ClinicalEvidence

Heartburn in pregnancy

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ABSTRACT

INTRODUCTION: Heartburn is a common complaint during pregnancy; the incidence is reported to be between 17% and 45%. METHODS AND OUTCOMES: We conducted a systematic overview and aimed to answer the following clinical question: What are the effects of interventions to prevent or treat heartburn in pregnancy? We searched Medline, Embase, The Cochrane Library, and other important databases up to December 2014 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). RESULTS: At this update, searching of electronic databases retrieved 80 studies. After deduplication and removal of conference abstracts, 59 records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of 58 studies and the further review of one full publication. The full article evaluated did not meet our reporting criteria, and thus no new evidence was added at this update. We performed a GRADE evaluation for two PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for six interventions, based on information about the effectiveness and safety of acid-suppressing drugs, antacids with or without alginates, raising the head of the bed, reducing caffeine intake, reducing intake of fatty foods, and reducing the size and frequency of meals.

QUESTIONS

INTERVENTIONS

Key points

- Heartburn is common during pregnancy; the incidence is reported to be between 17% and 45%.

  We searched for evidence of effectiveness from RCTs and systematic reviews of RCTs for interventions to prevent and treat heartburn in pregnancy.
- Antacids may provide effective heartburn relief in pregnancy.
- We don't know whether acid-suppressing drugs, such as ranitidine, are beneficial in treating heartburn in pregnancy.
- We don't know whether dietary and lifestyle modifications are beneficial in preventing or treating heartburn in pregnancy. However, recommendations have been made that lifestyle and dietary modifications, including reducing the intake of fatty foods and reducing the size and frequency of meals, should remain first-line treatment for heartburn in pregnant women. Other lifestyle modifications that could be considered are reducing caffeine intake and raising the head of the bed.

Clinical context

GENERAL BACKGROUND

Heartburn is a common complaint during pregnancy; the incidence is reported to be between 17% and 45%. Serious complications are rare, although it may be associated with severe nausea and vomiting, and the condition usually resolves soon after delivery.

FOCUS OF THE REVIEW

The review assesses the efficacy and safety (primarily related to teratogenic adverse effects) of several interventions used to manage heartburn during pregnancy, ranging from lifestyle changes to antacids and acid-suppressing drugs.

COMMENTS ON EVIDENCE

We found no direct evidence from RCTs regarding the role of lifestyle measures or acid-suppressing agents (H_2 receptor antagonists and PPIs) compared with placebo or no treatment in the management of heartburn in pregnancy. One systematic review, which included one relevant RCT, found that antacids may provide effective heartburn relief in pregnancy compared with placebo. Another systematic review, also with one relevant RCT, found no difference

between antacid alone and antacid plus acid-suppressing drug in terms of symptoms relief. Overall, the quality of evidence was low.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, February 2010, to December 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the review, please see the Methods section. Searching of electronic databases retrieved 80 studies. After deduplication and removal of conference abstracts, 59 records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of 58 studies and the further review of one full publication. The full article evaluated did not meet our reporting criteria, and thus no new evidence was added at this update. One systematic review was added to the Comment section.

ADDITIONAL INFORMATION

The National Institute of Health and Care Excellence (NICE) antenatal care guidelines recommend that women who present with symptoms of heartburn in pregnancy should be offered information regarding lifestyle and diet modification. [1] Antacids may be offered to women whose heartburn remains troublesome despite lifestyle and diet modification.

DEFINITION

Heartburn is defined as a sensation of 'burning' in the upper part of the digestive tract, including the throat. [2] [3] It can be associated with oesophagitis. [4] One study reported the results of endoscopy on 73 pregnant women with heartburn and found endoscopic and histological evidence of oesophagitis in most women. [5] As complications associated with heartburn during pregnancy are rare (e.g., erosive oesophagitis), upper endoscopy and other diagnostic tests, such as oesophageal manometry and pH studies, are infrequently needed. [3] [6] Therefore, the diagnosis of heartburn is mainly clinical, based on the history.

INCIDENCE/ PREVALENCE

Heartburn is one of the most common gastrointestinal symptoms in pregnant women, with an incidence in pregnancy of 17% to 45%. [7] [8] [9] In some studies, the prevalence of heartburn has been found to increase from 22% in the first trimester to 39% in the second trimester to between 60% and 72% in the third trimester. [4] [10] However, one prospective cohort study found that, in most pregnant women, heartburn, acid regurgitation, or both began in the first trimester and disappeared during the second trimester; [8] and another cohort study also found that gastrointestinal symptoms, such as heartburn and nausea, were more common in the first trimester. [7] The study also found that primigravidae reported more gastrointestinal symptoms than multiparae. [7]

AETIOLOGY/ RISK FACTORS

The cause of heartburn during pregnancy is multifactorial. [9] Increased amounts of progesterone or its metabolites cause relaxation of smooth muscle, which results in a reduction in gastric tone and motility, and a decrease in lower oesophageal sphincter pressure. [10] [11] [12] It has also been found that, during pregnancy, the lower oesophageal sphincter is displaced into the thoracic cavity (an area of negative pressure), [11] which allows food and gastric acid to pass from the stomach into the oesophagus, leading to oesophageal inflammation and a sensation of 'burning'. Pressure of the growing uterus on gastric contents as the pregnancy progresses may worsen heartburn, [2] [13] although some authors believe that mechanical factors have a smaller role. [3] [6] [9] [14] Heartburn may also be caused by abnormal gastric emptying, delayed small bowel transit, or by some medications taken during pregnancy, such as anti-emetics. [3] [15]

PROGNOSIS

Most cases of heartburn improve with lifestyle modifications. Women who smoke or drink alcohol should be advised to abstain. Dietary changes (e.g., consumption of smaller meals, not eating late at night, and avoiding known triggers) may be of benefit to some. [3] [9] Despite these measures, however, heartburn severity may increase throughout the course of pregnancy. [5] [10]

AIMS OF INTERVENTION

To prevent heartburn in pregnancy; to relieve or reduce the severity of symptoms; to minimise and avoid adverse effects of treatment on the mother and fetus (including teratogenicity).

OUTCOMES

Symptom severity (prevalence of heartburn, pain from heartburn, symptom diaries, number of additional antacids used, number of visits to physician/healthcare facilities, number of days off work, and inability to perform daily activities); **quality of life** (e.g., maternal satisfaction); **adverse effects** on mother, adverse effects on fetus (including teratogenicity).

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal December 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to December 2014, Embase 1980 to December 2014, The Cochrane Database of Systematic Reviews 2014, issue 4 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this review

were systematic reviews and RCTs published in English, at least single-blinded for pharmacological interventions (blinding was not necessary for RCTs evaluating lifestyle and dietary interventions), and containing 20 or more individuals (10 in each arm), of whom more than 80% were followed up. There was no minimum length of follow-up. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed a priori with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the review. In addition, information that did not meet our predefined criteria for inclusion in the benefits and harms section, may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Data and quality** To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue which may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 8). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of interventions to prevent or treat heartburn in pregnancy?

OPTION ANTACIDS WITH OR WITHOUT ALGINATES

Symptom severity

Antacids compared with placebo Antacids may be more effective than placebo at relieving heartburn symptoms and at reducing need for additional antacids (low-quality evidence).

Antacids compared with antacids plus acid-suppressing drugs We don't know how antacid alone and antacid plus ranitidine (an H_2 receptor antagonist) compare at relieving heartburn (low-quality evidence).

For GRADE evaluation of interventions for heartburn in pregnancy, see table, p 8 .

Benefits:

Antacids versus placebo:

We found one systematic review (search date 2008), [16] which identified one RCT assessing antacids for heartburn in pregnant women. [17] The RCT (156 pregnant women with heartburn) compared a magnesium- and aluminium hydroxide-based antacid in combination with simethicone versus placebo. [17] The review found that a significantly larger proportion of women in the antacid group reported either complete or partial relief from heartburn compared with placebo (77/83 [93%] with antacid *v* 48/73 [66%] with placebo; RR 1.41, 95% CI 1.18 to 1.68). The method of randomisation of the RCT was not clear.

We found one additional RCT (50 women with heartburn), which compared three interventions for 7 days: magnesium hydroxide plus aluminium hydroxide (antacid) plus oxethazaine (anaesthetic; 15 women); magnesium hydroxide plus aluminium hydroxide without oxethazaine (17 women); and placebo (18 women). [18] The intervention of antacid plus anaesthetic is not covered by our inclusion criteria. However, we have reported the data here as the RCT does not report a statistical analysis for the comparison of antacid alone with placebo. The RCT found that antacid with or

without oxethazaine was associated with a significant improvement in heartburn symptoms compared with placebo, although the improved relief was of borderline significance (mean heartburn relief score [scale ranging from 1 = mild symptoms to 5 = severe symptoms]: 3.9 with antacid plus oxethazaine *v* 3.3 with antacid alone *v* 2.9 with placebo; P = 0.05 for among-group difference; difference reported as significant). The RCT found that additional antacids were used significantly less frequently in the antacid groups compared with placebo (use of other antacids [% of days per participant]: 7% with antacid plus oxethazaine *v* 13% with antacid alone *v* 29% with placebo; P = 0.0003 for among-group difference).

Antacids alone versus antacids plus acid-suppressing drugs:
We found one systematic review (search date 2008), [16] which identified one RCT (30 pregnant women) comparing calcium-based antacid plus ranitidine (an H_2 receptor antagonist) with antacid alone. [19] After 1 week of open-label treatment with antacid alone, women with four or more moderate-to-severe episodes of heartburn during the week (30 women) were randomised to either continued treatment with antacid alone or to antacid plus ranitidine. The review found no significant difference between antacid alone and antacid plus ranitidine in heartburn intensity at 2 weeks, although scores were lower in the antacid plus ranitidine group (mean difference in score [measured using a 10-point visual analogue scale, where 0 = no pain and 10 = disabling] –2.13, 95% CI –4.37 to +0.11). [16] The method of randomisation in the RCT was unclear.

Harms:

Antacids versus placebo:
The review reported that there was limited information on adverse effects associated with the preparations identified. [16] The RCT identified by the review found that antacid was associated with a lower rate of adverse effects (including constipation, headache, cramps, and dry mouth) compared with placebo (5/83 [6%] with antacid *v* 7/73 [10%] with placebo; significance not assessed). [17]

The additional RCT comparing antacid with or without oxethazaine versus placebo gave no information on adverse effects. [18]

Antacids versus antacids plus acid-suppressing drugs:
The review reported that there was limited information on adverse effects associated with the preparations identified. [16] The RCT identified by the review reported that there were no adverse effects associated with ranitidine and that birth outcomes were favourable; no comparative data on adverse effects were reported. [19]

Comment:

Clinical guide
A consensus document has recommended that antacids should be used 'on demand' as the first-choice drug treatment for heartburn in pregnancy because they provide effective and rapid symptom relief. [4] The preferred choice should be calcium-based antacids because adverse effects are rare and calcium-based antacids have been shown to be beneficial for the prevention of hypertension and pre-eclampsia, and to reduce the composite outcome of maternal death or serious morbidity. [20] RCTs have shown that magnesium sulfate reduces the risk of eclampsia by more than 50%, and reduces the risk of maternal death. [21]

The UK National Institute for Health and Care Excellence (NICE) antenatal care guidelines recommend that antacids should be offered to women whose heartburn remains troublesome despite lifestyle and diet modification. [1] A panel of experts has agreed that, in pregnant women, H_2 receptor antagonists, such as ranitidine, can be combined with antacids when symptoms persist with antacids alone. [4]

OPTION ACID-SUPPRESSING DRUGS (H2 RECEPTOR ANTAGONISTS AND PROTON PUMP INHIBITORS ONLY)

Symptom severity
Acid-suppressing drugs plus antacids compared with antacids alone We don't know how antacid plus ranitidine (an H_2 receptor antagonist) and antacid alone compare at relieving heartburn (low-quality evidence).

Note
We found no direct information from RCTs about whether acid-suppressing drugs are better than no active treatment to treat heartburn in pregnancy.

For GRADE evaluation of interventions for heartburn in pregnancy, see table, p 8 .

Benefits:

Acid-suppressing drugs versus placebo:
We found no systematic review or RCTs comparing acid-suppressing drugs with placebo for heartburn in pregnancy.

Acid-suppressing drugs plus antacids versus antacids alone:
See Benefits of Antacids with or without alginates, p 3 .

Harms:

Acid-suppressing drugs versus placebo:
We found no RCTs.

Acid-suppressing drugs plus antacids versus antacids alone:
See Harms of Antacids with or without alginates, p 3 .

Comment:

One systematic review (search date 2008, 4 cohort studies [2 prospective, 2 retrospective], 122,290 people) assessing the safety of H_2 receptor antagonists during pregnancy found no significant difference in risk of congenital malformation between exposure to H_2 receptor antagonist and no exposure (112/2398 [4.7%] with exposure *v* 5699/119,892 [4.8%] with no exposure; 1.14, 95% CI 0.89 to 1.45). [22] Further analysis found that exposure to H_2 receptor antagonist did not increase risk of spontaneous abortion (2 studies, based on 738 exposures and 1575 unexposed controls; OR 0.62, 95% CI 0.36 to 1.05), preterm delivery (4 studies, based on 2421 exposures and 119,072 unexposed controls; OR 1.17, 95% CI 0.94 to 1.47), or infant being small for gestational age (2 studies, based on 611 exposures and 794 unexposed controls; OR 0.28, 95% CI 0.06 to 1.22; absolute numbers not reported for listed outcomes).

Another systematic review by the same group (search date 2008, 7 studies, 134,940 people) found no significant difference in risk of major congenital birth defects between exposure to proton pump inhibitor (PPI) and no exposure (OR 1.12, 95% CI 0.86 to 1.45). [23] Similarly, exposure to PPIs did not appear to increase the risk of spontaneous abortion (OR 1.29, 95% CI 0.84 to 1.97) or preterm delivery (OR 1.13, 95% CI 0.96 to 1.33). [23]

Clinical guide
A panel of experts has agreed that, in pregnant women, H_2 receptor antagonists can be combined with antacids when symptoms persist with antacids alone. [4] A PPI may be an option for women who do not experience sufficient relief with an H_2 receptor antagonist. Based upon available evidence, exposure to PPI therapy does not appear to increase the risk of adverse fetal effects. [24]

OPTION RAISING THE HEAD OF THE BED (INCLUDING SPECIAL BEDS AND MORE PILLOWS)

We found no direct information from RCTs about raising the head of the bed to prevent or treat heartburn in pregnancy.

For GRADE evaluation of interventions for heartburn in pregnancy, see table, p 8 .

Benefits: We found no systematic review or RCTs of raising the head of the bed to prevent or treat heartburn in pregnancy.

Harms: We found no RCTs.

Comment:

Clinical guide
The UK National Institute for Health and Care Excellence (NICE) antenatal care guidelines recommend that women who present with symptoms of heartburn in pregnancy should be offered information regarding lifestyle and diet modification. [1] A consensus document suggests avoiding or reducing intake of reflux-inducing foods (such as greasy and spicy foods, tomatoes, highly acidic citrus products, and carbonated drinks). [4] Caffeine and non-steroidal anti-inflammatory drugs should also be avoided. The consensus document also recommends other lifestyle changes to reduce the risk of reflux, such as avoiding lying down within 3 hours after eating. [4] However, if heartburn is severe enough to warrant this action, medication should begin after consultation with a healthcare professional. [4]

OPTION REDUCING CAFFEINE INTAKE

We found no direct information from RCTs about reducing caffeine intake to prevent or treat heartburn in pregnancy.

For GRADE evaluation of interventions for heartburn in pregnancy, see table, p 8 .

Benefits: We found no systematic review or RCTs of reducing caffeine intake to prevent or treat heartburn in pregnancy.

Harms: We found no RCTs.

Comment: **Clinical guide**
The UK National Institute for Health and Care Excellence (NICE) antenatal care guidelines recommend that women who present with symptoms of heartburn in pregnancy should be offered information regarding lifestyle and diet modification. [1] A consensus document suggests avoiding or reducing intake of reflux-inducing foods (such as greasy and spicy foods, tomatoes, highly acidic citrus products, and carbonated drinks). [4] Caffeine and non-steroidal anti-inflammatory drugs should also be avoided. The consensus document also recommends other lifestyle changes to reduce the risk of reflux, such as avoiding lying down within 3 hours after eating. [4] However, if heartburn is severe enough to warrant this action, medication should begin after consultation with a healthcare professional. [4]

OPTION REDUCING THE INTAKE OF FATTY FOODS

We found no direct information from RCTs about reducing intake of fatty foods to prevent or treat heartburn in pregnancy.

For GRADE evaluation of interventions for heartburn in pregnancy, see table, p 8 .

Benefits: We found no systematic review or RCTs of reducing intake of fatty foods to prevent or treat heartburn in pregnancy.

Harms: We found no RCTs.

Comment: **Clinical guide**
The UK National Institute for Health and Care Excellence (NICE) antenatal care guidelines recommend that women who present with symptoms of heartburn in pregnancy should be offered information regarding lifestyle and diet modification. [1] A consensus document suggests avoiding or reducing intake of reflux-inducing foods (such as greasy and spicy foods, tomatoes, highly acidic citrus products, and carbonated drinks). [4] Caffeine and non-steroidal anti-inflammatory drugs should also be avoided. The consensus document also recommends other lifestyle changes to reduce the risk of reflux, such as avoiding lying down within 3 hours after eating. However, if heartburn is severe enough to warrant this action, medication should begin after consultation with a healthcare professional. [4]

OPTION REDUCING THE SIZE AND FREQUENCY OF MEALS

We found no direct information from RCTs about reducing meal size and frequency to prevent or treat heartburn in pregnancy.

For GRADE evaluation of interventions for heartburn in pregnancy, see table, p 8 .

Benefits: We found no systematic review or RCTs of reducing meal size and frequency to prevent or treat heartburn in pregnancy.

Harms: We found no RCTs.

Comment: **Clinical guide**
The UK National Institute for Health and Care Excellence (NICE) antenatal care guidelines recommend that women who present with symptoms of heartburn in pregnancy should be offered information regarding lifestyle and diet modification. [1] A consensus document suggests avoiding or reducing intake of reflux-inducing foods (such as greasy and spicy foods, tomatoes, highly acidic citrus products, and carbonated drinks). [4] Caffeine and non-steroidal anti-inflammatory drugs should also be avoided. The consensus document also recommends other lifestyle changes to reduce the risk of reflux, such as avoiding lying down within 3 hours after eating. [4] However, if heartburn is severe enough to warrant this action, medication should begin after consultation with a healthcare professional. [4]

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

SUBSTANTIVE CHANGES

Acid-suppressing drugs (H_2 receptor antagonists and proton pump inhibitors only) No new evidence found. One systematic review added to the Comment section. [22] Categorisation unchanged (unknown effectiveness).

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Competing interests: JCV declares that he has no competing interests.

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TABLE **GRADE evaluation of interventions for heartburn in pregnancy**

Important outcomes	**Symptom severity, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of interventions to prevent or treat heartburn in pregnancy?									
2 (206) [16] [17] [18]	Symptom severity	Antacids *v* placebo	4	–2	0	0	0	Low	Quality points deducted for unclear method of randomisation and no between group statistical analysis in one RCT
1 (30) [16] [19]	Symptom severity	Antacid *v* antacid plus acid-suppressing drug	4	–2	0	0	0	Low	Quality points deducted for sparse data and for unclear method of randomisation

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio