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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 7
OBJECTIVES 9
METHODS 9
RESULTS 13
Figure 1. 14
Figure 2. 16
Figure 3. 17
DISCUSSION 19
AUTHORS' CONCLUSIONS 19
ACKNOWLEDGEMENTS 19
REFERENCES 21
CHARACTERISTICS OF STUDIES 23
DATA AND ANALYSES 27
Analysis 1.1. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 1 Improvement in constipation. 27
Analysis 1.2. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 2 Abdominal discomfort. 27
Analysis 1.3. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 3 Diarrhoea. 28
Analysis 1.4. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 4 Women's satisfaction. 28
Analysis 2.1. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 1 Improvement in constipation. 29
Analysis 2.2. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 2 Abdominal discomfort. 29
Analysis 2.3. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 3 Diarrhoea. 30
Analysis 2.4. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 4 Women's satisfaction (rated as good or acceptable). 30
Analysis 3.1. Comparison 3 Fibre supplementation versus no intervention, Outcome 1 Frequency of stools (per week). 31
ADDITIONAL TABLES 31
APPENDICES 32
WHAT'S NEW 32
CONTRIBUTIONS OF AUTHORS 32
DECLARATIONS OF INTEREST 32
SOURCES OF SUPPORT 32
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 33
INDEX TERMS 33

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[Intervention Review]

Interventions for treating constipation in pregnancy

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ABSTRACT

Background

Constipation is a common symptom experienced during pregnancy. It has a range of consequences from reduced quality of life and perception of physical health to haemorrhoids. An understanding of the effectiveness and safety of treatments for constipation in pregnancy is important for the clinician managing pregnant women.

Objectives

To assess the effectiveness and safety of interventions (pharmacological and non-pharmacological) for treating constipation in pregnancy.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 April 2015), ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) (30 April 2015) and reference lists of retrieved studies.

Selection criteria

We considered all published, unpublished and ongoing randomised controlled trials (RCTs), cluster-RCTs and quasi-RCTs, evaluating interventions (pharmacological and non-pharmacological) for constipation in pregnancy. Cross-over studies were not eligible for inclusion in this review. Trials published in abstract form only (without full text publication) were not eligible for inclusion.

We compared one intervention (pharmacological or non-pharmacological) against another intervention, placebo or no treatment.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy.

Main results

Four studies were included, but only two studies with a total of 180 women contributed data to this review. It was not clear whether they were RCTs or quasi-RCTs because the sequence generation was unclear. We classified the overall risk of bias of three studies as moderate and one study as high risk of bias. No meta-analyses were carried out due to insufficient data.

There were no cluster-RCTs identified for inclusion. Comparisons were available for stimulant laxatives versus bulk-forming laxatives, and fibre supplementation versus no intervention. There were no data available for any other comparisons.

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During the review process we found that studies reported changes in symptoms in different ways. To capture all data available, we added a new primary outcome (improvement in constipation) - this new outcome was not prespecified in our published protocol.

Stimulant laxatives versus bulk-forming laxatives

No data were identified for any of this review's prespecified primary outcomes: pain on defecation, frequency of stools and consistency of stools.

Compared to bulk-forming laxatives, pregnant women who received stimulant laxatives (Senokot or Normax) had an improvement in constipation (risk ratio (RR) 1.59, 95% confidence interval (CI) 1.21 to 2.09; 140 women, one study, *moderate quality of evidence*), but also had more abdominal discomfort (RR 2.33, 95% CI 1.15 to 4.73; 140 women, one study, *low quality of evidence*), and a borderline difference in diarrhoea (RR 4.50, 95% CI 1.01 to 20.09; 140 women, one study, *moderate quality of evidence*). In addition, there was no clear difference in women's satisfaction (RR 1.06, 95% CI 0.77 to 1.46; 140 women, one study, *moderate quality of evidence*).

One of the stimulant laxatives, Normax (dioctyl sodium sulphosuccinate and dihydroxy anthraquinone) is no longer used for the treatment of constipation in pregnant women (and the package information advises that it should not be used during pregnancy or breastfeeding). We therefore carried out a non-prespecified sensitivity analysis with the data for Senokot and Normax presented separately. Results for Senokot and Normax were very similar, thus results for the individual drugs largely reflected findings for the combined analysis, although when individual drugs were compared with bulk-forming laxatives there was no longer a clear difference between groups in terms of abdominal discomfort and diarrhoea.

No usable data were identified for any of this review's secondary outcomes: quality of life; dehydration; electrolyte imbalance; acute allergic reaction; or asthma.

Fibre supplementation versus no intervention

Pregnant women who received fibre supplementation had a higher frequency of stools compared to no intervention (mean difference (MD) 2.24 times per week, 95% CI 0.96 to 3.52; 40 women, one study, *moderate quality of evidence*). Fibre supplementation was associated with improved stool consistency as defined by trialists (hard stool decreased by 11% to 14%, normal stool increased by 5% to 10%, and loose stool increased by 0% to 6%).

No usable data were reported for either the primary outcomes of pain on defecation and improvement in constipation or any of this review's secondary outcomes as listed above.

Quality

Five outcomes were assessed with the GRADE software: improvement in constipation, frequency of stools, abdominal discomfort, diarrhoea and women's satisfaction. These were assessed to be of moderate quality except for abdominal discomfort which was assessed to be of low quality. The results should therefore be interpreted with caution. There were no data available for evaluation of pain on defecation or consistency of stools.

Authors' conclusions

There is insufficient evidence to comprehensively assess the effectiveness and safety of interventions (pharmacological and non-pharmacological) for treating constipation in pregnancy, due to limited data (few studies with small sample size and no meta-analyses). Compared with bulk-forming laxatives, stimulant laxatives appear to be more effective in improvement of constipation (*moderate quality evidence*), but are accompanied by an increase in diarrhoea (*moderate quality evidence*) and abdominal discomfort (*low quality evidence*) and no difference in women's satisfaction (*moderate quality evidence*). Additionally, fibre supplementation may increase frequency of stools compared with no intervention (*moderate quality evidence*), although these results were of moderate risk of bias.

There were no data for a comparison of other types of interventions, such as osmotic laxatives, stool softeners, lubricant laxatives and enemas and suppositories.

More RCTs evaluating interventions for treating constipation in pregnancy are needed. These should cover different settings and evaluate the effectiveness of various interventions (including fibre, osmotic, and stimulant laxatives) on improvement in constipation, pain on defecation, frequency of stools and consistency of stools.

PLAIN LANGUAGE SUMMARY

Interventions for treating constipation in pregnancy

What is the issue?

The term 'constipation' is defined as difficulty in passing stool and reduced frequency of bowel movements. It is characterised by discomfort, excessive straining, hard or lumpy stools, a sensation of incomplete evacuation, and infrequent bowel movements. Constipation is a common symptom experienced during pregnancy. This can result from a combination of factors, including changes in

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hormones during pregnancy affecting the digestive system, reduced physical activity and changes in dietary habits during pregnancy. In addition, as the baby grows it can press on the mother's intestines and cause digestive delays/obstructions.

Why is this important?

Constipation during pregnancy is associated with impaired quality of life and distress for pregnant women as well as physical problems including, occasionally, haemorrhoids. There are a range of suggested treatments with drugs, supplements or dietary modifications.

Generally, non-pharmacological interventions (changes in diet, water intake and exercise) are recommended initially, followed by pharmacological interventions if the non-pharmacological interventions fail or are insufficient. Pharmacological interventions include medications from a wide range of drug classes including lubricants, bulk-forming agents, osmotic laxatives, stimulant laxatives, stool softeners, and enemas and suppositories.

This review looked at the benefits of drug and non-drug interventions for constipation in pregnancy and whether they are safe for women and babies.

What evidence did we find?

We identified four studies, but only two studies (with a total of 180 women) provided data for analysis.The studies looked at stimulant laxatives compared with bulk-forming laxatives and dietary fibre supplementation versus no intervention. The included studies were judged to be of moderate quality.

We looked at two main comparisons. In the first, we found that stimulant laxatives may be more effective in improving constipation than bulk-forming laxatives (*moderate quality evidence*) but may also cause more abdominal discomfort (*low quality evidence*) and diarrhoea (*moderate quality evidence*) and we found no difference in women's satisfaction (*moderate quality evidence*). However, when we removed data relating to an intervention called Normax (dioctyl sodium sulphosuccinate and dihydroxy anthraquinone), which is no longer routinely used in pregnancy, there was no longer a clear difference between stimulant and bulk-forming laxatives in terms of abdominal discomfort and diarrhoea.

The second comparison, between fibre supplementation and no intervention, found that fibre supplementation may be effective in increasing the frequency of stools (*moderate quality evidence*). Fibre supplementation was associated with improved stool consistency as defined by trialists (hard stool decreased by 11% to 14%, normal stool increased by 5% to 10%, and loose stool increased by 0% to 6%).

There were no studies that looked at others types of interventions like osmotic laxatives, stool softeners, lubricant laxatives and enemas and suppositories.

What does this mean?

What little evidence there is, suggests that dietary fibre supplementation may increase the frequency of stools. If choosing between stimulant and bulk-forming laxatives, then stimulant may relieve constipation better but may cause more abdominal discomfort and diarrhoea.

More research in this area is needed.

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Summary of findings for the main comparison. Stimulant laxatives versus bulk-forming laxatives for treating constipation in pregnancy

Stimulant laxatives versus bulk-forming laxatives for treating constipation in pregnancy						
Patient or population: women with treating constipation in pregnancy **Settings:** trial located in UK **Intervention:** stimulant laxatives versus bulk-forming laxatives						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**Stimulant laxatives versus bulk-forming laxatives**				
Primary outcome - constipation improvement	**486 per 1000**	**772 per 1000** (588 to 1000)	**RR 1.59** (1.21 to 2.09)	140 (1 study)	⊕⊕⊕⊖ **moderate** [1]	
Primary outcome - pain on defecation - not reported	See comment	See comment	Not estimable	-	See comment	
Primary outcome - frequency of stools	**Study population**		Not estimable	0 (0[2])	See comment	
	See comment	See comment				
	Moderate					
Primary outcome - consistency of stools	See comment	See comment	Not estimable	0 (0[2])	See comment	
Secondary outcome - abdominal discomfort	**Study population**		**RR 2.33** (1.15 to 4.73)	140 (1 study)	⊕⊕⊕⊖ **moderate** [1]	
	129 per 1000	**300 per 1000** (148 to 608)				
	Moderate					
	129 per 1000	**301 per 1000** (148 to 610)				

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Secondary outcome - diarrhoea	**Study population**		**RR 4.5** (1.01 to 20.09)	140 (1 study)	⊕⊕⊖⊖ **low** [1,3]
	29 per 1000	**129 per 1000** (29 to 574)			
	Moderate				
	29 per 1000	**131 per 1000** (29 to 583)			
Secondary outcome - women's satisfaction	**Study population**		**RR 1.06** (0.77 to 1.46)	140 (1 study)	⊕⊕⊕⊖ **moderate** [1]
	500 per 1000	**530 per 1000** (385 to 730)			
	Moderate				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1] Unclear risk of selection and assessment biases and high risk of performance bias
[2] No included study for this outcome
[3] Wide range of confidence interval

Summary of findings 2. Fibre supplementation versus no intervention for treating constipation in pregnancy

Fibre supplementation versus no intervention for treating constipation in pregnancy

Patient or population: Women being treated for constipation in pregnancy
Settings: trial located in UK
Intervention: Fibre supplementation versus no intervention

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Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Fibre supplementation versus no supplement				
Primary outcome - frequency of stools		The mean frequency of stools in the intervention groups was **2.24 higher** (0.96 to 3.52 higher)		40 (1 study)	⊕⊕⊕⊖ **moderate** [1]	
Primary outcome - pain on defecation - not reported	See comment	See comment	Not estimable	-	See comment	
Primary outcome - improvement in constipation - not reported	See comment	See comment	Not estimable	-	See comment	
Primary outcome - consistency of stools - not reported	See comment	See comment	Not estimable	-	See comment	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1] Unclear risk of selection and assessment biases and high risk of performance bias

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BACKGROUND

Description of the condition

The term 'constipation' is defined as difficulty in passing stool and reduced frequency of bowel movements that is not secondary to an underlying cause (Moriarty 1992). It is characterised by discomfort, excessive straining, hard or lumpy stools, a sensation of incomplete evacuation, and infrequent defecation (Bradley 2007). Constipation is a common symptom experienced during pregnancy.This is the result of a combination of factors, including the effect of altered hormone levels on the gastrointestinal (GI) tract, mechanical effects of the growing fetus, reduced physical activity and changes in dietary habits (Cullen 2007). Gastrointestinal transit time is significantly prolonged in the second and third trimester (from 125 to 137 minutes) when compared with either the first trimester of pregnancy or the postpartum period (from 75 to 99 minutes) (Lawson 1985). In relation to hormones, an increase of progesterone reduces smooth muscle contractility, prolonging bowel transit time (Prather 2004). In addition, the compressive effects of the enlarging gravid uterus result in mechanical obstruction of the intestines. Other causes include decreased maternal activity, anxiety, iron supplementation and poor fluid intake. Commonly, many of these factors combine over the course of the pregnancy. Moreover, many women who are affected by constipation pre-conception tend to have worsening symptoms during pregnancy (Wald 2003). The prevalence of constipation in pregnancy ranges from 11% to 44% (Prather 2004; Bradley 2007; Shafe 2011; Trottier 2012). Part of this significant variation is due to variation in the definitions of constipation (Shafe 2011).

Constipation may be complicated by haemorrhoids due to the excessive straining associated with the condition (Longo 2010). Constipation is connected with reduced quality of life for various reasons including discomfort and negative body image perception, and may have broader psychological complications including frustration and low mood (Irvine 2002; Portalatin 2012; Johnson 2014). Those suffering constipation are more likely to report poor general health, poor physical functioning, reduced vitality and poorer social functioning (Wald 2007). The Rome II Criteria is a standard clinical measure of assessing functional constipation; however diagnosis is complex, requiring relatively detailed recall of the patient's bowel movements (Drossman 2006). Cullen proposed a simplified diagnostic criterion based on a history of low frequency of stools (less than three stools per week), hard stools and/or difficulties with evacuation of faeces (Cullen 2007). This self-reported criterion was found to be more sensitive than the Rome II criterion and has the advantage of being more practical for both healthcare worker and patient (Ponce 2008).

Description of the intervention

In this review, we will consider pharmacological and non-pharmacological interventions for treating constipation in pregnancy. Generally, non-pharmacological interventions are recommended initially, followed by pharmacological interventions if the non-pharmacological interventions fail or are insufficient; however there is no formal guideline on how to approach this (NICE 2008). The British National Formulary suggests if laxatives are required in pregnancy to consider starting with a bulking agent, then an osmotic agent and then a stimulant; however this is not a formal guideline (BNF 2010). A 2009 survey of 1648 pregnant women with constipation found that 44.2% had been treated with laxatives, a figure which had increased since an earlier survey in 2005 (Shafe 2011). Pharmacological interventions include medications from a wide range of drug classes including lubricants, bulk-forming agents, osmotic laxatives, stimulant laxatives, stool softeners, and enemas and suppositories (Portalatin 2012). Non-pharmacological interventions include changes in diet, water intake and exercise. In this review, we categorise medicinal fibres, such as psyllium, and synthetic polymers, such as polycarbophil and methylcellulose, into pharmacological interventions; dietary fibres are classified under non-pharmacological interventions.

A report from the US recommends the amount of dietary fibre to be 20 to 35 g/day (Marlett 2002). The suggested oral dose of bulk-forming laxatives is: 6.4 to 10 g/day (psyllium), 4.8 to 9.6 g/day (methylcellulose), 2 to 8 g/day (polycarbophil); of osmotic laxatives is 15 to 30 mL/day (lactulose), 15 to 30 mL/day (sorbitol), 17 to 34 mL/day (polyethylene glycol (PEG)), 30 to 45 mL/day (magnesium oxide); and of stimulant laxatives is: 7.5 to 30 mg/day (senna), 10 to 15 mg/day orally or 10 mg/day rectally (bisacodyl) (Prather 2004). The suggested dose of glycerol suppository is 2250 mg (MIMS 2014). For docusate sodium it is 50 to 500 mg/day orally in one to four divided doses or 0.12 g rectally as docusate sodium in a 10 g enema gel (MIMS 2014).

Pharmacological interventions

Laxatives, as with any medication in pregnancy, should ideally be effective, non-teratogenic, not excreted in breast milk and well-tolerated.

The LUCK (Laxative Usage in patients with GP- diagnosed Constipation in the UK) study was a cohort study using the General Practice Research Database (GPRD). The highest prevalence was observed amongst females aged between 30 and 44, possibly reflecting an increase in the risk of constipation during pregnancy. The prescribing trends of laxatives in pregnancy over the five-year study period have been changing from lactulose to macrogol.

Lubricant laxatives

Lubricant laxatives, such as mineral oil or paraffin, have no direct pharmacological effect on the gastrointestinal mucosa but instead have a direct lubricating effect on stool (Shafe 2011). They are not commonly prescribed in pregnancy according to the LUCK study (Shafe 2011). An important potential complication associated with long-term use is maternal malabsorption of fat-soluble vitamins (e.g. vitamins A, D, E and K) (Cullen 2007). In the case of vitamin K, this can lead to hypoprothrombinaemia and haemorrhage (Cullen 2007).

Bulk laxatives

Bulk laxatives such as psyllium, methycellulose and calcium polycarbophil are fibre supplements which expand with water to increase stool bulk (Leung 2011). They are generally safe for long-term use in pregnant women and are often the first line of treatment for constipation in pregnancy that does not respond to non-pharmacological interventions (Trottier 2012). Bulk laxatives are generally understood to be well-tolerated, however, a report by Tytgat indicates that they may cause abdominal bloating and cramping at therapeutic doses (Tytgat 2003).

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Osmotic laxatives

Osmotic laxatives are a group of hyperosmolar laxatives characterised by very low levels of absorption, which increase stool water content due to their osmotic properties (Trottier 2012). They include subcategories such as salts, saccharine, alcohols and macrogols (Klaschik 2003). In the LUCK study, they were the most commonly prescribed type of laxative to pregnant women with constipation (Shafe 2011). There are a number of established side-effects: first, saccharated osmotics (e.g. lactulose or sorbitol) may cause flatulence and bloating (Portalatin 2012) and, in women with nausea, they may exacerbate it (Wald 2003). Second, salt osmotics (e.g. magnesium or sodium salts) may cause maternal sodium retention (Cullen 2007). Finally, polyethylene glycol (PEG) or macrogol may cause abdominal bloating and cramps (Portalatin 2012).

Stimulant laxatives

Stimulant laxatives, such as senna and bisacodyl, stimulate peristalsis. They are relatively infrequently used in pregnancy in the LUCK study (Shafe 2011). Stimulant laxatives may be accompanied by side-effects such as abdominal cramps, salt overload, hypokalaemia, hyponatraemia, and dehydration from severe diarrhoea (Wald 2003; Portalatin 2012). There is a range of specific side-effects: senna, an anthroquinone, may cause abdominal cramps (Trottier 2012) and also small amounts are excreted in breast milk (Cullen 2007), however is not associated with teratogenic effects and is considered to be safe in pregnancy (Acs 2002; MIMS 2014). Diphenylmethanes (e.g. bisacodyl) may cause abdominal discomfort, diarrhoea and hypokalaemia (MIMS 2014), and castor oil may cause premature uterine contractions (Cullen 2007).

Stool softeners

Stool softeners, also known as emollient laxatives, belong to a group of anionic surfactants that allow water to enter the stool more readily (Trottier 2012). The most frequently used are the docusate salts, sodium docusate and calcium docusate, although there are other forms also available (Trottier 2012). They are generally considered to have no significant adverse effects based on the results of several studies (Trottier 2012). However, one study did show that docusate sodium may be associated with symptomatic hypomagnesaemia in the neonate (Wald 2003).

Enemas and suppositories

Enemas and suppositories are preparations of the previously discussed classes of laxatives which are administered rectally (Klaschik 2003). They are generally considered for short-term relief after oral laxatives have failed (Clemens 2013). The key advantages are that they are locally acting and can give rapid relief (Clemens 2013). There are certain issues including inconvenient mode of administration, local irritation, and discomfort (Twycross 2012; MIMS 2014).

Non-phamacological interventions

The key non-pharmacological interventions are increasing dietary fibre intake, increasing water intake and increasing light physical activity (Prather 2004). These interventions provide a starting point for the management of constipation in pregnancy. They are generally understood to have few side-effects; however, high-fibre diets may cause abdominal bloating or flatulence (Tytgat 2003).

How the intervention might work

Phamacological interventions

Lubricant laxatives

Lubricant laxatives act as a lubricant to coat the stool, and also soften the stool, both of which mean that passing the stool is easier (Klaschik 2003). They are relatively pharmacologically inert, that is, the effect is a direct one (Klaschik 2003).

Bulk laxatives

Bulk laxatives increase fecal water content, stimulate bowel motility, and decreased colonic transit time. Their desired effects may take a few days to achieve, so it is not appropriate for acute treatment (Tytgat 2003). The dose of bulk laxatives can be titrated to achieve continued relief throughout pregnancy as predisposition to constipation changes (Longo 2010). These agents are purported to be the most physiologic and safest pharmacological therapy for constipation in pregnancy (Wald 2003). Psylium (Ispaghula) has high water-binding capacity and is known to ferment in the colon. Side-effects include delayed gastric emptying, loss of appetite, and, less frequently, serious acute allergic reactions and asthma (Vaswani 1996; Xing 2001). Methylcellulose, a synthetic polymer fibre, leads to resistance to bacterial fermentation. It absorbs water into the colonic lumen thereby increasing fecal mass, stimulating motility and reducing colonic transit time. Polycabophil, a hydrophilic resin, is not metabolised by intestinal bacteria, therefore may be less likely to cause gas and bloating. Where women are unresponsive to bulking agents alone, combination therapy with other agents should be considered (Portalatin 2012).

Osmotic laxatives

Osmotic laxatives are poorly absorbed by the intestine thus increase fluid retained in the bowel by increasing intra-luminal osmotic pressure (Prather 2004). As mentioned, the different types include salts, saccharine, alcohols and macrogols (Klaschik 2003). Saline osmotics (e.g. magnesium and sodium salts) are inadvisable for pregnant women because they can cause maternal sodium retention (Wald 2003). Saccharated osmotic (e.g. lactulose and sorbitol) promote intestinal motility and stool frequency. Lactulose is a poorly absorbed synthetic disaccharide metabolised by colonic bacteria. Macrogol, also known as Polyethylene glycol (PEG), is conventionally an osmotic laxative, however it may be prepared with other laxatives to form an isosmotic laxative (Corazziari 2000). It modifies stool consistency and increases stool bulk without significant fluid shifts, hence theoretically has less risk of dehydration or severe diarrhoea (Corazziari 2000; Grossmann 2000).

Stimulant laxatives

Where constipation is unresponsive to bulk or osmotic laxatives, stimulant laxatives may be considered (Prather 2004). They have a fast onset of action, working within hours in a dose-dependent manner (Portalatin 2012). Low doses prevent absorption of water and sodium, however high doses stimulate secretion of sodium into the colonic lumen causing an osmotic fluid shift, which may result in abdominal cramping and severe diarrhoea (Portalatin 2012). Anthraquinones (e.g. senna) increase electrolyte transportation into the colonic lumen and stimulate myenteric plexuses to increase intestinal motility. They induce defecation six to eight

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hours after ingestion (Portalatin 2012). Diphenylmethanes (e.g. bisacodyl) affect the colon in the same way as anthraquinones. These laxatives are most suitable for single-dose use in pregnant women with temporary constipation (Portalatin 2012).

Stool softeners

Stool softeners facilitate the passage of water into the stool mass by lowering its surface tension (Trottier 2012). Ducusate sodium, and other docusate salts, soften stool by facilitating intestinal fluid secretion into the fecal mass (Portalatin 2012). Mineral oil, another example, is an indigestible liquid compound which softens fecal contents by reducing water absorption and by direct lubrication (Portalatin 2012).

Enemas and suppositories

Enemas are solutions that take various forms including water, phosphate and sugar. Phosphate enemas are hypertonic solutions, which increase stool water content due to their osmotic properties and also stimulate the rectal mucosa (Portalatin 2012). Saline enemas also have osmotic properties and may cause rectal distension and discomfort (Portalatin 2012). Docusate sodium enemas act as a lubricant type of laxative and also increase the penetration of fluid into the faeces (MIMS 2014).

Enemas and suppositories (glycerine, bisacodyl, phosphate) act by local direct contact with the rectal mucosa after dissolution of the suppositories. Their effect on reducing constipation is rapid (Clemens 2013). As they are simply rectally-administered preparations of the previously discussed oral laxatives, their mechanism of action is similar, albeit local (Klaschik 2003). Suppositories contain an active laxative compound dispersed in a base ingredient such as vegetable oil or water. Bisacodyl suppositories are available in two preparations including polyethylene glycol-based and hydrogenated vegetable oil-based (Potter 2005). Bisacodyl, a diphenylmethane derivative, has stimulant properties and acts on neurons mainly in the large intestine, stimulating motility (Portalatin 2012). The onset of action of bisacodyl suppository is 20 minutes to three hours (mean one hour) (Twycross 2012), so they are useful for relieving constipation quickly. In addition, they can be helpful for pregnant women who cannot swallow tablets. Where possible, wearing clean gloves to insert the suppository maintains personal hygiene. Glycerin is an osmotic dehydrating agent that works by stimulating the lining of the intestine, as well as increasing fecal water content, making it easier for stools to pass (Kyle 2006; Portalatin 2012).

Non-phamacological interventions

There are various non-pharmacological interventions. The National Institute for Health and Care Excellence (NICE) clinical guidelines on routine antenatal care recommend a change in diet to increase dietary fibre for treating constipation in pregnancy (Vazquez 2010). Naturally-occurring dietary fibre comes from plants and a high-fibre diet can include things like fruit, vegetables and wholegrain cereals (Muller-Lissner 1988). Dietary fibre is indigestible and retains water, thus increasing fecal weight and volume (Muller-Lissner 1988). Ensuring adequate water intake is thought to be an important cofactor to dietary change, however the evidence is unclear on this intervention (Vazquez 2010). Moderate physical exercise, defined as any activity that is equivalent in difficulty to brisk walking, promotes regular bowel movements in pregnancy (Pate 1995; Derbyshire 2006). The recommendation for pregnant women with no medical or obstetric complication is 30 minutes a day of moderate exercise on most, if not all, days of the week (Artal 2003).

Why it is important to do this review

Constipation is a very common symptom during pregnancy, and is associated with impaired quality of life, haemorrhoids, and distress for pregnant women. Many interventions are available and have varying side-effect profiles. Pharmacological interventions may be considered when diet and lifestyle modifications are not effective. An understanding of the potential teratogenicity and safety of medications used in pregnancy is vital for the clinician managing these pregnant women. This review is important for establishing the safety and efficacy of different treatments for constipation in pregnancy.

The previous Cochrane review on this topic (Jewell 2001) is now out of date and has been relinquished by the authors.

OBJECTIVES

To assess the effectiveness and safety of interventions (pharmacological and non-pharmacological) for treating constipation in pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (including trials using a cluster-randomised design and quasi-randomised trials) evaluating interventions for constipation in pregnancy. Studies using a cross-over design, or studies reported only in abstract form (without full text) were not eligible for inclusion.

Types of participants

Pregnant women complaining of constipation, defined as infrequent and difficult defecation.

Types of interventions

All interventions (pharmacological and non-pharmacological agents) for treating constipation in pregnancy were considered.

We compared one intervention (pharmacological or non-pharmacological) against another intervention, placebo or no treatment. We did not pool all the pharmacological or non-pharmacological interventions together.

Types of outcome measures

Primary outcomes

1. Improvement in constipation (as measured/ defined by trialists) (outcome not prespecified in our published protocol - Rungsiprakarn 2014)
2. Pain on defecation
3. Frequency of stools
4. Consistency of stools (as measured/defined by trialists)

During the review process, we found that studies reported changes in symptoms in different ways. To capture all data

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available, we added "improvement in constipation". This broader banner encapsulates a more woman-centred understanding of constipation in pregnancy.

Secondary outcomes

Maternal

1. Women's satisfaction
2. Quality of life
3. Abdominal discomfort (cramping, bloating, and flatulence)
4. Dehydration
5. Diarrhoea
6. Electrolyte imbalance
7. Acute allergic reactions
8. Asthma

Neonatal/fetal

1. Electrolyte imbalance

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (30 April 2015).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (OVID);
3. weekly searches of Embase (OVID);
4. monthly searches of CINAHL (Ebsco);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE, Embase and CINAHL, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) (30 April 2015) for unpublished, planned and ongoing trial reports, using the terms listed in Appendix 1.

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors, Phassawan Rungsiprakarn (PR) and Pisake Lumbiganon (PL) independently assessed for inclusion all of the potentially relevant studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third review author, Malinee Laopaiboon (ML). We created a study flow diagram to map out the number of records identified, included and excluded.

Data extraction and management

We designed a form to extract data. For eligible studies, PR, Ussanee Sangkomkamhang (US) and ML extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted PL. We entered data into Review Manager software (RevMan 2014) and checked the data for accuracy. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors, PR and ML, independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by consulting PL.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the method as:

- low risk of bias (e.g. telephone or central randomisation; consecutively-numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

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(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed the methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

The quality of the evidence was assessed using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following outcomes for the main comparisons:

1. improvement in constipation;
2. frequency of stools;
3. abdominal discomfort;
4. diarrhoea;
5. women's satisfaction.

We used GRADEprofiler (GRADE 2014) to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes were produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if outcomes were measured using the same scale between trials. We planned to use the standardised mean difference to combine trials that measured the same outcome with different scales.

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Unit of analysis issues

Cluster-randomised trials

In future updates of the review, we will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their standard errors using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials were not eligible for inclusion in this review.

Multi-armed trials

We included one multi-armed trial in the analyses. We included the relevant intervention groups in a pair-wise comparison of intervention groups that met the criteria for including studies in the review. We combined groups to create a single pair-wise comparison using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

In future updates of the review for all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

In future updates of the review, we will assess statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either a T^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

In future updates of the review, if there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). In future updates of the review we will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

Planned subgroup analyses were not conducted due to insufficient data. In future updates of this review, if we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses.

1. Type of pharmacological agents; bulk-forming laxatives, stool softeners, osmotic laxatives, and stimulant laxatives.
2. Short-term (two weeks or less) intervention use versus prolonged (more than two weeks) use of the intervention.
3. Different route of interventions such as oral route versus rectal route.

The following outcomes will be used in subgroup analysis: increased frequency of defecation and softened stools.

We will assess subgroup differences by the interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We did not carry out our planned sensitivity due to insufficient data. In future updates, if required, we will carry out sensitivity analyses for all primary outcomes to explore the effect of trial quality based on concealment of allocation. We will exclude trials rated as 'high risk of bias' or 'unclear risk of bias' for allocation concealment in order to assess any substantive difference in the overall result.

In our comparison of stimulant laxatives versus bulk-forming laxatives (comparison 1) we included data from a trial with four treatment arms (two stimulant laxatives [Senokot and Normax] and two different bulk-forming laxatives). However, one of the stimulant laxatives, Normax (dioctyl sodium sulphosuccinate and dihydroxy anthraquinone) is no longer used for the treatment of constipation in pregnant women (and package information advises

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that it should not be used during pregnancy or breastfeeding). We therefore carried out a sensitivity analysis (not prespecified in our protocol) with the data for Senokot and Normax presented separately.

RESULTS

Description of studies

Results of the search

See: Figure 1.

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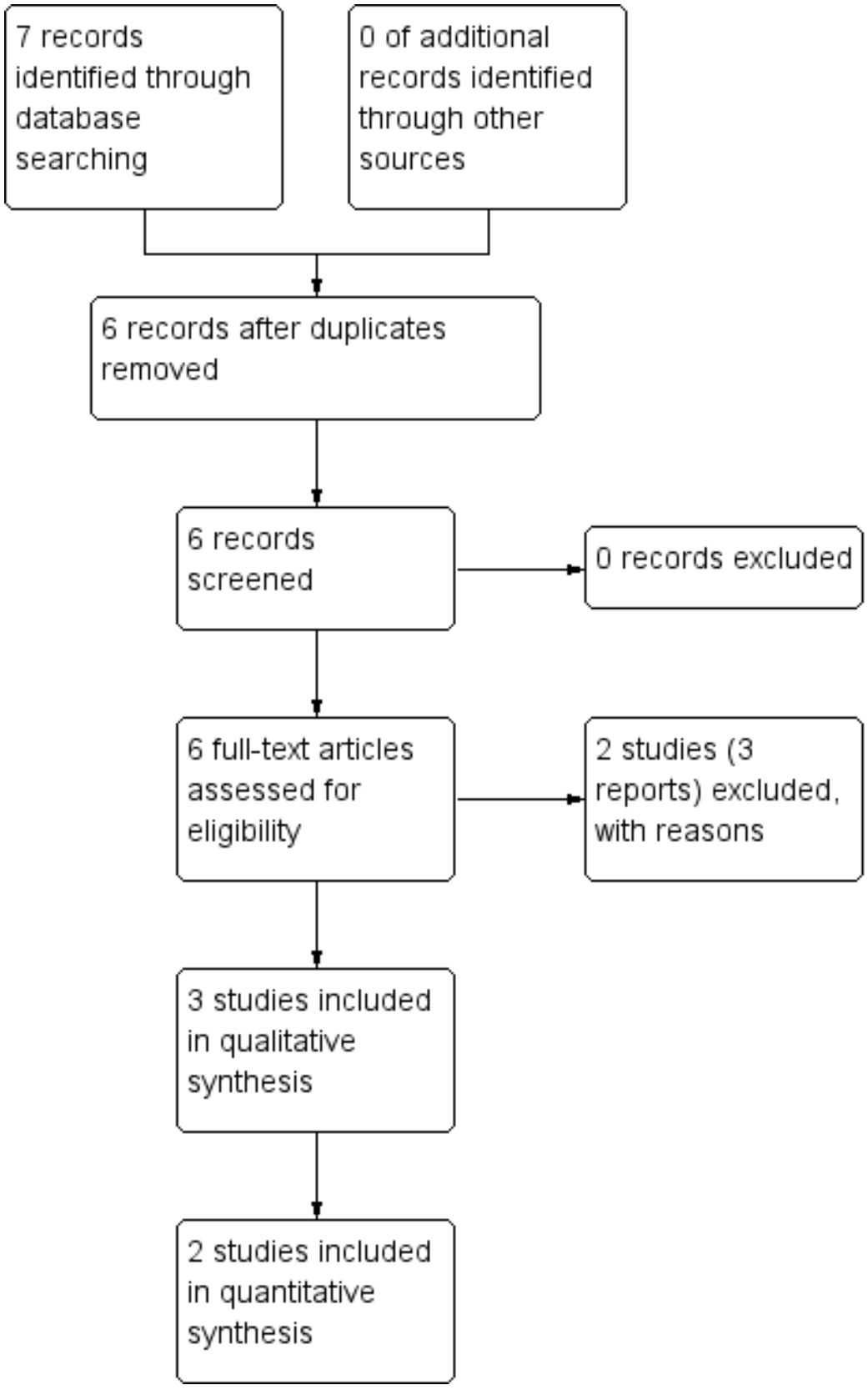
Figure 1. Study flow diagram.



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The search identified seven trial reports (relating to six studies) published between 1957 and 2013. Two reports were from the same study (Ghahramani 2013). Four studies were included in this review (Greenhalf 1973; Gregersen 1985; Anderson 1985; Amadeo 1990) and two were excluded (Browne 1957; Ghahramani 2013).

Included studies

For detailed characteristics of the included studies, *see* Characteristics of included studies. Amadeo 1990 (40 pregnant women) did not report any data relevant to the primary or secondary outcomes of this review. Gregersen 1985 (250 pregnant women) also did not contribute any usable data to the review.

Design

All the included studies were reported to be randomised controlled trials (RCTs) (Greenhalf 1973; Gregersen 1985; Anderson 1985; Amadeo 1990). It was not clear whether they were RCTs or quasi-RCTs because the sequence generation was unclear.

Sample size

The total number of participants included in trials contributing data to the review was 180 pregnant women. There was no loss to follow-up. The sample size of each study varied from 40 to 140.

Setting

Two trials were conducted in the UK (Greenhalf 1973; Anderson 1985) whilst the third, Amadeo 1990, was conducted in Italy. Gregersen 1985 took place in Denmark.

Participants

Anderson 1985 studied 20 to 38 year old women in their third trimester who had no medical problems aside from constipation. Amadeo 1990 studied 19 to 42 year old pregnant women with primary constipation. Greenhalf 1973 included both constipated pregnant and puerperal breast-feeding women with constipation; however, only data from pregnant women were used in this review. Gregersen 1985 studied pregnant women with constipation (20 to 36 weeks' gestation).

Interventions

Greenhalf 1973 (n = 140) compared two types of stimulant and two types of bulk-forming laxatives: Senokot, two tablets daily, consisting of 7 mg of standard senna; Normax, two capsules a day, contains 60 mg of dioctyl sodium sulphosuccinate and 50 mg of dihydroxyanthraquinone; Normacol standard, two teaspoonfuls a day, contains sterculia British Pharmaceutical Codex (B.P.C.) and frangular B.P.C.; Normacol special, two teaspoonfuls a day, contains sterculia B.P.C.. Each intervention had 35 participants.

Gregersen 1985 (n = 250) compared fibre tablets (Dumovital) with placebo tablets. Women in the intervention arm received Dumovital fibre tablets (n = 133) - two initial weeks with no tablets, third week, three per day, fourth week, six per day, weeks five to nine, nine tablets per day. Women in the placebo arm received placebo tablets (n = 117) according to an identical regimen.

Anderson 1985 (n = 40) compared two different dietary fibre supplements and no intervention. After two weeks of baseline observation, the women were randomly allocated into one of three groups (Fibermed, a 10 g corn-based biscuit (n = 13); 23 g wheat bran (n = 14) or no intervention (n = 13)) for a further two weeks.

Amadeo 1990 (n = 40) compared glucomannan and minerals (n = 20) with placebo (n = 20). Women in the intervention group received Dimanel 500 mg to 1500 mg (500 mg/capsule). If symptoms persisted, the dose was raised to 1000 mg twice daily. Women in the control group received a placebo (formulation unspecified) two to three capsules twice daily which could be raised by two capsules twice daily keeping in line with the treatment group.

Outcomes

Greenhalf 1973 (n = 140) had improvement in constipation as the primary outcome and reported secondary outcomes of maternal abdominal discomfort and diarrhoea. Anderson 1985 (n = 40) had frequency of stools and a change to a softer stool consistency as the primary outcomes. Thus three primary outcomes (improvement in constipation, frequency of stools and consistency of stools) and three secondary outcomes (abdominal discomfort, diarrhoea and women's satisfaction) were reported in these two included studies.

One study (n = 40) did not have data on relevant outcomes data (Amadeo 1990).

Gregersen 1985 measured the number of bowel movements in a 14-day period, but the data were not presented in usable form. Gregersen 1985 also reported reasons why 110/240 women failed to complete the study, and these reasons included our secondary outcome of diarrhoea. However, the adverse effects outcomes were only reported for women leaving the study, and so we did not consider the data complete or usable.

Excluded studies

For detailed characteristics of the excluded trials, see Characteristics of excluded studies.

We excluded Browne 1957 because the participants were not restricted to pregnant women. We excluded Ghahramani 2013 because the study was investigating prevention of constipation, not treatment.

Risk of bias in included studies

Risk of bias in the included studies varied. For sequence generation, allocation concealment, and blinding, the two included studies that contributed data had unclear or high risk of bias. However, for incomplete outcome data, selective reporting, and other biases, the risk of bias was low.

We classified the overall risk of bias of three studies (Amadeo 1990; Anderson 1985; Greenhalf 1973) as moderate and one study (Gregersen 1985) as high.

For an overview of review authors' judgments about each 'Risk of bias' item for individual included studies, *see* Figure 2 and Figure 3.

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Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

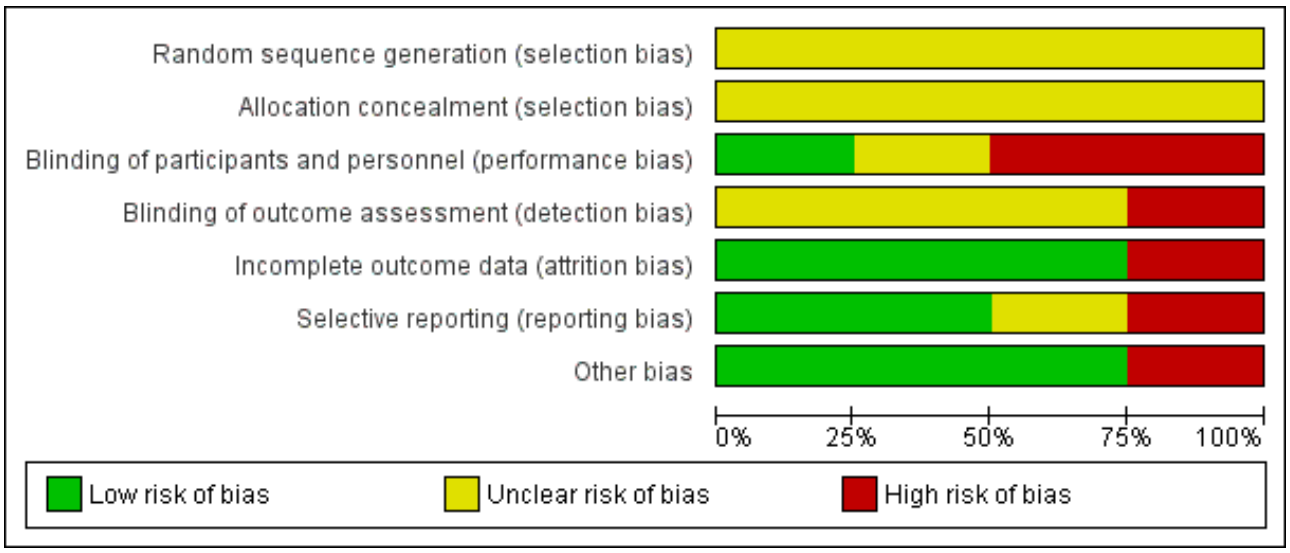

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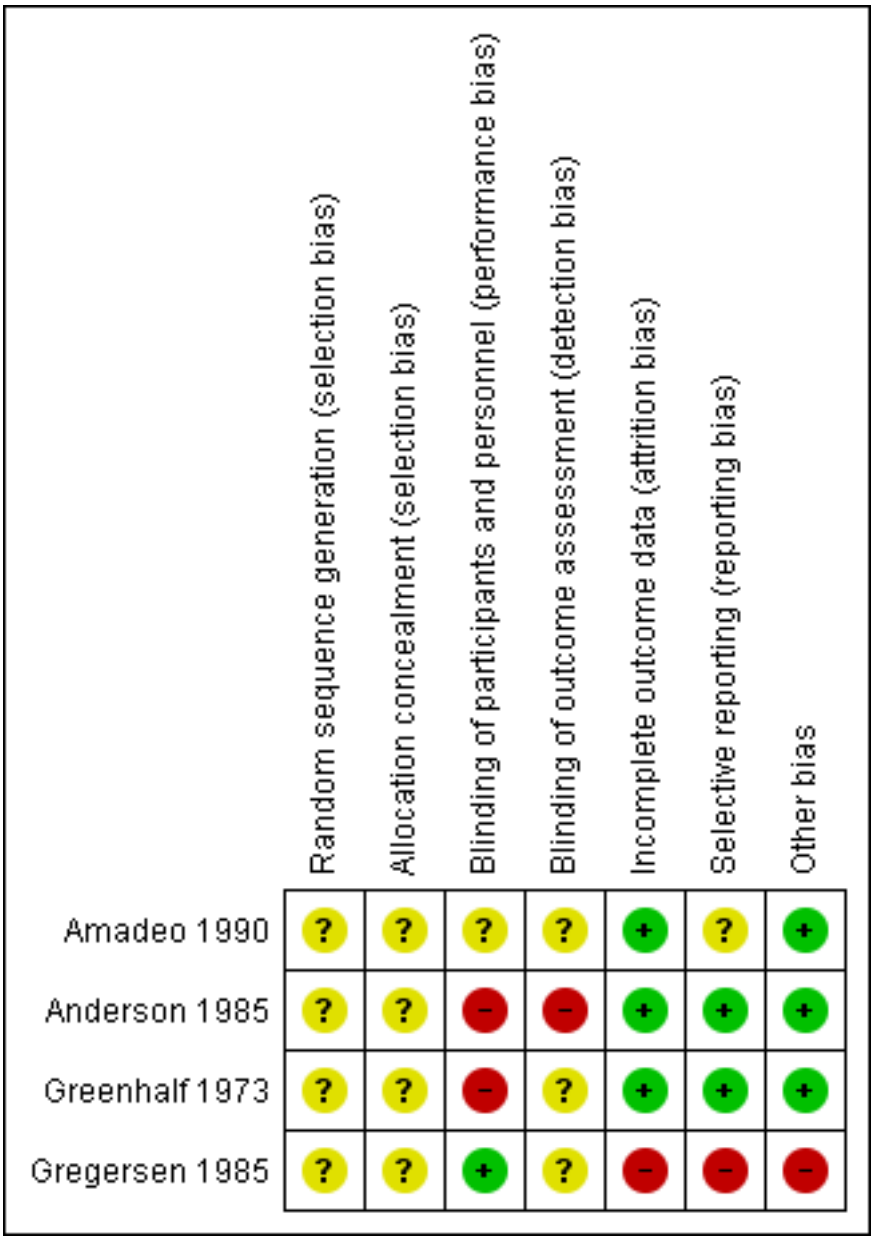
Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Three studies (Greenhalf 1973; Gregersen 1985; Amadeo 1990) did not report details of sequence generation or allocation concealment. One study was not clear on the sequence generation and allocation concealment (Anderson 1985). We therefore classified all studies as having an unclear risk of selection bias.

Blinding

One study (Amadeo 1990) did not provide adequate information about blinding. We judged this study as unclear risk of detection and performance bias.

Two studies (Greenhalf 1973; Anderson 1985) did not use an identical placebo and were judged as high risk of performance bias.

For detection bias, one study (Greenhalf 1973) did not provide any information and was judged as unclear risk. However, the outcome assessors in one study (Anderson 1985) were not blinded, we therefore judged this study to be as high risk for detection bias.

Gregersen 1985 was described as placebo-controlled and double-blind. We were unclear if women and staff would have been aware of assignment, but blinding may have been achieved because women self-administered tablets in the community. We assessed the trial as of low risk for performance bias. Women self-reported outcome data, and we assessed the trial as of unclear risk for detection bias.

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Incomplete outcome data

All recruited participants were in the analyses of all three studies (Greenhalf 1973; Anderson 1985; Amadeo 1990); we therefore judged them to be at low risk of attrition bias.

Gregersen 1985 was at high risk of attrition bias because 110/240 women failed to complete the study, some due to adverse effects of treatment. These side-effects data are not fully reported and not usable.

Selective reporting

All reported outcomes were pre-specified in the method part of all three studies (Greenhalf 1973; Anderson 1985; Amadeo 1990). We therefore judged them to be at a low risk of selective reporting bias. Gregersen 1985 reported side-effects for only the women who left the study and was assessed as of high risk of bias.

Other potential sources of bias

None identified, apart from Gregersen 1985, a trial we considered to be of high risk because the primary outcome was reported in graph form only, rendering the data unusable.

Effects of interventions

See: **Summary of findings for the main comparison** Stimulant laxatives versus bulk-forming laxatives for treating constipation in pregnancy; **Summary of findings 2** Fibre supplementation versus no intervention for treating constipation in pregnancy

During the review process we found that studies report changes in symptoms in different ways. To capture all data available, it was essential that the primary outcomes were altered. One study (Amadeo 1990) did not contribute to any comparison because there were no relevant data on the translated document. Gregersen 1985 also contributed no usable data.

Comparison 1 - Stimulant laxatives versus bulk-forming laxatives

Primary outcomes

One study (Greenhalf 1973), involving 140 women, provided data for this comparison.

No data were identified for any of this review's prespecified primary outcomes: pain on defecation, frequency of stools and consistency of stools.

Improvement in constipation, was higher in those women taking stimulant laxative compared with bulk-forming laxatives (risk ratio (RR) 1.59, 95% confidence interval (CI) 1.21 to 2.09; 140 women, one study (Analysis 1.1)).

Secondary outcomes

Data were available for three secondary outcomes: **abdominal discomfort**, **diarrhoea** and **women's satisfaction**. Pregnant women who received stimulant laxatives had more **abdominal discomfort** (RR 2.33, 95% CI 1.15 to 4.73; 140 women, one study, (Analysis 1.2)), borderline difference in **diarrhoea** (RR 4.50, 95% CI 1.01 to 20.09; 140 women, one study (Analysis 1.3)) than those who were given bulk-forming laxatives and no difference in **women's satisfaction** (RR 1.06, 95% CI 0.77 to 1.46; 140 women, one study (Analysis 1.4)). For this review's other secondary outcomes, there were no data available for **quality of life**, **dehydration, electrolyte imbalances, acute allergic reaction** or **asthma**.

Comparison 2 - Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis, Senokot and Normax data separated)

In comparison one we combined the data for two different stimulant laxatives (Senokot and Normax) and compared them with combined data for two similar bulk-forming laxatives (Normacol standard and Normacol special). One of the stimulant drugs, Normax (dioctyl sodium sulphosuccinate and dihydroxy anthraquinone) is no longer used for the treatment of constipation in pregnant women (and the package information advises against its use during pregnancy or breastfeeding). We therefore carried out a non-prespecified sensitivity analysis with the data for Senokot and Normax presented separately. Results for Senokot and Normax were similar, and results for the individual drugs largely reflect findings for the combined analysis.

Compared with bulk-forming laxatives both Senokot and Normax led to an improvement in constipation (RR 1.53, 95% CI 1.03 to 2.26; participants = 70, and, RR 1.65, 95% CI 1.13 to 2.41; participants = 70, respectively). Comparison one (combined data) showed that stimulant drugs increased abdominal discomfort and diarrhoea compared with bulk-forming laxatives, but when data for Senokot and Normax were presented separately there was no clear difference between groups, although the direction and size of effect was similar for both drugs. There was no clear difference between groups in terms of women's satisfaction with different types of laxatives, with similar numbers of women (approximately half) rating Senokot, Normax and bulk-forming laxatives as good or acceptable (Analysis 2.4).

Comparison 3 - Fibre supplementation versus no intervention

Primary outcomes

One study (Anderson 1985), involving 40 women, provided data for this comparison. Gregersen 1985 was relevant to this comparison, but there were no usable data in the trial report.

No data were identified for one of this review's prespecified primary outcomes: **pain on defecation** or**improvement in constipation.**

Data were available for **frequency of stools** and **consistency of stools**. Pregnant women who received fibre supplementation had higher frequency of stools than those in the no intervention group (mean difference (MD) 2.24 times per week, 95% CI 0.96 to 3.52; 40 women, one study (Analysis 3.1)). Similarly, Anderson 1985 reported that fibre supplementation was associated with improved stool consistency as defined by trialists (hard stool decreased by 11% to 14%, normal stool increased by 5% to 10%, and loose stool increased by 0% to 6%) (see Table 1). Anderson 1985, reported these changes in stool consistency as being different for bran compared with no intervention but not so for Fibermed compared with placebo.

Secondary outcomes

There were no usable data available for **women's satisfaction, quality of life, abdominal discomfort, dehydration, diarrhoea, electrolyte imbalances, acute allergic reaction** or **asthma**.

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DISCUSSION

Summary of main results

There was an overall paucity of data with only two of the four included studies contributing data to the review. The included studies were judged to be of moderate risk of bias. Only two comparisons with one study each were able to be analysed. No meta-analysis was possible.

The results suggest that stimulant laxatives were significantly more effective than bulk-forming laxatives in terms of improvement in constipation, but were associated with significantly higher abdominal discomfort and diarrhoea. We added a new primary outcome 'improvement in constipation' at the review stage. This review's prespecified primary outcomes: pain on defecation, frequency of stools and consistency of stools are components of constipation. It became obvious during the review process that studies report changes in symptoms in different ways, as such, to capture all data available, it was essential that the primary outcomes were altered. Furthermore, this broader banner encapsulates a more woman-centred understanding of constipation in pregnancy.

Fibre supplementation was more effective for treating constipation in pregnant women than no intervention in terms of frequency and consistency of stools. The results on consistency of stools were re-reported (not analysed in this review).

Overall completeness and applicability of evidence

There were only four included studies suggesting that there are very little randomised data available. Furthermore, there were no additional eligible studies since the previous Cochrane review on this topic in 2001 (Jewell 2001).

We feel that with the search strategy conducted this does indeed reflect the full gamut of randomised data available. Of the studies included, the two that provided data were both set in the UK whilst the others were set in Italy and Denmark. Confining the population studied to high-income countries introduces issues around generalisability.

No data were reported for the following primary outcomes: pain on defecation.

No usable data were identified for any of this review's secondary outcomes: quality of life; dehydration; electrolyte imbalance; acute allergic reaction; or asthma.

Furthermore, given the limited data available on adverse effects, it is difficult to infer the acceptability of the treatments studied.

Quality of the evidence

The two of four included studies that contributed data to this review had only 180 women. The overall risk of bias of these two studies was moderate. The results should be interpreted with caution. All five available outcomes including improvement in constipation, frequency of stools, abdominal discomfort, diarrhoea and women's satisfaction were assessed with the GRADE software. These were assessed to be of moderate quality except for evidence on abdominal discomfort, which was assessed to be of low quality. The prespecified primary outcomes 'pain on defecation' and 'consistency of stools' were not able to be analysed due to lack of data. The scores of moderate and low quality reflect the assessment of bias, wide confidence intervals and lack of meta-analysis.

Potential biases in the review process

We followed methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to minimise biases in the review process.

Agreements and disagreements with other studies or reviews

We are not aware of any other systematic reviews assessing the effectiveness and adverse effects of interventions for constipation during pregnancy. In this review, no further studies were added since the previous Cochrane review on this topic was published by Jewell 2001, as such, there are no major changes to its conclusions. This review is in agreement with one of its key findings, that more randomised data are required in order to draw firm conclusions on the management of constipation in pregnancy.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to recommend the use of dietary fibre supplementation, stimulant and bulk-forming laxatives for treating constipation during pregnancy.

There were no data for the comparison among others types of interventions such as osmotic laxatives, stool softener, lubricant laxatives and enemas and suppositories.

Implications for research

More randomised controlled trials covering different settings (high-, middle-, and low-income countries) evaluating the effectiveness of various interventions such as dietary fibre, osmotic, and stimulant laxatives on improvement in constipation, pain on defecation, frequency of stool and consistency of stools are needed.

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The named authors alone are responsible for the views expressed in this publication.

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Amadeo 1990

Methods	Randomised controlled trial.
Participants	19-42 year old pregnant women presenting with primary constipation.
Interventions	A formulation of glucomannan and minerals (Dimanel noctre) (n = 20) and placebo (no mention of what the substance was) (n = 20). The dose of Dimanel was 500-1500 mg (500 mg/capsule). If symptoms persisted the dose was raised to 1000 mg twice daily.
Outcomes	Relief of constipation (palpable faecal mass, abdominal pain, painful bowel evacuation and abdominal or/and rectal fullness feeling).
Notes	This study was set in Italy. This trial did not contribute data as the results of the primary outcomes were not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	Quote (from translation): "Paper stated the trial was randomised and double blinded. Nevertheless, it only states that participants were divided into 2 equal groups. There is a suggestion that it may have been coded at a pharmacy but it's not explicit, so I am unable to ascertain the quality of allocation concealment".
Blinding of participants and personnel (performance bias)	Unclear risk	Available information was not clear.

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Amadeo 1990 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Available information was not clear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited participants were in the analysis.
Selective reporting (reporting bias)	Unclear risk	Result of primary outcome was not available.
Other bias	Low risk	No other obvious biases.

Anderson 1985

Methods	Randomised controlled trial. Women were randomised into 3 groups, method of randomisation not stated.
Participants	Pregnant women (20-38 years old) with constipation in their third trimester and no known medical or obstetric problems. Recruited from routine antenatal clinics in Cambridge, UK. The mean gestational age is 30.92 (28-36 weeks).
Interventions	After 2 weeks of baseline observation the women were randomly allocated into 3 groups for 2 weeks: Group A (n = 13) - 'Fibermed', 10 g corn-based biscuit; Group B (n = 14) - 23 g wheat bran; Group C (n = 13) - no intervention. We have put Group A and Group B together as dietary fibre supplementation group (n = 27) compared with no intervention group (n = 13).
Outcomes	Frequency of stools and a change to a softer stool consistency over 2 weeks of treatment.
Notes	Some participants were taking iron and vitamin supplements and symptomatic treatments for heartburn, but none altered their medications during the study.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly allocated into three groups''.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The fibre supplements could be eaten at any time of day, the corn-based biscuits either alone or with sweet or savoury spreads, the wheat bran mixed with cereal, casseroles or deserts''. Comment: no blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The fibre supplements could be eaten at any time of day, the corn-based biscuits either alone or with sweet or savoury spreads, the wheat bran mixed with cereal, casseroles or deserts''. Comment: no blinding.

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Anderson 1985 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes described in the method part were reported in the results.
Other bias	Low risk	Baseline characteristics among participants in the 3 groups were comparable. No other obvious biases.

Greenhalf 1973

Methods	Randomised controlled trial. Women randomised into 4 groups, method not stated.
Participants	Constipated women attending the antenatal clinic at Kingston Hospital, UK and constipated puerperal breast-feeding women delivered in the obstetric unit. 175 women recorded as being entered, but data only available for 140 (35 in each group).
Interventions	The participants were offered 1 of the 4 laxatives. There were 2 different stimulant laxatives (senokot and normax) and 2 different bulk-forming laxatives (normacol standard and normacol special). Senokot, 2 tablets daily, consists of 7 mg of standard senna (n = 35). Normax, 2 capsules a day, contains 60 mg of dioctyl sodium sulphosuccinate and 50 mg of dihydroxyanthraquinone (n = 35) . Normacol standard, 2 teaspoonfuls a day, contains sterculia B.P.C. and frangular B.P.C. (n = 35). Normacol special, 2 teaspoonfuls a day, contains sterculia B.P.C. (n = 35).
Outcomes	Improvement in constipation, abdominal discomfort, diarrhoea and women's satisfaction.
Notes	For the quantitative analysis, group 1 and 2 were combined as stimulant laxatives and groups 3 and 4 as bulk-forming laxatives. This review included only pregnant women.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization of laxative used was achieved by random distribution by the nurse in charge of the antenatal clinic".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The drugs did not have an identical appearance, flavour or taste".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited participants were in the analysis.
Selective reporting (reporting bias)	Low risk	All outcomes described in the method were reported in the result.

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Greenhalf 1973 *(Continued)*

Other bias	Low risk	No other obvious bias.

Gregersen 1985

Methods	Double-blind randomised trial in Copenhagen, Denmark. Feb 1980 - Aug 1981.
Participants	Pregnant women 20-36 weeks' gestation, with constipation. Outpatients.
Interventions	Arm 1: Dumovital fibre tablets (n =133) - 2 initial weeks with no tablets, 3rd week 3 per day, 4th week 6 per day, weeks 5-9 9 tablets per day. Arm 2: placebo tablets (n = 117) according to regimen above.
Outcomes	Number of bowel movements in a 14-day period.
Notes	This trial contributed no usable data to the review. Original publication in Danish, Jan 1995. Tables in the original Danish publication are in English.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described. Trial described as randomised and double blind.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial described as blinded. Blinding may have been achieved if tablets were similar in appearance. Women also took tablets in the community, so there would be little chance of coming across the alternate tablet.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes were self-reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	140 of 250 randomised failed to complete the study. Reasons for all women are stated, including side-effects of treatment (diarrhoea). However, these outcomes are only reported for women leaving the study, and so we did not use these data.
Selective reporting (reporting bias)	High risk	Primary outcome is reported, but side-effects reported only for women leaving the study.
Other bias	High risk	Data for primary outcome of number of bowel movements reported in graph form only with no averages per randomised group presented.

Characteristics of excluded studies *[ordered by study ID]*

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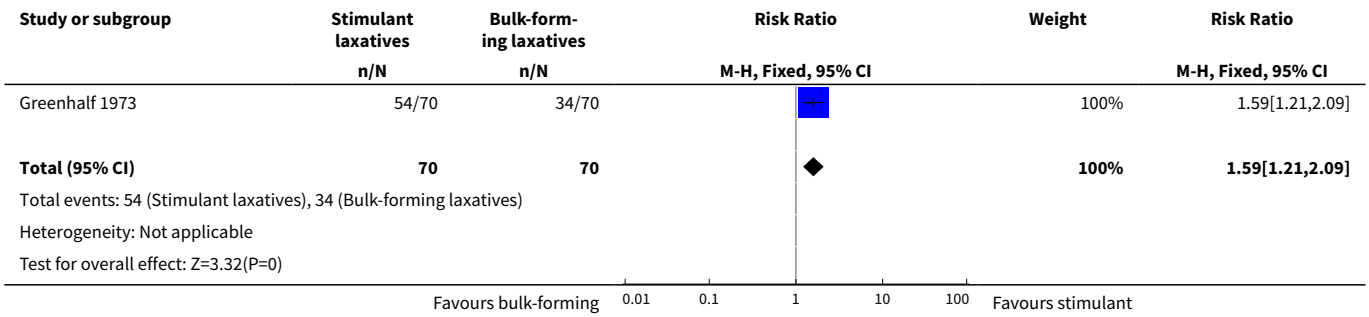
Study	Reason for exclusion
Browne 1957	Participants were not only pregnant women. Separate information for pregnant women only was not available.
Ghahramani 2013	This study did not examine treatment of constipation. The study investigated whether giving pregnant women Psyllium herbal laxative powder prevented constipation, haemorrhoids and anal fissure during pregnancy.

DATA AND ANALYSES

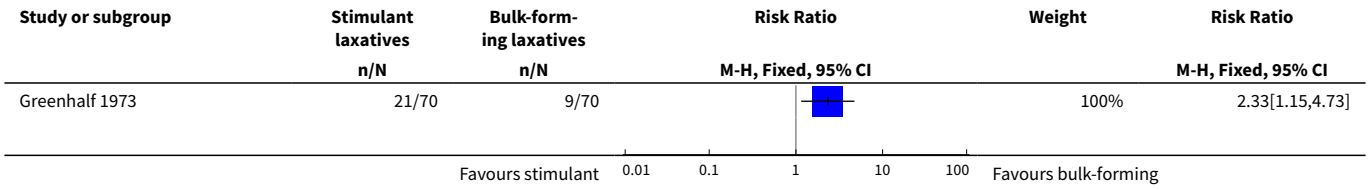
Comparison 1. Stimulant laxatives versus bulk-forming laxatives

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in constipation	1	140	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.21, 2.09]
2 Abdominal discomfort	1	140	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [1.15, 4.73]
3 Diarrhoea	1	140	Risk Ratio (M-H, Fixed, 95% CI)	4.5 [1.01, 20.09]
4 Women's satisfaction	1	140	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.77, 1.46]

Analysis 1.1. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 1 Improvement in constipation.



Analysis 1.2. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 2 Abdominal discomfort.



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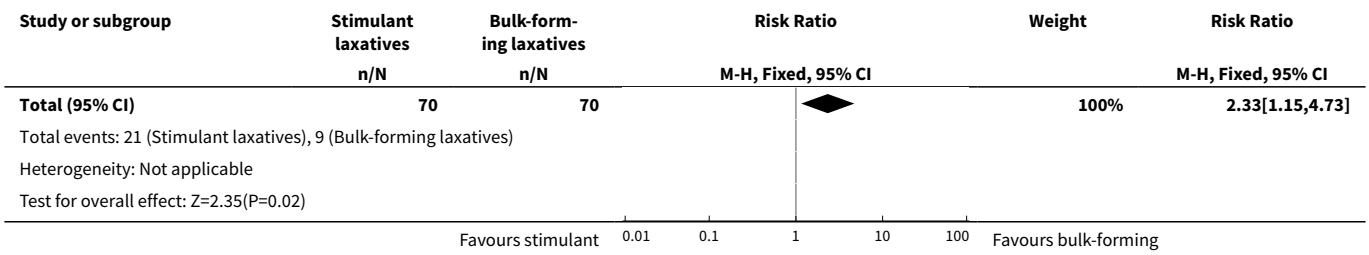
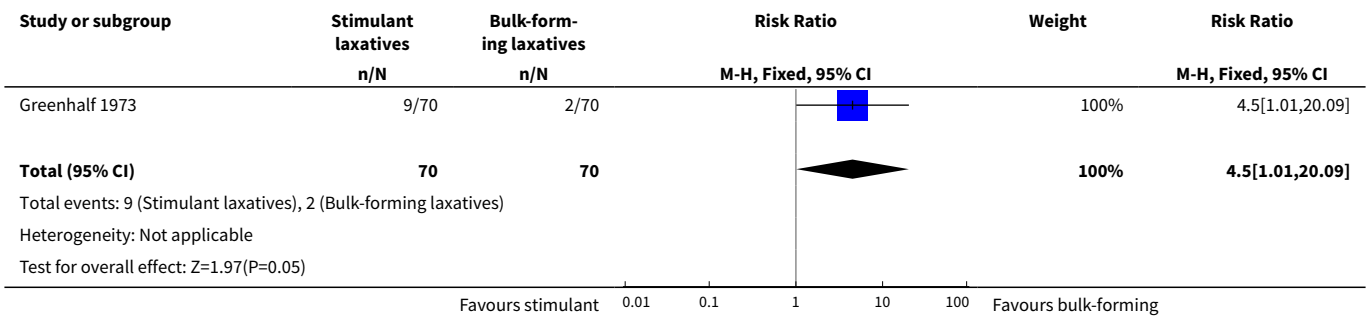
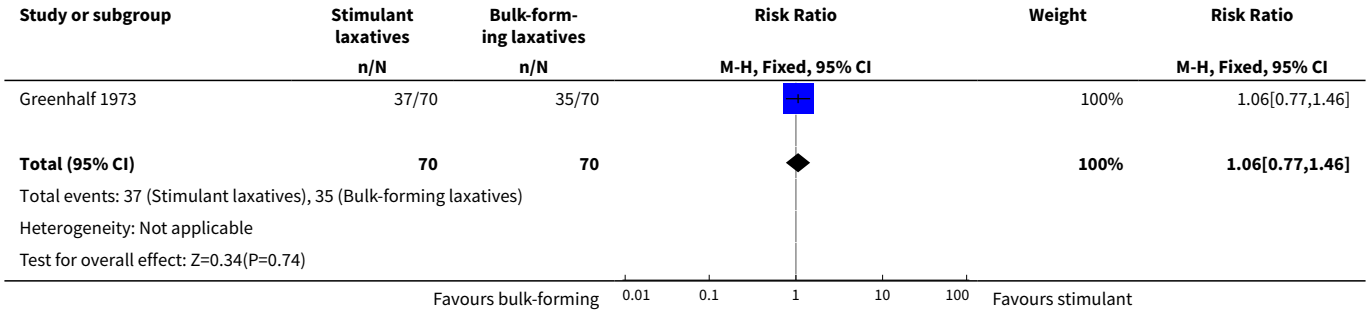


Analysis 1.3. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 3 Diarrhoea.



Analysis 1.4. Comparison 1 Stimulant laxatives versus bulk-forming laxatives, Outcome 4 Women's satisfaction.



Comparison 2. Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in constipation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Senokot	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.03, 2.26]
1.2 Normax	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [1.13, 2.41]
2 Abdominal discomfort	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

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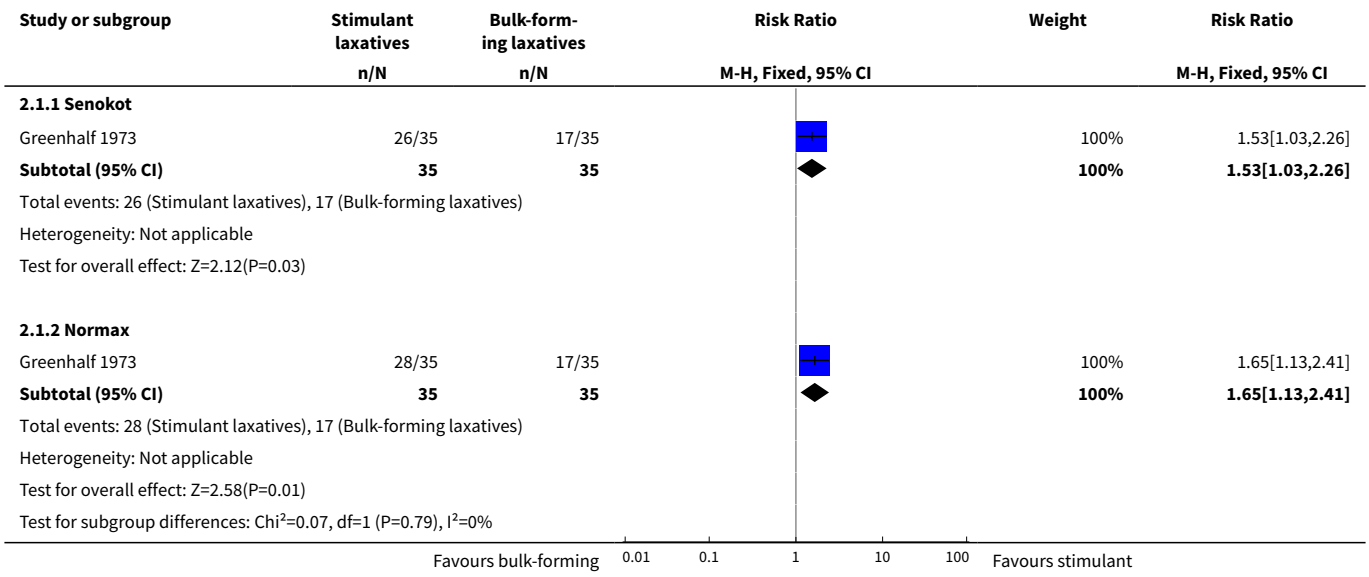
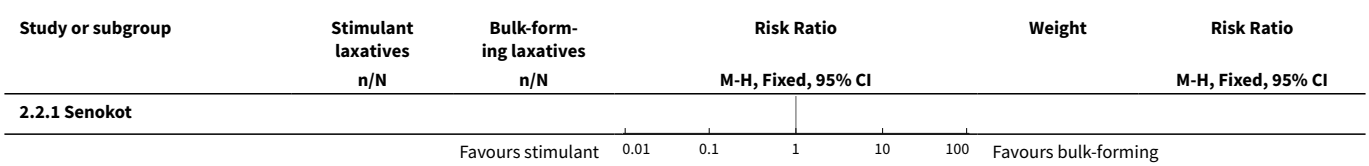
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Senokot	1	70	Risk Ratio (M-H, Fixed, 95% CI)	2.2 [0.85, 5.68]
2.2 Normax	1	70	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.87, 7.22]
3 Diarrhoea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Senokot	1	70	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.62, 40.64]
3.2 Normax	1	70	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.47, 34.02]
4 Women's satisfaction (rated as good or acceptable)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Senokot	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.62, 1.62]
4.2 Normax	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.72, 1.71]

Analysis 2.1. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 1 Improvement in constipation.



Analysis 2.2. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 2 Abdominal discomfort.



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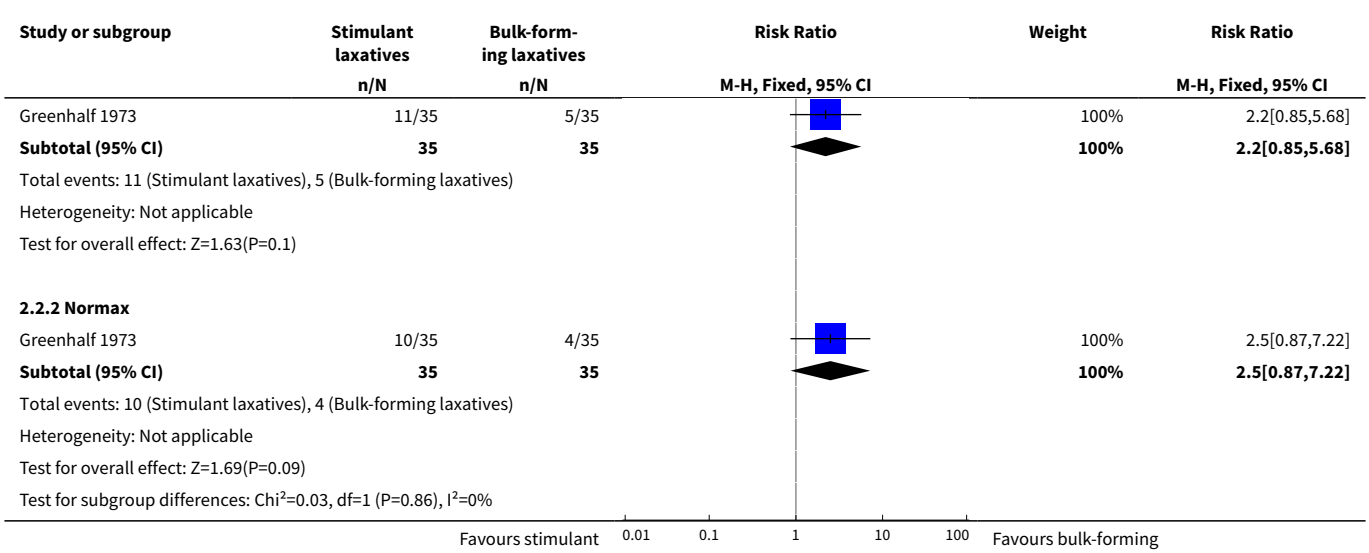
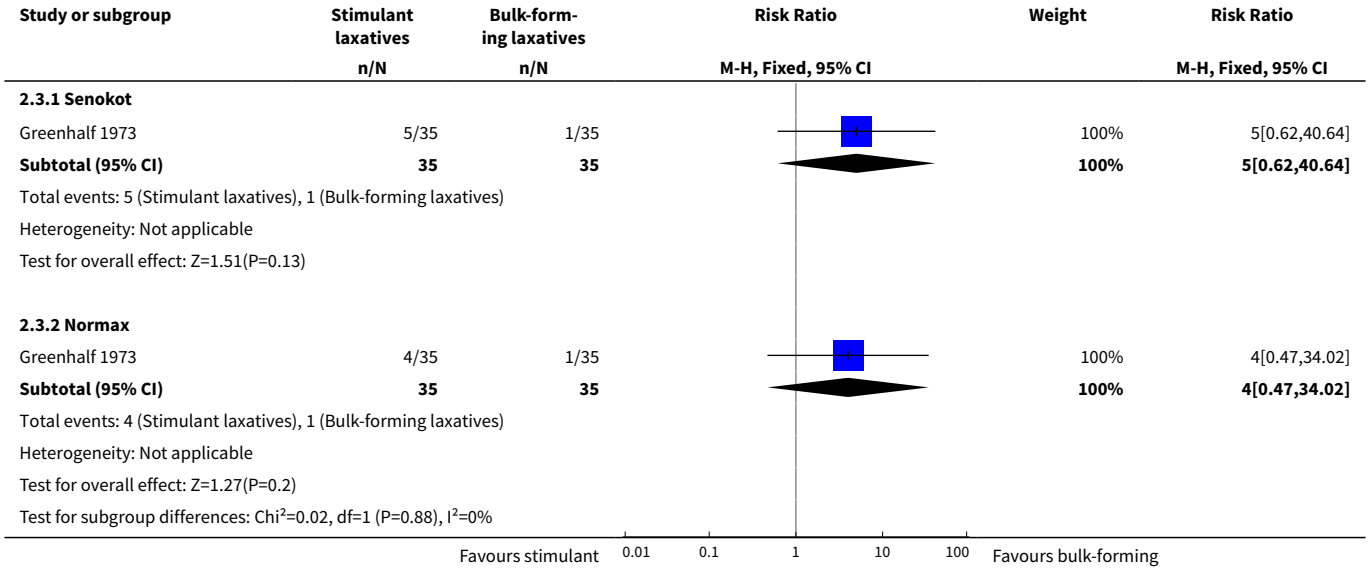
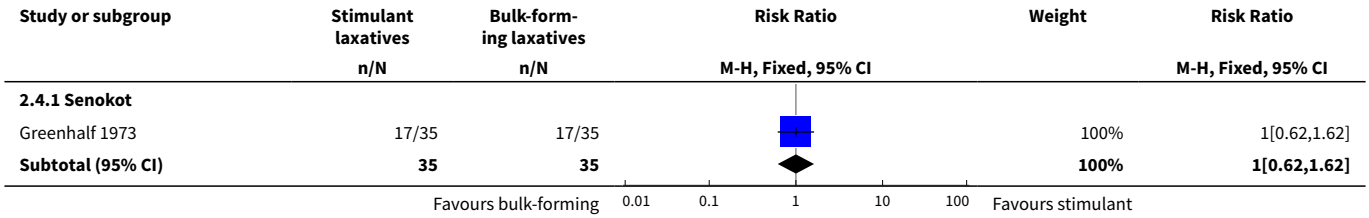


Analysis 2.3. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 3 Diarrhoea.



Analysis 2.4. Comparison 2 Stimulant laxatives versus bulk-forming laxatives (Sensitivity analysis: Senokot and Normax data separated), Outcome 4 Women's satisfaction (rated as good or acceptable).



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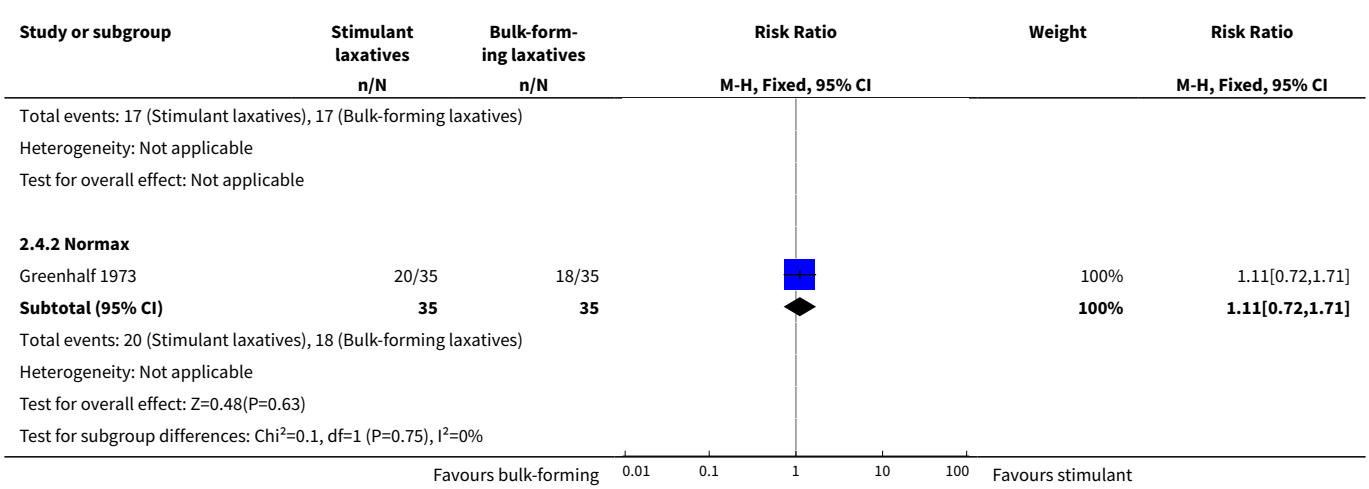
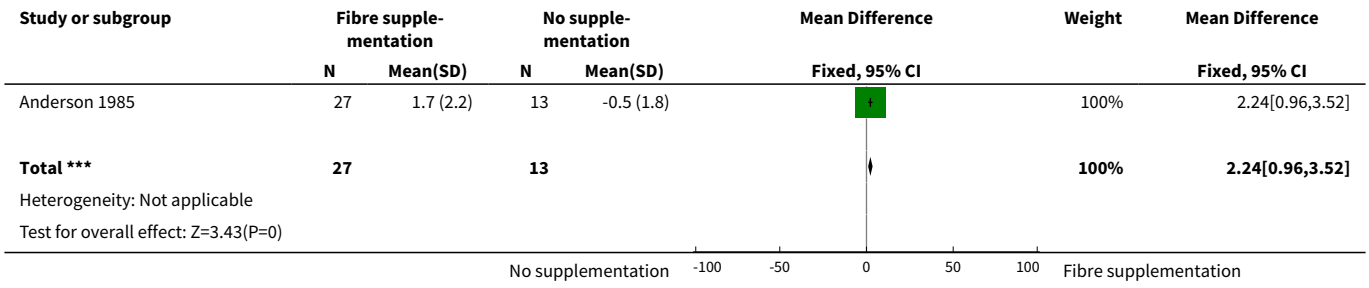


Comparison 3. Fibre supplementation versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of stools (per week)	1	40	Mean Difference (IV, Fixed, 95% CI)	2.24 [0.96, 3.52]

Analysis 3.1. Comparison 3 Fibre supplementation versus no intervention, Outcome 1 Frequency of stools (per week).



ADDITIONAL TABLES

Table 1. Percent change in stool consistency

	Fibermed	Bran	Untreated
Hard	-14	-11	-2
Normal	5	10	0
Loose	6	0	2

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Extracted from figure 2 of Anderson 1985.

APPENDICES

Appendix 1. Search terms

ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) (7 January 2015)

constipation AND pregnancy

WHAT'S NEW

Date	Event	Description
4 November 2015	Amended	We included one trial in our comparison of stimulation laxatives versus bulk-forming laxatives (comparison 1) - the trial contains four arms (two different bulk-forming laxatives and two different stimulant laxatives [Senokot and Normax]). It has come to our attention that Normax (dioctyl sodium sulphosuccinate and di-hydroxy anthraquinone) is no longer used for the treatment of constipation in pregnant women (and the package information advises that it should not be used during pregnancy or breast-feeding). We have highlighted this in the review and carried out a sensitivity analysis (comparison 2) with the data for Senokot and Normax presented separately.

CONTRIBUTIONS OF AUTHORS

Phassawan Rungsiprakarn developed the review. Malinee Laopaiboon, Pisake Lumbiganon and Ussanee Sangkomkamhang edited and commented on the review. Jeremy Pratt provided feedback and suggested edits in response to final editorial comments. All authors approved the final version for publication.

DECLARATIONS OF INTEREST

Phassawan Rungsiprakarn: none known.

Malinee Laopaiboon: none known.

Ussanee S Sangkomkamhang: none known.

Pisake Lumbiganon: none known.

Jeremy J Pratt: none known.

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Internal sources

- Faculty of Medicine, Khon Kaen University, Thailand.

  Logistical support
- Faculty of Public Health, Khon Kaen University, Thailand.

  Logistical support
- Thai Cochrane Network, Thailand.

  Technical support

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External sources

- Thailand Research Fund/Distinguished professor award, Thailand.

  Basic honorarium and travel expenses for contact person

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A new primary outcome has been added at the full review stage: improvement in constipation. This outcome was not prespecified in our published protocol (Rungsiprakarn 2014). The other prespecified primary outcomes (pain on defecation, frequency of stool, and consistency of stool) are components of constipation. It became obvious during the review process that studies report changes in symptoms in different ways, as such, to capture all data available, it was essential that the primary outcomes were altered. Furthermore, this broader banner encapsulates a more woman-centred understanding of constipation in pregnancy.

During the review process we found that all four potential included studies had unclear sequence generation, we were not clear whether they were randomised controlled trials (RCTs) or quasi-RCTs. We therefore added quasi-RCTs to the eligibility criteria.

In our comparison of stimulant laxatives versus bulk-forming laxatives (comparison 1) we included data from a trial with four treatment arms (two stimulant laxatives [Senokot and Normax] and two different bulk-forming laxatives). However, one of the stimulant laxatives, Normax (dioctyl sodium sulphosuccinate and dihydroxy anthraquinone) is no longer used for the treatment of constipation in pregnant women (and package information advises that it should not be used during pregnancy or breastfeeding). We therefore carried out a sensitivity analysis (not prespecified in our protocol) with the data for Senokot and Normax presented separately.

INDEX TERMS

Medical Subject Headings (MeSH)

Constipation [*therapy]; Dietary Fiber [*therapeutic use]; Laxatives [*therapeutic use]; Pregnancy Complications [*therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Pregnancy

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