overall: High risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	*Data not presented separately for treatment groups. **Inclusion criteria** Pregnant women complaining of heartburn or pyrosis. **Exclusion criteria** Not reported.				

CI: confidence interval; IQR: interquartile range; ITT: intention to treat; MCS: mental composite score; NRS: numerical rating scale; OR: odds ratio; PCS: physical composite score; PPI: proton pump inhibitor; RCT: randomised controlled trial; ROBINS-I: Risk of Bias in Non-randomised Studies of Interventions; SD: standard deviation; VAS: visual analogue scale

Appendix E – Forest plots

Forest plots for review question: What interventions are effective in treating heartburn during pregnancy?

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

Antacids versus alginate reflux suppressant for pregnant women with heartburn

Figure 2: Gastrointestinal side-effects of interventions whilst receiving treatment - Constipation

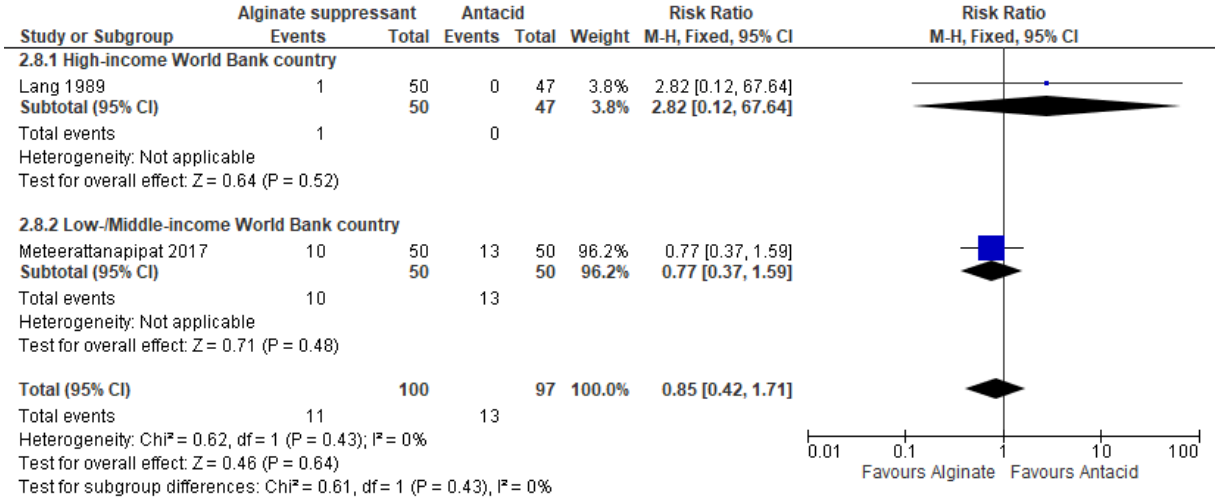


Figure 3: Gastrointestinal side-effects of interventions whilst receiving treatment - Diarrhoea

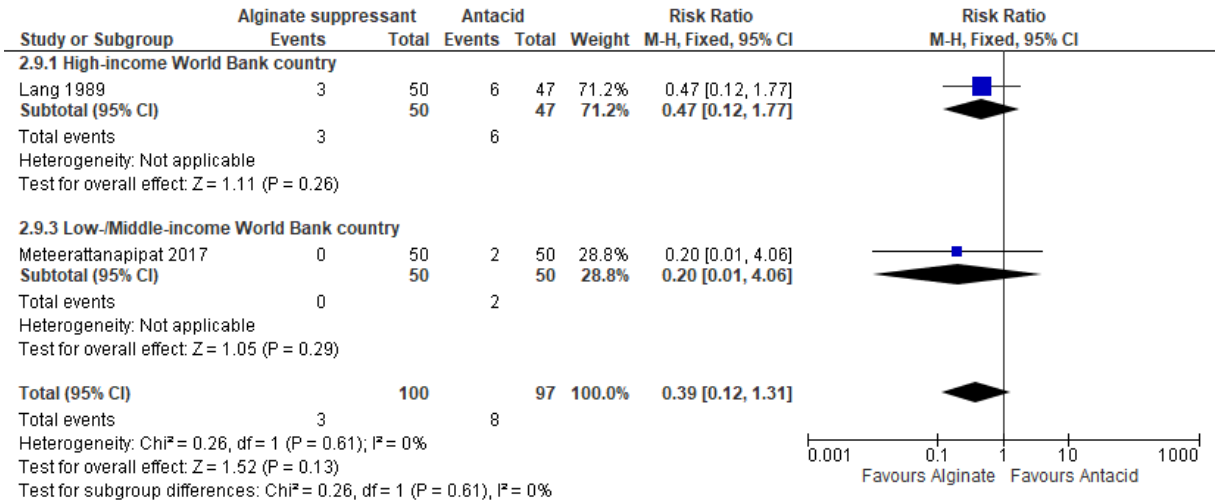
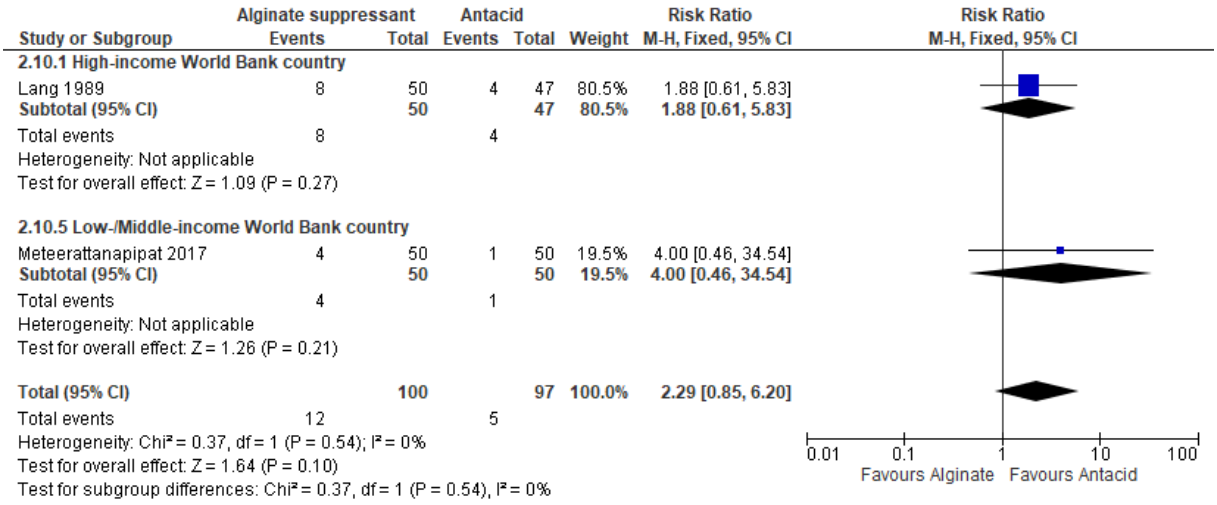


Figure 4: Gastrointestinal side-effects of interventions whilst receiving treatment - Nausea



Appendix F – GRADE tables

GRADE tables for review question: What interventions are effective in treating heartburn during pregnancy?

Table 5: Clinical evidence profile for acupuncture versus no acupuncture for treatment of heartburn during pregnancy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupuncture	No acupuncture	Relative (95% CI)	Absolute		
Relief of heartburn - Change from baseline in severity and frequency of heartburn (measured with: Numerical Rating Scale; range of scores: 0-10; Better indicated by lower values)												
1 (da Silva 2009)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	20	16	-	MD 4.2 lower (6.36 to 2.04 lower)	⊕OOO VERY LOW	CRITICAL
Quality of life - Improvement of at least 50% in the ability to sleep (assessed with: Numerical Rating Scale)												
1 (da Silva 2009)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	14/20 (70%)	4/16 (25%)	RR 2.8 (1.14 to 6.86)	450 more per 1000 (from 35 more to 1000 more)	⊕OOO VERY LOW	IMPORTANT
Quality of life - Improvement of at least 50% in the ability to eat (assessed with: Numerical Rating Scale)												
1 (da Silva 2009)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	15/20 (75%)	5/16 (31.3%)	RR 2.4 (1.11 to 5.18)	438 more per 1000 (from 34 more to 1000 more)	⊕OOO VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio.
[1] Evidence downgraded by 2 levels due to unclear risk of bias in da Silva 2009 regarding random sequence generation, blinding of personnel and participants, blinding of outcome assessment, and selective reporting
[2] Evidence downgraded by 1 level because participants in da Silva 2009 had dyspepsia, of which heartburn is one of the symptoms. Although the mean heartburn frequency and intensity, as rated by a numerical rating scale (range 0-10, lower scores better) at baseline was greater than 5.0, not clear if all participants had heartburn.
[3] Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).

Table 6: Clinical evidence profile for comparison alginate-based reflux suppressant versus antacid for treatment of heartburn during pregnancy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alginate-based reflux suppressant	Antacid	Relative (95% CI)	Absolute		
Relief of heartburn - Improvement of heartburn frequency (assessed with: Self-report/diary)												
1 (Meteerattanapipat 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	40/50 (80%)	44/50 (88%)	RR 0.91 (0.77 to 1.08)	79 fewer per 1000 (from 202 fewer to 70 more)	⊕⊕⊕O MODERATE	CRITICAL
Relief of heartburn - Improvement of heartburn intensity (assessed with: Visual analogue scale (range 0-100))												
1 (Meteerattanapipat 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	46/50 (92%)	46/50 (92%)	RR 1 (0.89 to 1.12)	0 fewer per 1000 (from 101 fewer to 110 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Relief of heartburn - Cured/improved during day												
1 (Lang 1989)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	36/50 (72%)	38/47 (80.9%)	RR 0.89 (0.71 to 1.11)	89 fewer per 1000 (from 234 fewer to 89 more)	⊕OOO VERY LOW	CRITICAL
Relief of heartburn - Cured/improved during night												
1 (Lang 1989)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	41/50 (82%)	36/47 (76.6%)	RR 1.07 (0.87 to 1.31)	54 more per 1000 (from 100 fewer to 237 more)	⊕OOO VERY LOW	CRITICAL
Relief of heartburn - 50% reduction in daily heartburn frequency (assessed with: Self-report/diary)												
1 (Meteerattanapipat 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	28/50 (56%)	26/50 (52%)	RR 1.08 (0.75 to 1.55)	42 more per 1000 (from 130 fewer to 286 more)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alginate-based reflux suppressant	Antacid	Relative (95% CI)	Absolute		
Relief of heartburn - 50% reduction of heartburn intensity (assessed with: Visual analogue scale (0-100))												
1 (Meteerattanapipat 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32/50 (64%)	40/50 (80%)	RR 0.8 (0.62 to 1.03)	160 fewer per 1000 (from 304 fewer to 24 more)	⊕⊕⊕O MODERATE	CRITICAL
Gastrointestinal side-effects of interventions whilst receiving treatment - Anorexia												
1 (Lang 1989)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/50 (2%)	0/47 (0%)	RR 2.82 (0.12 to 67.64)	20 more per 1000 (from 30 fewer to 70 more)	⊕OOO VERY LOW	IMPORTANT
Gastrointestinal side-effects of interventions whilst receiving treatment - Lack of appetite												
1 (Lang 1989)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/50 (2%)	0/47 (0%)	RR 2.82 (0.12 to 67.64)	20 more per 1000 (from 30 fewer to 70 more)	⊕OOO VERY LOW	IMPORTANT
Gastrointestinal side-effects of interventions whilst receiving treatment - Bloating (assessed with: Self-report/diary)												
1 (Meteerattanapipat 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	7/50 (14%)	4/50 (8%)	RR 1.75 (0.55 to 5.61)	60 more per 1000 (from 36 fewer to 369 more)	⊕⊕OO LOW	IMPORTANT
Gastrointestinal side-effects of interventions whilst receiving treatment - Chalk-like taste (assessed with: Self-report/diary)												
1 (Meteerattanapipat 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	11/50 (22%)	7/50 (14%)	RR 1.57 (0.66 to 3.72)	80 more per 1000 (from 48 fewer to 381 more)	⊕⊕OO LOW	IMPORTANT
Gastrointestinal side-effects of interventions whilst receiving treatment - Constipation												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alginate-based reflux suppressant	Antacid	Relative (95% CI)	Absolute		
2‡	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	11/100 (11%)	13/97 (13.4%)	RR 0.85 (0.42 to 1.71)	20 fewer per 1000 (from 78 fewer to 95 more)	⊕⊕OO LOW	IMPORTANT
Gastrointestinal side-effects of interventions whilst receiving treatment - Constipation - High-income World Bank country												
1 (Lang 1989)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/50 (2%)	0/47 (0%)	RR 2.82 (0.12 to 67.64)	20 more per 1000 (from 30 fewer to 70 more)	⊕OOO VERY LOW	IMPORTANT
Gastrointestinal side-effects of interventions whilst receiving treatment - Constipation - Low-/Middle-income World Bank country												
1 (Meteerattanapipat 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	10/50 (20%)	13/50 (26%)	RR 0.77 (0.37 to 1.59)	60 fewer per 1000 (from 164 fewer to 153 more)	⊕⊕OO LOW	IMPORTANT
Gastrointestinal side-effects of interventions whilst receiving treatment - Diarrhoea												
2‡	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/100 (3%)	8/97 (8.2%)	RR 0.39 (0.12 to 1.31)	50 fewer per 1000 (from 73 fewer to 26 more)	⊕OOO VERY LOW	IMPORTANT
Gastrointestinal side-effects of interventions whilst receiving treatment - Diarrhoea - High-income World Bank country												
1 (Lang 1989)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/50 (6%)	6/47 (12.8%)	RR 0.47 (0.21 to 1.77)	68 fewer per 1000 (from 101 fewer to 98 more)	⊕OOO VERY LOW	IMPORTANT
Gastrointestinal side-effects of interventions whilst receiving treatment - Diarrhoea - Low-/Middle-income World Bank country												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alginate-based reflux suppressant	Antacid	Relative (95% CI)	Absolute		
1 (Meteerattanapipat 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/50 (0%)	2/50 (4%)	RR 0.2 (0.01 to 4.06)	32 fewer per 1000 (from 40 fewer to 122 more)	⊕⊕OO LOW	IMPORTANT
Gastrointestinal side-effects of interventions whilst receiving treatment - Nausea												
2‡	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	12/100 (12%)	5/97 (5.2%)	RR 2.29 (0.85 to 6.2)	66 more per 1000 (from 8 fewer to 268 more)	⊕OOO VERY LOW	IMPORTANT
Gastrointestinal side-effects of interventions whilst receiving treatment - Nausea - High-income World Bank country												
1 (Lang 1989)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	8/50 (16%)	4/47 (8.5%)	RR 1.88 (0.61 to 5.83)	75 more per 1000 (from 33 fewer to 411 more)	⊕OOO VERY LOW	IMPORTANT
Gastrointestinal side-effects of interventions whilst receiving treatment - Nausea - Low-/Middle-income World Bank country												
1 (Meteerattanapipat 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	4/50 (8%)	1/50 (2%)	RR 4.0 (0.46 to 34.54)	60 more per 1000 (from 11 fewer to 671 more)	⊕⊕OO LOW	IMPORTANT
Gastrointestinal side-effects of interventions whilst receiving treatment - Vomiting												
1 (Lang 1989)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/50 (12%)	8/47 (17%)	RR 0.7 (0.26 to 1.88)	51 fewer per 1000 (from 126 fewer to 150 more)	⊕OOO VERY LOW	IMPORTANT
Quality of life - SF-12 Change in Physical health composite score (median) (measured with: Short Form 12 item (version 2) health survey; range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alginate-based reflux suppressant	Antacid	Relative (95% CI)	Absolute		
1 (Meteerattanapipat 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	50	50	Alginate reflux suppressant, median +7.7 (IQR 0-15.3) Antacid, median +7.6 (IQR 0-15.9)	P=0.82	⊕⊕OO LOW	IMPORTANT
Quality of life - SF-12 Change on Mental health composite score (median) (measured with: Short Form 12 item (version 2) health survey; range of scores: 0-100; Better indicated by higher values)												
1 (Meteerattanapipat 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	50	50	Alginate reflux suppressant, median +11.4 (IQR 0.9-21.7) Antacid, median +6.8 (IQR 0.5-18.1)	P=0.35	⊕⊕OO LOW	IMPORTANT
Women's experience and satisfaction of care during or after treatment for heartburn (assessed with: Satisfied or very satisfied with treatment)												
1 (Meteerattanapipat 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	40/50 (80%)	40/50 (80%)	RR 1 (0.82 to 1.22)	0 fewer per 1000 (from 144 fewer to 176 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

CI: confidence interval; IQR: interquartile range; RR: risk ratio.
[1] Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).
[2] Evidence downgraded by 2 levels because Lang 1989 was at very serious risk of bias, with a high risk of bias regarding incomplete outcome data, unclear risk of bias regarding random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment and selective reporting.
[3] Evidence downgraded by 2 levels because 95% CI crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).
[4] Evidence downgraded by 2 levels due to very serious imprecision surrounding small sample size.
‡ For references see corresponding Forest Plot

Table 7: Clinical evidence profile for comparison antacid versus placebo for treatment of heartburn during pregnancy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antacid	Placebo	Relative (95% CI)	Absolute		
Relief of heartburn during pregnancy - Complete relief of heartburn												
1 (Reisfield 1971)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	58/83 (69.9%)	25/73 (34.2%)	RR 2.04 (1.44 to 2.89)	356 more per 1000 (from 151 more to 647 more)	⊕OOO VERY LOW	CRITICAL
Relief of heartburn during pregnancy - No relief of heartburn												
1 (Reisfield 1971)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	6/83 (7.2%)	25/73 (34.2%)	RR 0.21 (0.09 to 0.49)	271 fewer per 1000 (from 175 fewer to 312 fewer)	⊕OOO VERY LOW	CRITICAL
Gastrointestinal side-effects of interventions whilst receiving treatment - Upsetting taste												
1 (Reisfield 1971)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/83 (1.2%)	3/73 (4.1%)	RR 0.29 (0.03 to 2.76)	29 fewer per 1000 (from 40 fewer to 72 more)	⊕OOO VERY LOW	IMPORTANT
Gastrointestinal side-effects of interventions whilst receiving treatment - Constipation												
1 (Reisfield 1971)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/83 (1.2%)	2/73 (2.7%)	RR 0.44 (0.04 to 4.75)	15 fewer per 1000 (from 26 fewer to 103 more)	⊕OOO VERY LOW	IMPORTANT

CI: confidence interval; RR: risk ratio

[1] Evidence downgraded by 2 levels due to serious risk of bias of Reisfield 1971 with unclear risk of bias regarding random sequence generation and selective reporting

[2] Evidence downgraded by 1 level because antacid used in this trial contained aluminium hydroxide and magnesium hydroxide, plus simethicone (which is an alginate-based reflux suppressant).

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

Table 8: Clinical evidence profile for comparison proton-pump inhibitor exposure versus no proton-pump inhibitor exposure for treatment of heartburn during pregnancy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Proton-pump inhibitor	No proton-pump inhibitor	Relative (95% CI)	Absolute		
Fetal death (assessed with: Adjusted for gestational age and other variables)												
1 (Matok 2012)	observational studies	serious[1]	no serious inconsistency	serious[2,3]	very serious [4]	none	2/666 (0.3%)	1348/108878 (1.2%)	aOR 0.32 (0.08 to 1.31)	8 fewer per 1000 (from 11 fewer to 4 more)	⊕OOO VERY LOW	CRITICAL
Small for gestational age (assessed with: Low birth weight <2500g adjusted for gestational age and other variables)												
1 (Matok 2012)	observational studies	serious[1]	no serious inconsistency	serious[2]	serious [5]	none	40/666 (6%)	8988/108878 (8.3%)	aOR 0.7 (0.48 to 1.03)	23 fewer per 1000 (from 41 fewer to 2 more)	⊕OOO VERY LOW	IMPORTANT
Preterm birth (assessed with: Adjusted for gestational age and other variables)												
1 (Matok 2012)	observational studies	serious[1]	no serious inconsistency	serious[2]	serious [5]	none	38/666 (5.7%)	7105/108878 (6.5%)	aOR 0.86 (0.62 to 1.19)	9 fewer per 1000 (from 24 fewer to 11 more)	⊕OOO VERY LOW	IMPORTANT

CI: confidence interval; aOR: adjusted odds ratio

[1] Serious risk of bias for Matok 2012: risk for confounding bias, serious risk for selection bias, serious risk for classification, no information for deviations and serious risk for missing data bias.

[2] Participants identified from medical codes - inference that presence of codes equals presence of condition.

[3] Data includes fetal deaths and early neonatal deaths (outcome reported in study as 'perinatal mortality').

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

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

Appendix G – Economic evidence study selection

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

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

Appendix H – Economic evidence tables

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

No economic evidence was identified which was applicable to this review question.

Appendix I - Economic evidence profiles

Health economic evidence profiles for review question: What interventions are effective in treating heartburn during pregnancy?

No economic evidence was identified which was applicable to this review question.

Appendix J – Health economic analysis

Health economic analysis for review question: What interventions are effective in treating heartburn during pregnancy?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies list for review question: What interventions are effective in treating heartburn during pregnancy?

Table 9: Clinical studies

Study	Reason for exclusion
Anonymous,, Pregnancy and drugs used in gastro-oesophageal reflux, Prescrire international, 24, 297-299, 2015	Study design does not meet protocol eligibility criteria - Non-systematic review
Anonymous,, Pantoprazole available without a prescription: new status. Better than H2 receptor agonists, but not for pregnant women, Prescrire international, 18, 250, 2009	Narrative summary.
Anton, C., The importance of diagnosis and treatment in functional gastrointestinal dismotility management during pregnancy, Journal of Gastrointestinal and Liver Diseases, 26 (Supplement 1), 10-11, 2017	Study design does not meet protocol eligibility criteria - Conference abstract
Armentano, G., Bracco, P. L., Di Silverio, C., Ranitidine in the treatment of reflux oesophagitis in pregnancy, Clinical and Experimental Obstetrics and Gynecology, 16, 130-133, 1989	Study design does not meet protocol eligibility criteria - case report.
Atlay, R. D., Weekes, A. R., Entwistle, G. D., Parkinson, D. J., Treating heartburn in pregnancy: comparison of acid and alkali mixtures, British medical journal, 2, 919-20, 1978	Study design does not meet protocol eligibility criteria - crossover design.
Bower, D., The use of prostigmine in the heartburn of pregnancy, Journal of Obstetrics & Gynaecology of the British Empire, 68, 846-7, 1961	Study intervention does not meet protocol eligibility criteria - anticholinesterase vs placebo.
Brew, Bronwyn K., Almqvist, Catarina, Acid Suppressant Use in Pregnancy and Asthma in Offspring: Should We Be Worried?, Pediatrics, 141, 1-3, 2018	Study design does not meet protocol eligibility criteria - commentary.
Brunclik, V., Privrel, T., Double-blind comparison of an oxetacain-antacid combination against the antacid alone in the treatment of heartburn in pregnancy, Schweizerische rundschau fur medizin praxis, 77, 587â€• 591, 1988	Study intervention does not meet protocol eligibility criteria - antacid/anaesthetic.
Carne, S., Double-Blind Trial of Mucaine in Heartburn of Pregnancy, The Journal of the College of General Practitioners, 8, 135-139, 1964	Study design does not meet protocol eligibility criteria - consecutive case series; RCT evidence is available for mucaine.
Cea Soriano, L., Hernandez-Diaz, S., Johansson, S., Nagy, P., Garcia-Rodriguez, L. A., Exposure to acid-suppressing drugs during pregnancy and the risk of asthma in childhood: An observational cohort study, Alimentary Pharmacology and Therapeutics, 43, 427-437, 2016	Study outcomes not relevant to protocol eligibility criteria - incidence of asthma.
Chen, H., Zhao, Y., Caritis, S., Hebert, M., Hankins, G., Miodovnik, M., Venkataramanan, R., Pharmacokinetics of ranitidine and its	Study design does not meet protocol eligibility criteria - conference abstract.

Study	Reason for exclusion
metabolite during pregnancy, Reproductive Sciences, 1), 182A, 2015	
Christopher, L., The role of proton pump inhibitors in the treatment of heartburn during pregnancy, Journal of the American Academy of Nurse Practitioners, 17, 4-8, 2005	Systematic review: no additional relevant studies.
Diav-Citrin, O., Arnon, J., Shechtman, S., Schaefer, C., van Tonningen, M. R., Clementi, M., De Santis, M., Robert-Gnansia, E., Valti, E., Malm, H., Ornoy, A., The safety of proton pump inhibitors in pregnancy: a multicentre prospective controlled study, Alimentary pharmacology & therapeutics, 21, 269-75, 2005	Study population does not meet protocol eligibility criteria - indications for PPI treatment included treatment against H. pylori associated with peptic ulcers, peptic ulcer disease and reflux oesophagitis; outcomes not reported separately for eligible population.
Donde, S., Effectiveness and safety of antacids in pregnant women suffering from GERD/hyperacidity symptoms, Value in Health, 15 (7), A326-A327, 2012	Study design does not meet protocol eligibility criteria - conference abstract.
Erichsen, R., Mikkelsen, E., Pedersen, L., Sorensen, H. T., Maternal use of proton pump inhibitors during early pregnancy and the prevalence of hypospadias in male offspring, Pharmacoepidemiology and Drug Safety, 1), S265-S266, 2011	Study outcomes do not meet protocol eligibility criteria - congenital malformations (hypospadias).
Erichsen, R., Mikkelsen, E., Pedersen, L., Sorensen, H. T., Maternal use of proton pump inhibitors during early pregnancy and the prevalence of hypospadias in male offspring, American Journal of Therapeutics, 21, 254-259, 2014	Study outcome does not meet protocol eligibility criteria - hypospadias in male offspring (abnormalities)
Fill Malfertheiner, S., Malfertheiner, M. V., Kropf, S., Costa, S. D., Malfertheiner, P., A prospective longitudinal cohort study: evolution of GERD symptoms during the course of pregnancy, BMC Gastroenterology, 12 (no pagination), 2012	Study does not meet protocol eligibility criteria - prevalence of GERD in pregnant and non-pregnant women; questionnaire.
Gerson, L. B., Proton pump inhibitors and safety during pregnancy, Gastroenterology, 141, 389-391, 2011	Study design does not meet protocol eligibility criteria - comment on an the study publication Pasternak et al., 2010
Gill, S. K., Maltepe, C., Mastali, K., Koren, G., The effect of Acid-reducing pharmacotherapy on the severity of nausea and vomiting of pregnancy, Obstetrics & Gynecology International, 2009, 585269, 2009	Study population does not meet protocol eligibility criteria - (<66% pregnant women with heartburn); non-comparative cohort.
Gill,S.K., O'Brien,L., Einarson,T.R., Koren,G., The safety of proton pump inhibitors (PPIs) in pregnancy: A meta-analysis, American Journal of Gastroenterology, 104, 1541-1545, 2009	Systematic review - does not indicate which included studies are in pregnant women with heartburn.
Gill,S.K., O'Brien,L., Koren,G., The safety of histamine 2 (H2) blockers in pregnancy: a meta-analysis, Digestive diseases and sciences, 54, 1835-1838, 2009	Systematic review - included studies assessed for eligibility.
Groom, K. M., David, A. L., The role of aspirin, heparin, and other interventions in the prevention and treatment of fetal growth restriction, American Journal of Obstetrics and Gynecology, 218, S829-S840, 2018	Study design does not meet protocol eligibility criteria - narrative commentary, prevention and treatment of fetal growth restriction (mentions the impact of different treatments in commentary)

Study	Reason for exclusion
Hill, N., Smith, E., Pregnancy: Use of medicines in managing complications, Pharmaceutical Journal, 295, 84-87, 2015	Study design does not meet protocol eligibility criteria - narrative review.
Huang, J., Kuang, Y., Re: Safety of acupuncture during pregnancy: a retrospective cohort study in Korea, BJOG: An International Journal of Obstetrics and Gynaecology, 127, 427-428, 2020	Study design does not meet protocol eligibility criteria - letter in reply to an article Moon BJOG 2020 (cohort pregnant women, acupuncture vs control, impact on birth outcomes)
Kallen, B., Delivery outcome after the use of acid-suppressing drugs in early pregnancy with special reference to omeprazole, British Journal of Obstetrics and Gynaecology, 105, 877-881, 1998	Study outcomes do not meet protocol eligibility criteria - congenital malformations.
Kichler, A., Alzubaidi, M., Emery, J., Gabbard, S., Use of a positional therapy device significantly improves nocturnal gastroesophageal reflux disease symptoms in pregnant women, American Journal of Gastroenterology, 1), S703-S704, 2015	Study design does not meet protocol eligibility criteria - conference abstract.
Kovacs, G. T., Campbell, J., Francis, D., Hill, D., Adena, M. A., Is mucaine an appropriate medication for the relief of heartburn during pregnancy?, Asia-Oceania journal of obstetrics and gynaecology / AOFOG, 16, 357-362, 1990	Study intervention does not meet protocol eligibility criteria - antacid/anaesthetic vs placebo.
Lai, T., Wu, M., Liu, J., Luo, M., He, L., Wang, X., Wu, B., Ying, S., Chen, Z., Li, W., Shen, H., Acid-suppressive drug use during pregnancy and the risk of childhood asthma: A meta-analysis, Pediatrics, 141, e20170889, 2018	Study outcome does not meet protocol eligibility criteria - risk of childhood asthma.
Lalkin,A., Loebstein,R., Addis,A., Ramezani-Namin,F., Mastroiacovo,P., Mazzone,T., Vial,T., Bonati,M., Koren,G., The safety of omeprazole during pregnancy: a multicenter prospective controlled study, American Journal of Obstetrics and Gynecology, 179, 727-730, 1998	Study does not meet protocol eligibility criteria - pregnant women treated for reflux and heartburn (27%), peptic ulcer, gastritis, Crohn's disease etc.
Landi, S. N., Funk, M. J., Utilization of acid-suppressive medication during pregnancy in an insured U.S. Population, 2001-2014, Pharmacoepidemiology and Drug Safety, 26 (Supplement 2), 417-418, 2017	Study design does not meet protocol eligibility criteria - conference abstract.
Larson, J. D., Patatanian, E., Miner Jr, P. B., Rayburn, W. F., Robinson, M. G., Double-blind, placebo-controlled study of ranitidine for gastroesophageal reflux symptoms during pregnancy, Obstetrics and Gynecology, 90, 83-87, 1997	Study design does not meet protocol eligibility criteria - cross-over trial.
Larson, J. D., Patatanian, E., Miner, P. B., Jr., Rayburn, W. F., Robinson, M. G., Double-blind, placebo-controlled study of ranitidine for gastroesophageal reflux symptoms during pregnancy, Obstetrics and gynecology, 90, 83-7, 1997	Study design does not meet protocol eligibility criteria - triple crossover design.
Li, C. M., Zhernakova, A., Engstrand, L., Wijmenga, C., Brusselaers, N., Systematic review with meta-analysis: the risks of proton	Systematic review meets criteria - included studies checked and have already been included in the review.

Study	Reason for exclusion
pump inhibitors during pregnancy, Alimentary Pharmacology & Therapeutics, 51, 410-420, 2020	
Lindow,S.W., Regnell,P., Sykes,J., Little,S., An open-label, multicentre study to assess the safety and efficacy of a novel reflux suppressant (gaviscon advance) in the treatment of heartburn during pregnancy, International Journal of Clinical Practice, 57, 175-179, 2003	RCT evidence available for antacid.
Lockart, I., Knapman, B., Kanazaki, R., Pokorny, C., Managing common luminal GI disorders during pregnancy, Medicine Today, 17, 32-40, 2016	Study design does not meet protocol eligibility criteria - narrative review.
Macedo, M. S., Interventions for Treating Heartburn in Pregnancy, American Journal of Nursing, 116, 21, 2016	Study design does not meet protocol eligibility criteria - Abstract publication only of Cochrane review (Phupong 2015).
Magee,L.A., Inocencion,G., Kamboj,L., Rosetti,F., Koren,G., Safety of first trimester exposure to histamine H2 blockers. A prospective cohort study, Digestive Diseases and Sciences, 41, 1145-1149, 1996	Study population does not meet protocol eligibility criteria - pregnant women with heartburn <66% (41%).
Mulder, B., Hak, E., Schuiling-Veninga, C. C. M., De Vries, T. W., Jick, S. S., Acid-suppressive drug use during pregnancy and the risk of atopic dermatitis: A crossover study within the clinical practice research database, Pharmacoepidemiology and Drug Safety, 1), 302-303, 2014	Study design does not meet protocol eligibility criteria - conference abstract.
Mulder, B., Schuiling-Veninga, C. C. M., Bos, H. J., De Vries, T. W., Jick, S. S., Hak, E., Prenatal exposure to acid-suppressive drugs and the risk of allergic diseases in the offspring: A cohort study, Clinical and Experimental Allergy, 44, 261-269, 2014	Study outcomes do not meet protocol eligibility criteria - allergic diseases.
Naumann, C. R., Ko, C. W., Heartburn in pregnancy: A prospective look at incidence, risk factors, treatments, and outcomes, Gastroenterology, 1), S474, 2010	Study design does not meet protocol eligibility criteria - conference abstract.
Naumann,C.R., Zelig,C., Napolitano,P.G., Ko,C.W., Nausea, vomiting, and heartburn in pregnancy: A prospective look at risk, treatment, and outcome, Journal of Maternal-Fetal and Neonatal Medicine, 25, 1488-1493, 2012	Study design does not meet protocol eligibility criteria - Correlational study.
Nct,, Rebamipide in Combination With Esomeprazole in the Management of Asian Patients With Functional Dyspepsia, Https://clinicaltrials.gov/show/nct02134405, 2014	Clinical trial record - no results.
Nct,, Research of Efficient Use of Omeprazole in Combination With Domperidone in Gastroesophageal Reflux Disease of Mild to Moderate Severity, Https://clinicaltrials.gov/show/nct02140073, 2014	Clinical trial record - study population does not meet protocol eligibility criteria (exclusion criteria: pregnancy).

Study	Reason for exclusion
Nct,, Alginate-based Reflux Suppressant and Magnesium-aluminium Antacid Gel for Treatment of Heartburn in Pregnancy, Https://clinicaltrials.gov/show/nct02470117, 2015	Clinical trial record - no results.
Neilson, J. P., Interventions for heartburn in pregnancy, Cochrane Database of Systematic Reviews, 2008	Systematic review - Updated by Phupong Cochrane Review.
Nielsen, G. L., Sorensen, H. T., Thulstrup, A. M., Tage-Jensen, U., Olesen, C., Ekbom, A., The safety of proton pump inhibitors in pregnancy, Alimentary Pharmacology & Therapeutics, 13, 1085-9, 1999	Study does not meet protocol eligibility criteria - unclear whether pregnant women with heartburn; unclear whether unexposed reference pregnancies are women with heartburn.
Nikfar, S., Abdollahi, M., Moretti, M. E., Magee, L. A., Koren, G., Use of proton pump inhibitors during pregnancy and rates of major malformations: a meta-analysis, Digestive diseases and sciences, 47, 1526-9, 2002	Systematic review of cohort studies not specifically for heartburn - No additional relevant studies.
Pasternak,B., Hviid,A., Use of proton-pump inhibitors in early pregnancy and the risk of birth defects, New England Journal of Medicine, 363, 2114-2123, 2010	Study outcomes does not meet protocol eligibility criteria - prevalence of birth defects.
Paulus, W. E., Omeprazol in early pregnancy, Chirurgische Praxis, 59, 164-166, 2001	Non-English language paper.
Phupong, V., Hanprasertpong, T., Interventions for heartburn in pregnancy, Cochrane Database of Systematic Reviews, 2015	Cochrane Review - includes trials that do not meet protocol eligibility criteria; original publications of eligible RCTs included in the review.
Quartarone,G., Gastroesophageal reflux in pregnancy: a systematic review on the benefit of raft forming agents, Minerva Ginecologica, 65, 541-549, 2013	Systematic review exploring medications for treating GER in pregnancy - included studies checked.
Ramya, R. S., Jayanthi, N., Alexander, P. C., Vijaya, S., Jayanthi, V., Gastroesophageal reflux disease in pregnancy: a longitudinal study, Tropical gastroenterology : official journal of the Digestive Diseases Foundation, 35, 168-172, 2014	Study population does not meet protocol inclusion criteria - 20% women experienced heartburn; 10% experience heartburn and regurgitation); no intervention.
Ranchet, G., Gangemi, O., Petrone, M., Sucralfate in the treatment of pregnancy pyrosis, Giornale italiano di ostetricia e ginecologia, 12, 91-96, 1990	Study intervention does not meet protocol eligibility criteria - diet/lifestyle vs sucralfate.
Rayburn, W., Liles, E., Christensen, H., Robinson, M., Antacids vs. antacids plus non-prescription ranitidine for heartburn during pregnancy, International Journal of Gynecology and Obstetrics, 66, 35-37, 1999	Study does not meet protocol eligibility criteria - brief communication; no usable data for outcomes presented.
Rhim, A. D., Hardy, J. R., Haynes, K., Testani, J. M., Yang, Y. X., Maternal use of proton pump inhibitors (PPI) during pregnancy is associated with an increased risk for cardiac birth defects: Analysis of 208,951 pregnancies from the GPRD/THIN database, Gastroenterology, 1), S63, 2010	Study design does not meet protocol eligibility criteria - Conference abstract.

Study	Reason for exclusion
Rhim, A. D., Haynes, K., Hardy, J. R., Testani, J. M., Yang, Y. X., Maternal use of proton pump inhibitors (ppi) during pregnancy is associated with an increased risk for cardiac birth defects: Analysis of 208,951 pregnancies from the THIN database, Pharmacoepidemiology and Drug Safety, 1), S240, 2010	Study design does not meet protocol eligibility criteria - Conference abstract.
Ruigomez, A., Garcia Rodriguez, L. A., Cattaruzzi, C., Troncon, M. G., Agostinis, L., Wallander, M. A., Johansson, S., Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes, American Journal of Epidemiology, 150, 476-481, 1999	Study population does not meet protocol eligibility criteria - non-exposed pregnant women did not have heartburn.
Samji, N. S., Kanth, R., Antillon, M. R., Rivera, R. E., Roy, P. K., Safety of proton pump inhibitors in pregnancy-a meta-analysis of prospective cohort studies, Gastroenterology, 1), S557-S558, 2014	Study design does not meet protocol eligibility criteria - conference abstract.
Sharma, N., Ho, K. Y., The medical management of gastro-oesophageal reflux disease, Inflammatory Intestinal Diseases, 1, 96-99, 2016	Study design does not meet protocol eligibility criteria - narrative review.
Shaw, R. W., Randomized controlled trial of Syn-Ergel and an active placebo in the treatment of heartburn of pregnancy, Journal of International Medical Research, 6, 147-51, 1978	Study outcome data not in a useable format.
Shen, M. L., Hsu, W. T., The efficacy of Neiguan acupressure in patients with GERD: A randomized, controlled, single-blinded trial, Journal of Gastroenterology and Hepatology (Australia), 4), 63, 2015	Study design does not meet protocol eligibility criteria - conference abstract.
Skarica, B., Effectiveness of Manual Treatment on Pregnancy Symptoms: Usefulness of Manual Treatment in Treating Pregnancy Symptoms, Medicinski Arhiv, 72, 131-135, 2018	Study does not meet protocol eligibility criteria - manual treatment for pregnancy symptoms.
Strugala, V., Bassin, J., Swales, V. S., Lindow, S. W., Dettmar, P. W., Thomas, E. C. M., Assessment of the safety and efficacy of a raft-forming alginate reflux suppressant (Liquid Gaviscon) for the treatment of heartburn during pregnancy, ISRN Obstetrics and Gynecology, 481870, 2012	Study design does not meet protocol eligibility criteria - Prospective open-label study - RCT evidence on alginate reflux suppressant available.
Thelin, C. S., Richter, J. E., Review article: the management of heartburn during pregnancy and lactation, Alimentary Pharmacology and Therapeutics, 51, 421-434, 2020	Study design does not meet protocol eligibility criteria - non-systematic review article about management and treatment of reflux in pregnancy and lactation
Twigg, M. J., Lupattelli, A., Nordeng, H., Women's beliefs about medication use during their pregnancy: a UK perspective, International Journal of Clinical Pharmacy, 38, 968-976, 2016	Study does not meet protocol eligibility criteria - questionnaire relating to medication use and treatment of common conditions in pregnancy; reporting risk perceptions of drugs.
Vazquez, J. C., Heartburn in pregnancy, Clinical Evidence (Online), 08, 08, 2015	Systematic review: Included studies being checked for relevancy

Study	Reason for exclusion
Weberg, R., Berstad, A., Ladehaug, B., Thomassen, Y., Are aluminium containing antacids during pregnancy safe?, Acta Pharmacologica et Toxicologica, 59, 63-65, 1986	Study outcomes does not meet protocol eligibility criteria - reports serum aluminium concentration in mothers and their newborns.

Economic studies

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

Appendix L – Research recommendations

Research recommendations for review question: What interventions are effective in treating heartburn during pregnancy?

No research recommendations were made for this review question.