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Surgical treatment of adhesion-related chronic abdominal and pelvic pain after gynaecological and general surgery: a systematic review and meta-analysis

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BACKGROUND: Chronic pain is a frequent post-operative complication, affecting ~20–40% of patients who have undergone surgery of the female genital or alimentary tract. Chronic pain is an important risk factor for diminished quality of life after surgery. Adhesions are frequently associated with chronic post-operative pain; however, surgical treatment of adhesion-related pain is controversial.

OBJECTIVE AND RATIONALE: The aim of this study was to investigate the efficacy and harms of surgical interventions for chronic post-operative pain attributable to adhesions.

SEARCH METHODS: A search was conducted using PubMed, EMBASE and CENTRAL, without restrictions pertaining to date, publication status or language. Randomized trials and cohort studies from all surgical interventions for chronic post-operative pain were considered eligible. Patients with a concomitant diagnosis that could cause chronic pain (e.g. endometriosis or inflammatory conditions) were excluded. Outcome measures were graded according to clinical relevance, with improvement of pain at long-term follow-up regarded as most clinically relevant.

OUTCOMES: A total of 4294 unique citations were identified, of which 13 studies met the criteria for inclusion. Two of the analysed studies were randomized trials, of which one had a low risk of bias. Only one trial, randomizing between laparoscopic adhesiolysis without an adhesion barrier and diagnostic laparoscopy, reported improvement of pain at long-term follow-up. In this trial, pain improved in 55.8% of patients after adhesiolysis and in 41.7% of patients in the control group; however, the difference was not significant (relative risk (RR) 1.34; 95% CI: 0.89–2.02). Most non-randomized studies had mid-length follow-up (6–12 months). In pooled analyses of trials and non-randomized studies, improvement of pain was reported in 72% of patients who underwent adhesiolysis (95% CI: 61–83%) at any follow-up longer than 3 months. The incidence of negative laparoscopies was 20% (95% CI: 10–30%). The overall incidence of complications following laparoscopic adhesiolysis was 4% (95% CI: 1–6%).

WIDER IMPLICATIONS: Laparoscopic adhesiolysis reduces pain from adhesions in ~70% of patients in the initial phase after treatment. However, there is little evidence for long-term efficacy of adhesiolysis for chronic pain. Other drawbacks of laparoscopic adhesiolysis are the high rate of negative laparoscopies and the risk of bowel injury. At present, there is little evidence to support routine use of adhesiolysis in treatment for chronic pain. New research is needed to investigate whether the results of adhesiolysis can be improved with new techniques for diagnosis and prevention of adhesion reformation.

Key words: chronic pain / adhesions / adhesiolysis / laparoscopy / laparotomy / adhesion prevention

Introduction

Chronic abdominal and pelvic pain diminish quality of life in millions of patients, with particularly high disease burden being among women. The prevalence of chronic pelvic pain in women is estimated to be between 5 and 25% (Latthe *et al.*, 2006; Ahangari, 2014), with treatment costs estimated at £158 million annually in the UK (Daniels and Khan, 2010). Previous surgery is a predominant cause of chronic abdominal or pelvic pain; incidence of chronic pain following surgery of the female genital or digestive tract is estimated at 20–40% (Sperber *et al.*, 2008; van der Wal *et al.*, 2011; Ten Broek *et al.*, 2013a). Chronic pain is one of the main risk factors for decreased quality of life after surgery (Bruce and Krukowski, 2006).

Multiple studies have found post-operative adhesions to be the primary pathological finding in chronic abdominal and pelvic pain. Adhesions are the sole pathological finding in 60% of cases of chronic post-operative pain, and in 45% of pelvic pain cases (Howard *et al.*, 2000; Ten Broek *et al.*, 2013a). Further, a body of evidence exists supporting a causal relationship between adhesions and chronic pain. Chronic pain has been found to develop following elective gynaecological surgery for non-painful conditions, without relation to irritable bowel syndrome (Sperber *et al.*, 2008). Adhesion barriers have been shown to reduce functional abdominal complaints, including pain, at long-term follow-up (van der Wal *et al.*, 2011). Touching of adhesions has been found to precipitate pain in a pain-mapping experiment in conscious women (Howard *et al.*, 2000; Demco, 2004), consistent with findings that nerve fibres capable of processing pain stimuli exist within adhesions (Sulaiman *et al.*, 2001). Reformation of adhesions has been linked to relapse of pain after adhesiolysis (Steege, 1994; Nezhat *et al.*, 2000). Nonetheless, many physicians continue to reject the notion of the causality of adhesions in development of chronic pain.

While substantial evidence links adhesions and chronic pelvic pain, studies of adhesiolysis in the setting of post-operative chronic abdominal pain have yielded mixed results. Initial studies reported symptomatic improvement in greater than 80% of patients who underwent adhesiolysis (Fayez and Clark, 1994; Hallfeldt *et al.*, 1995). However, in a high-quality randomized trial with long-term follow-up, while 56% of patients reported improvement of pain at 1 year of follow-up after laparoscopic adhesiolysis, this represented a non-significant difference from the 42% improvement seen in the diagnostic laparoscopy control group (Swank *et al.*, 2003). The study authors explained these results by attributing a placebo effect to the invasiveness of the control procedure (Kaptchuk *et al.*, 2000; Swank *et al.*, 2003). An alternative explanation is that filmy adhesions were disrupted by the pneumoperitoneum and handling of the tissue for inspection. Such filmy adhesions attached to the parietal peritoneum, or to organs such as the bladder and uterus, were the most painful in the conscious pain-mapping experiment of Demco *et al.* (Demco, 2004). It is also notable that this study did not make use of adhesion barriers to control for reformation of adhesions following adhesiolysis.

Now, more than a decade after the landmark trial of Swank *et al.*, recent advances in the diagnosis and treatment of adhesion-related chronic pain hold the potential to improve the management of this debilitating condition (Ten Broek *et al.*, 2016). Non-invasive diagnosis and mapping of adhesions is now possible with the use of novel imaging techniques such as cine-MRI (Lienemann *et al.*, 2000; Randall *et al.*, 2016). Additionally, there is mounting evidence concerning the efficacy of adhesion barriers in preventing adhesion formation and reformation (Ten Broek *et al.*, 2014a). These

improvements in practice are complimented by an improved understanding of pain processing and sensitization in chronic visceral pain disorders (Bouwense et al., 2013).

Despite these recent advancements, the overall efficacy of adhesiolysis in patients with chronic pain attributable to adhesions remains a topic of considerable debate. It is additionally unclear whether adhesiolysis results can be improved through the use of adhesion barriers and new diagnostic imaging techniques (Ten Broek et al., 2014a, 2016). The purpose of this systematic review is to investigate the efficacy and harms of adhesiolysis with or without use of an adhesion barrier for treatment of chronic post-operative pain attributable to adhesions. Secondarily, we assess the dissemination of new insights in clinical practice concerning the diagnosis and treatment of adhesion-related pain.

Methods

This systematic review focused on randomized trials and cohort studies evaluating patients with adhesion-related chronic post-operative pain, who were treated by adhesiolysis with or without use of an adhesion barrier. Inclusion criteria were pain and adhesions from prior surgery, chronic pain of at least 3 months' duration, and a minimum follow-up interval of 3 months. Exclusion criteria were patients with a concomitant diagnosis and studies not presenting original data. Studies that included patients with adhesions from different aetiologies (e.g. endometriosis and inflammatory disease) were considered eligible only if data from the subgroup of patients with post-operative adhesions could be extracted separately. The full review protocol was registered with PROSPERO under registration number CRD 42015024902. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in reporting the results.

Search

Searches included the following MeSH descriptors: 'abdominal pain', 'chronic pain', 'laparotomy', 'laparoscopy', 'abdomen/surgery', 'postoperative complications', 'tissue adhesions', 'pain, postoperative'. Searches were performed in PubMed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL). A detailed description of our search technique can be found in Supplementary Table I. No language or date restrictions were applied. The search was performed in March 2016. Reference lists of identified trials were additionally searched to identify additional trials, including those published in 'grey' literature. Supplemental searches were performed to find relevant grey literature and unpublished trials (Supplementary Table I).

Risk of systematic error (bias)

The risk of systematic error was assessed in all analysed studies using the Cochrane Collaboration's tool for bias risk assessment (Higgins and Green, 2011). Six components associated with a risk of bias were evaluated: generation of the allocation sequence, allocation concealment, blinding of outcome assessors, selective outcome reporting, incomplete follow-up and other potential sources of bias. Studies with a low risk for all six bias components were designated as 'low risk of bias studies'. Studies in which one or more of the six bias components were assessed as being unclear or as having high risk of bias were defined to be 'high risk of bias studies'. Since blinding the surgeon is impossible, surgical studies that applied blinding to patients and outcome assessors were considered to have a low risk of bias in the blinding domain.

Data extraction

Two reviewers independently extracted and checked the data. For relevant articles, we extracted information on study design, including the use of non-invasive techniques for diagnosis of adhesions, use of adhesion barriers, characteristics, number of participants and outcomes reported. Outcome measures extracted from the literature were graded according to clinical relevance ('critical for decision-making', 'important for decision-making' or 'of limited importance') as suggested by the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) working group (Guyatt et al., 2008). Efficacy outcomes defined as 'critical for decision-making' were improvement of pain at long-term follow-up (1 year or longer), and improved quality of life measured by a validated score at long-term follow-up (1 year or longer). Efficacy outcomes graded as 'important for decision-making' were improvement of pain at any follow-up (3 months or longer), improved quality of life at any follow-up (3 months or longer), pain scores at any follow-up (3 months or longer) and return to daily activity or work. The efficacy outcome 'of limited importance' was patients' recommendation of treatment to others.

Harm outcomes defined as 'critical for decision-making' were mortality, bowel injuries, complications resulting in life-threatening situations, ICU admission, reoperation and permanent disability. Harm outcomes defined as 'important for decision-making' were overall incidence of complications and negative diagnostic laparoscopy.

When outcome measures were registered during several time intervals within the same study, we used the data from the longest follow-up period.

Data analysis

We used the inverse variance method of pooling prevalence and continuous data. The Mantel–Haenszel method was applied for the pooling of dichotomous data, with results presented as the relative risk (RR) with 95% CI. A P-value of <0.05 was considered to be statistically significant. Heterogeneity was explored using I^2 tests, as recommended by the Cochrane Handbook for Systematic Reviews of Intervention. An I^2 value between 50 and 75% was defined as substantial heterogeneity, and an I^2 value of 75% or greater was defined as considerable heterogeneity. A fixed-effects model was applied for the meta-analysis. In the presence of significant statistical heterogeneity, a random-effects model was used. Subgroups analyses were made for the type of intervention (adhesion barriers vs. no adhesion barrier), study type (randomized trial vs. cohort), quality of study (low risk of bias vs. high risk of bias), setting (general surgery vs. gynaecology), population (female patients vs. mixed cohort) and location of pain (pelvic pain vs. other or mixed).

Data were analysed using Review Manager 5.0 (RevMan; Version 5.1; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2011) and R version 2.12.0.

Results

Search results

Figure 1 depicts the number of studies identified, reviewed and selected, as well as the reasons for exclusion. A total of 4294 unique citations were retrieved, of which 91 were considered to be potentially eligible. After full-text review, 78 papers were excluded. Thus, a total of 13 studies involving 533 patients were included for analysis.

Characteristics of included studies

Characteristics of included studies are listed in Table I. Two randomized trials were included, one each in the subgroup with and without

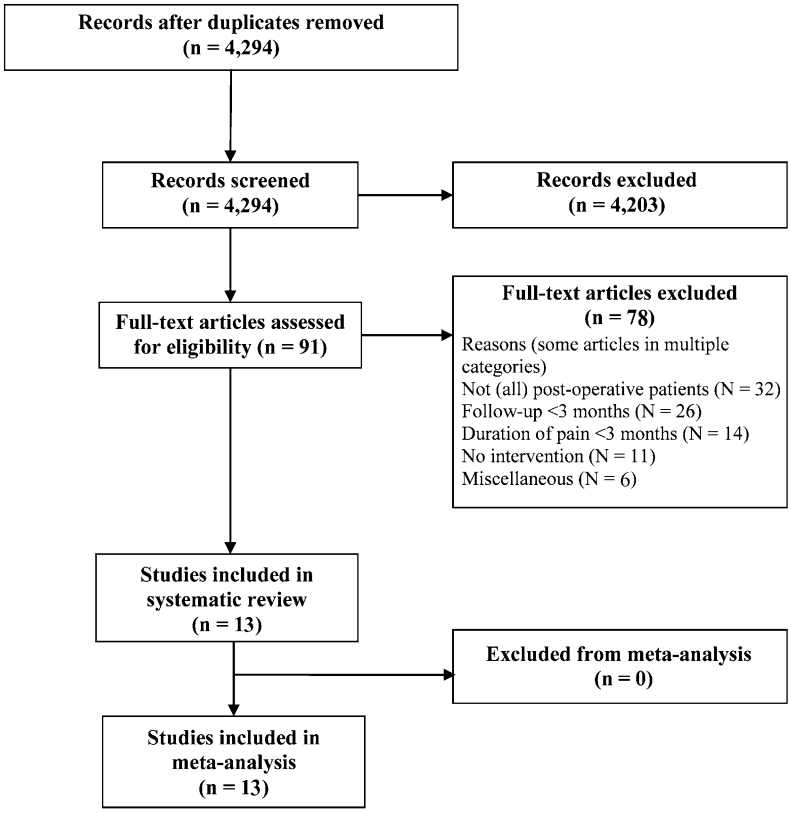

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of search strategy.

adhesion barriers (Swank *et al.*, 2003; Cheong *et al.*, 2014a). In all studies, adhesiolysis was performed through laparoscopy. Adhesion barriers were used in three studies (Nezhat *et al.*, 2000; Khaitan *et al.*, 2003; Cheong *et al.*, 2014a). In 10 studies, no adhesion barriers were applied. In three of the studies without adhesion barrier (30%), other techniques were applied with the intention to reduce adhesion reformation. These other techniques were fixation of the uterus in one study, and installation of Ringer's lactate in one study (Goldstein *et al.*, 1979; Fayez and Clark, 1994). The third study employed a more complex method to prevent reformation, with performance of interval outpatient laparoscopies through Tenckhoff catheters that were left in place between procedures, and through which Ringer's lactate was also infused (Steege, 1994).

The pre-treatment diagnosis of adhesions was generally made based on a history of previous surgery followed by physical examination, and occasional imaging studies to rule out alternative diagnoses. One study only included patients with documented adhesions by a previous intervention (Steege, 1994). In the two randomized trials, randomization was performed after confirmation of adhesions by diagnostic laparoscopy (Swank *et al.*, 2003; Cheong *et al.*, 2014a). None of the identified studies employed non-invasive techniques for diagnosing adhesions, such as visceral slide on ultrasound or cine-MRI, as part of the work-up for patients.

In five papers, all included patients were female (Arndt and Creutzfeldt, 1976; Goldstein *et al.*, 1979; Steege and Stout, 1991; Fayez and Clark, 1994; Nezhat *et al.*, 2000; Cheong *et al.*, 2014a). The studies with mixed populations also had a strong female predominance, with the percentage of women near 90% (Table I). The location of pain was pelvic in four studies (Goldstein *et al.*, 1979; Steege and Stout, 1991; Nezhat *et al.*, 2000; Cheong *et al.*, 2014a). In most studies, the exact location was not reported; cohorts often seemed to be a mix of patients with pain in pelvic area and patients with pain in other abdominal quadrants. In both the gynaecological and general surgery studies, the majority of patients had a mixed history of both previous gynaecological and general surgery interventions (Fayez and Clark, 1994; Hallfeldt *et al.*, 1995; Nezhat *et al.*, 2000; Khaitan *et al.*, 2003; Swank *et al.*, 2003; Dunker *et al.*, 2004).

Results for the risk of bias assessment are presented in Table II. Only one of the randomized trials had a low risk of bias (Swank *et al.*, 2003).

Results of adhesiolysis without adhesion barrier

Results of our full analysis are summarized in Table III. One trial randomized between adhesiolysis without adhesion barrier or diagnostic laparoscopy (Swank *et al.*, 2003). At long-term follow-up of 1 year, improvement of pain was reported in 55.8% of patients in the adhesiolysis group and 41.7% of patients in the control group. The difference between these groups was not significant (RR 1.34; 95% CI: 0.89–2.02; Fig. 2). Difference in quality of life (measured by Short Form (SF)-36 pain domain) was also not significant, with a mean difference of 1.30 (95% CI: −7.71–10.31). Also pain scores did not significantly differ (mean difference: −1.60; 95% CI: −11.44–8.24).

Table I Characteristics of included studies.

Study	Patients	Location of pain/adhesions	Surgical history[†]	Diagnostic work-up	Intervention	Follow-up	Outcome measures
Laparoscopic adhesiolysis with anti-adhesion barrier							
Cheong *et al.* (2014a)	78 patients (gynaecology) 100% female	Pelvic	Type: not reported Pain: 40%	History taking, physical examination, diagnostic laparoscopy	RCT: adhesiolysis vs. diagnostic laparoscopy Anti-adhesion barrier: Icodextrin 4% solution	6 months	Improvement of pain Pain scores QOL (SF-12 EHP-30) Complications Negative laparoscopies
Khaitan *et al.* (2003)	19 patients (general surgery) 89.5% female	15.8% only pelvic 84.2% both pelvic and abdominal	Type: 63.2% mixed 15.8% gynaecology 10.5% general surgery Pain: not reported	History taking, physical examination, diagnostic laparoscopy	Lysis and placement of hyaluronic acid- carboxy methylcellulose membrane	4.5 months (range 1–32)	Improvement of pain Complications
Nezhat *et al.* (2000)	48 patients (gynaecology)100% female	Pelvic	Mixed*, including hysterectomy in allPain: not reported	History taking, physical examination, diagnostic laparoscopy	Lysis using laser Regenerated oxidized cellulose barrier	2–8 weeks, 6–12 months and 2–5 years	Improvement of pain Complications
Laparoscopic adhesiolysis without anti-adhesion barrier							
Arndt and Creutzfeldt (1976)	7 patients (general surgery) 100% female	Abdominal	Type: 28.6% mixed 71.4% general surgery Pain: 14.2%	History taking, physical examination, diagnostic laparoscopy	Sharp dissection of adhesions	6–18 months	Improvement of pain
Bremers *et al.* (2000)	12 patients (general surgery) 91.7% female	Not reported	Type: not reported Pain: not reported	History taking, physical examination, imaging on indication, diagnostic laparoscopy	Sharp or diathermic dissection	3, 6 and 12 months	QOL (GIQLI MOS-SF36) Complications Negative laparoscopies
Dunker *et al.* (2004)	23 patients (general surgery) 95.7% female	Abdominal	Type: 73.9% mixed 22.7% gynaecology 4.3% general surgery Pain: not reported	History taking, physical examination, diagnostic laparoscopy	Lysis not specified	3, 6, 12, 24 months with second-look laparoscopy	Improvement of pain QOL (GIQLI MOS-SF36) Complications Negative laparoscopies
Fayez and Clark (1994)	198 patients (gynaecology) 100% female	Abdominal and pelvic	Type: mixed, but majority only gynaecological Pain: not reported	History taking, physical examination, imaging on indication, diagnostic laparoscopy	Lysis using laser Ringer's Lactate	12 months	Improvement of pain Return to daily activity Complications Negative laparoscopies
Goldstein *et al.* (1979)	26 adolescents patients (gynaecology)	Pelvic pain	Type: mixed 7.7% Gynaecology 26.9% General surgery 65.4% Pain: ≤26.9%	History taking, physical examination, diagnostic laparoscopy	Lysis with scissors and fixation of uterus	Range 1–51 months	Improvement of pain Negative laparoscopies
Hallfeldt *et al.* (1995)	16 patients (general surgery) 93.8% female	Abdominal	Type: 25.0% mixed 62.5% general surgery 12.5% gynaecologic Pain: 12.5%	History taking, physical examination and imaging on indication, diagnostic laparoscopy	Scissors with diathermia	9 months (range 4–18)	Improvement of pain Pain scores Recommendation Complications Negative laparoscopies
Kleinhaus (1984)	2 patients (general surgery) 100% female	Abdominal	50.0% mixed 50.0% general surgery Pain: 0%	Diagnostic laparoscopy	Lysis of adhesions	6 and 12 months	Improvement of pain
Steege (1994)	8 patients (gynaecology)	Pelvic	Type: 100% had a gynaecological	At least one previous adhesiolysis attempt	4× Lysis using laser through Tecnkhoff catheter	7–11 months	Improvement of pain

	100% female		intervention—general surgery not reported Pain: not reported	Ringer's Lactate			
Swank *et al.* (2003)	109 patients (general surgery) 87% female	Not reported	Type: Mixed, 50% involved a gynaecological intervention Pain: not reported	History taking, physical examination and imaging on indication, diagnostic laparoscopy	Ultrasonic dissection	12 months	Improvement of pain Pain scores QOL (MOS-SF36) Complications Negative laparoscopies
Tschudi *et al.* (1993)	15 patients (general surgery) % female unclear	Not reported	Type: not reported Pain: not reported	Diagnostic laparoscopy	Lysis not specified	18.3 months (range 5–36)	Improvement of pain

RCT, randomized control trial; GIQLI, Gastro-intestinal Quality of Life Index; QOL, Quality of Life.
[1]Summary of surgical history includes: (1) type of previous interventions i.e. percentage of patients with history of gynaecological or general surgery, or mixed (both gynaecological and general) surgery and (2) percentage of patients in whom indication of index surgery was chronic pain.

Return to daily activity and recommendation of treatment were not reported.

There was no mortality reported in this trial. Two bowel perforations occurred in the adhesiolysis group compared with none in the diagnostic laparoscopy group (RR 4.62; 95% CI: 0.23–93.9). Overall six complications were registered in five patients, all in the adhesiolysis group (RR 10.2; 95% CI: 0.58–179.2). The incidence of negative diagnostic laparoscopies was 8% (95% CI: 3–13%).

In addition to the trial detailed above, eight non-comparative cohorts of adhesiolysis without adhesion barrier were identified (Arndt and Creutzfeldt, 1976;Goldstein *et al.*, 1979; Tschudi *et al.*, 1993; Fayez and Clark, 1994; Steege, 1994; Hallfeldt *et al.*, 1995; Bremers *et al.*, 2000; Dunker *et al.*, 2004). With respect to outcomes 'critical' for decision-making, five studies reported improvement of pain at long-term follow-up. The pooled incidence of long-term improvement was 68% (95% CI: 48–88%) in 249 patients. Quality of life at long-term follow-up, measured with the Gastro-intestinal Quality of Life Index (GIQLI) score (ranging from 0 to 144), was 92.7 (95% CI: 47.7–137.7) in four patients; using the overall SF-36 (ranging from 0 to 100) the score was 53.2 (95% CI: 31.2–75.3) in 52 patients; using only the pain domain from the SF-36 pain, the score was 51 (95% CI: 44.5–57.5).

Regarding outcomes 'important' for decision-making, improvement of pain at any follow-up was 74% (95% CI: 60–88%) in pooled analyses of nine studies comprising 291 patients (Fig. 3). Pain scores were also significantly decreased compared with baseline following laparoscopic adhesiolysis (Table III). One study reported return to daily activities in all 156 patients. On outcomes of 'limited' importance, one study reported that 69% (95% CI: 46–91%) of patients would recommend laparoscopic adhesiolysis to other patients with chronic pain.

Regarding harm outcomes 'critical' for decision-making, five studies reported no peri-operative mortality. A total of three bowel injuries occurred in 307 patients who underwent adhesiolysis or diagnostic laparoscopy. For harm outcomes 'important' for decision-making, the incidence of complications following laparoscopic adhesiolysis was 3% (95% CI: 0–6%). The incidence of negative laparoscopy was 16% (95% CI: 6–26%).

Results of adhesiolysis with adhesion barrier

There was one trial, randomizing between adhesiolysis with adhesion barrier and diagnostic laparoscopy (Cheong *et al.*, 2014a). Follow-up in this trial was limited to 6 months, thus no benefit outcomes graded 'critical' for decision-making were reported. Pain had improved in 61.5% of patients undergoing adhesiolysis at 6 months of follow-up compared with 26.7% in the control group. The difference was not significant, RR 2.31 (95% CI 0.90–5.92; Fig. 2). SF-12 pain domain scores at follow-up were significantly better in the group treated by laparoscopic adhesiolysis, with a mean difference of 26.2 (5.93–46.47). The SF-12 emotional domain did not differ significantly between groups (mean difference 6.00; −13.12–25.12). Pain scores, as measured by Visual Analogue Score (VAS), did not significantly differ between laparoscopic adhesiolysis with an adhesion barrier and diagnostic laparoscopy (mean difference: −8.2; 95% CI: −22.19–11.79).

Regarding the 'harm' outcomes, there was no mortality and no bowel injuries reported in this trial. There were also no other

Table II Risk of bias assessment using the Cochrane Collaboration Tool.

Study	Adequate sequence generation	Allocation concealment	Blinding (participant)	Blinding (observer)	Adequate reporting on loss to follow-up	Free of reporting bias	Free of other bias
Arndt and Creutzfeldt (1976)	No	No	No	No	No	Yes	Unknown
Bremers *et al.* (2000)	No	No	No	No	No	Yes	Unknown
Cheong *et al.* (2014a)	Yes	Yes	Yes	Yes	Yes	No	Yes
Dunker *et al.* (2004)	No	No	No	No	No	Yes	Unknown
Fayez and Clark (1994)	No	No	No	No	Unknown	Yes	Unknown
Goldstein *et al.* (1979)	No	No	No	No	Unknown	No	Unknown
Hallfeldt *et al.* (1995)	No	No	No	No	Yes	Yes	Unknown
Khaitan *et al.* (2003)	No	No	No	No	Yes	Yes	Yes
Kleinhaus (1984)	No	No	No	No	Yes	No	Yes
Nezhat *et al.* (2000)	No	No	No	No	Unknown	Yes	Unknown
Steege (1994)	No	No	No	No	Unknown	Unknown	Unknown
Swank *et al.* (2003)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tschudi *et al.* (1993)	No	No	No	No	Yes	Yes	Unknown

complications. The incidence of negative diagnostic laparoscopies was 36% (95% CI: 25–47%).

Two additional non-randomized studies reported on the efficacy of adhesiolysis with an adhesion barrier (Nezhat *et al.*, 2000; Khaitan *et al.*, 2003). Long-term improvement was reported in 67% (95% CI: 49–84%) of 27 patients in one study. Long-term quality of life was not reported. In three studies evaluating adhesiolysis without a barrier, improvement at any follow-up was reported in 66% (95% CI: 56–75%) of 59 patients (Fig. 3). Quality of life and pain scores were only reported in the trial of Cheong *et al.* as described above. Return to daily activity and recommendation of treatment were not reported.

Regarding harm outcomes 'critical' for decision-making, three studies reported no peri-operative mortality. A total of four bowel injuries occurred in 117 patients who underwent adhesiolysis or diagnostic laparoscopy. Further, Nezhat reported that two patients who returned for repeat adhesiolysis sustained a bowel injury during the reoperation (Nezhat *et al.*, 2000). Enterocutaneous fistula, an additional severe complication, was reported in two patients (Khaitan *et al.*, 2003). For harm outcomes 'important' for decision-making, the incidence of complications following laparoscopic adhesiolysis was 6% (95% CI: 0–11%). The incidence of negative laparoscopy was 36% (95% CI: 25–47%).

Subgroup analysis

The incidence of negative laparoscopies was significantly higher in gynaecological studies compared with general surgery studies: 31% (95% CI: 18–44%) vs. 8% (95% CI: 3–12%) or when comparing cohorts with pelvic pain with cohorts of mixed or abdominal pain: 37% (95% CI: 28–47%) vs. 12 % (95% CI: 3–21%) (Supplementary Figs 1 and 2). The incidence of bowel injuries and complications was higher in general surgery studies compared with gynaecological studies, although the difference was not significant (bowel injury, 2% [95% CI: 0–5%] vs. 1% [95% CI: 0–2%] (Supplementary Fig. 3); complications, 6% [95% CI: 2–10%] vs. 2% [95% CI: 0–5%] (Supplementary Fig. 4)). Further subgroup analyses yielded no clinically relevant differences.

Discussion

Summary of evidence

Laparoscopic adhesiolysis reduces chronic post-operative pain in ~70% of patients at a follow-up of any length, and significantly reduces VASs. However, the currently available evidence of long-term efficacy is insufficient and the results from randomized trials are equivocal. The only high-quality randomized trial conducted thus far found no difference in improvement of pain when comparing between patients who underwent laparoscopic adhesiolysis and those who received diagnostic laparoscopy. Morbidity from complications of adhesiolysis occurred in 4% of patients, with no reported mortality. New techniques for non-invasive diagnosis of adhesions have not been applied in any studies thus far, and adhesion barriers have only been used in a distinct minority of patients.

Strengths and limitations of the review

The present study is the first systematic review dedicated to treatment of chronic pain secondary to post-operative adhesions. We included both cohorts of gynaecological surgery and cohorts in which all patients were female, as well as general surgery cohorts with a mixture of female and male patients. Further, we also included cohorts dedicated only to patients with pelvic pain as well as cohorts that included patients with pain in other quadrants of the abdomen. We deliberately included these different cohorts, because we believe peritoneal adhesions should be considered and managed as a single entity whether occurring in the pelvis or in other parts of the abdomen. The mixed cohorts comprised 90% female patients. The few male patients seem to have little impact on the overall results of our analysis. Results in the various subgroup analyses were comparable, indicating that adhesion-related pain indeed responds equally effective to adhesiolysis whether located in the pelvis or elsewhere in the abdomen. The only difference in gynaecological cohorts and cohorts dedicated to pelvic pain on the one hand and the

Table III Tabular summary from the results of full analyses.

Outcome	Grade	Randomized trials	Overall studies
Benefit			
Improvement of pain at long-term follow-up	⊕⊕⊕	1 study—100 patients (LA− vs. DL): RR 1.34 (0.89–2.02)	1 study—27 patients (LA+): Portion: 67% (49–84%) 5 studies—249 patients (LA−): Portion: 68% (48–88%)
QOL at long-term follow-up	⊕⊕⊕	1 study—98 patients (LA− vs. DL) MD: 1.30 (−7.71–10.31)	2 studies—56 patients (LA−) GIQLI (4 patients): 92.7 (47.7–137.7) SF-36 (5 patients): 53.2 (31.2–75.3) SF-36 pain domain —102 patients: 51 (44.5–57.5)
Improvement of pain at intermediate or long-term	⊕⊕	1 study—28 patients (LA+ vs. DL): RR 2.31 (0.90–5.92) 1 study—100 patients (LA+ vs. DL): RR 1.34 (0.89–2.02) Overall LA vs. DL: RR 1.49 (1.02–2.17)	3 study—54 patients (LA+): Portion: 69% (57–81%) 9 Studies—291 patients (LA−): Portion: 74% (60–88%) overall LA: 73% (62–84%)
QOL at intermediate or long-term	⊕⊕	1 study—43 patients (LA+ vs. DL) SF-12 pain domain: MD: 26.20 (5.93–46.47) SF-12 emotional domain: MD: 6.00 (−13.12–25.12) 1 study—98 patients (LA− vs. DL) SF-36 pain domain: MD: 1.30 (−7.71–10.31)	1 study—23 patients (LA+): SF-12 pain domain: 81.3 (75.8–86.8) SF-12 physical domain: 70.9 (57.9–83.8) 2 studies—56 patients (LA−) GIQLI (4 patients): 92.7 (47.7–137.7) SF-36 (5 patients): 53.2 (31.2–75.3) SF-36 pain domain —102 patients: 51 (44.5–57.5)
Pain score	⊕⊕	1 study—43 patients (LA+ vs. DL) MD: −8.20 (−22.19–11.79) 1 study—100 patients (LA+ vs. DL):MD: −1.60 (−11.44–8.24)	Change in VAS between baseline and follow-up 1 study—23 patients (LA+): −2.62 (−3.09 to −2.15) 2 studies—68 patients (LA−): −3.29 (−6.38 to −0.20)
Return to daily activity	⊕⊕	NA	1 study—156 patients (LA−): 100% return to daily activity
Recommendation of treatment	⊕	NA	1 study—16 patients (LA−): Portion: 69% (46–91%)
Harm			
Mortality	⊕⊕⊕	1 study—43 patients (LA+ vs. DL)—No mortality reported 1 study—100 patients (LA+ vs. DL)—No mortality reported	3 Studies—222 patients (LA+)—No mortality reported 5 Study—195 patients (LA+)—No mortality reported
Bowel injuries	⊕⊕⊕	1 study—43 patients (LA+ vs. DL)—No bowel injuries 1 study—100 patients (LA+ vs. DL) RR 4.62 (0.23, 93.9)	3 studies—117 patients (LA+): 4 bowel injuries 5% (0–15%) 5 studies—307 patients (LA−): 3 bowel injuries 1% (0–2%)
Severe complications (life-threatening, ICU admission, reoperation or permanent disability)	⊕⊕⊕	1 study—43 patients (LA+ vs. DL)—No severe complications	1 study—50 patients (LA+): No severe injuries 6 studies—274 patients (LA−): 1% (0–2%)
Overall incidence of complications	⊕⊕	1 study—43 patients (LA+ vs. DL)—No complications reported 1 study—100 patients (LA+ vs. DL)—RR: 10.2 (0.6–179.2)	3 studies—117 patients (LA+): 6% (0–11%) 6 studies—274 patients (LA−): 3% (0–6%)
Negative diagnostic laparoscopy	⊕⊕	1 study—78 patients (LA+ vs. DL)—36% (25–47%) 1 study—109 patients (LA− vs. DL)—Incidence: 8% (3–13%)	1 study—78 patients (LA+): 36% (25–47%) 6 studies—368 patients (LA−): 16% (6–26%)

LA, laparoscopic adhesiolysis; LA+, laparoscopic adhesiolysis with adhesion barrier; LA−, laparoscopic adhesiolysis without adhesion barrier; DL, diagnostic laparoscopy; RR, risk ratio; MD, mean difference.

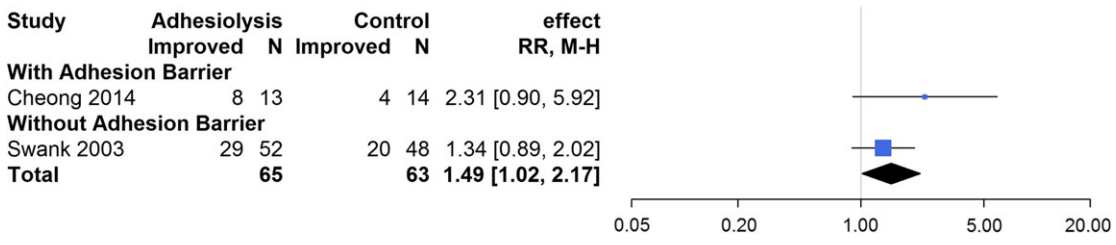

Figure 2 Forest plot of improvement of pain in randomized trials comparing laparoscopic adhesiolysis to diagnostic laparoscopy at intermediate or long-term follow-up.

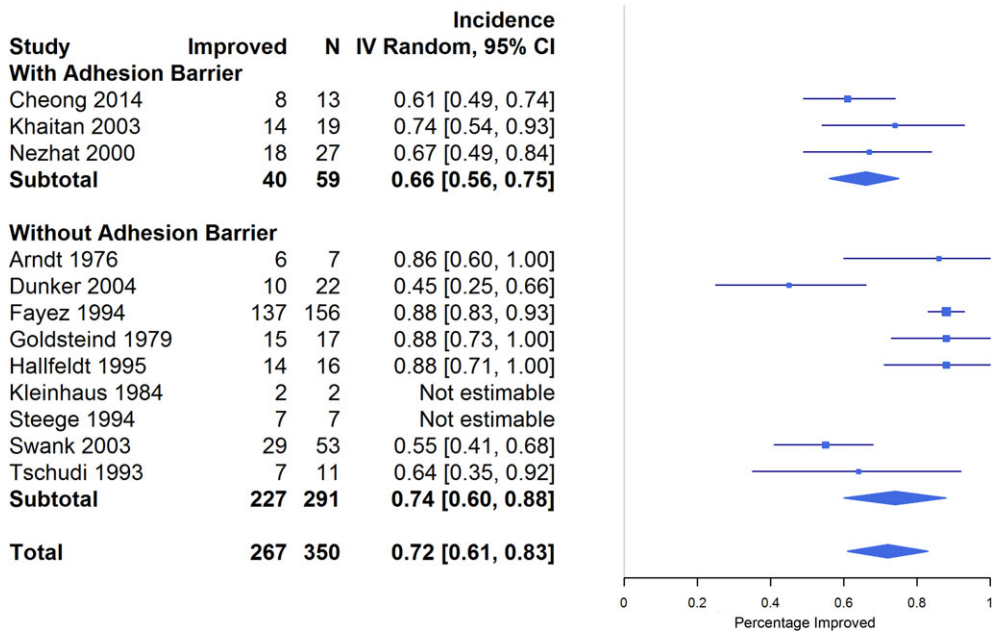

Figure 3 Forest plot of improvement of pain reported in cohorts of laparoscopic adhesiolysis at intermediate or long-term follow-up.

mixed cohorts on the other hand was the higher incidence of negative laparoscopies. These findings probably represent differences in patient selection; patients in the general surgery cohorts often had extensive surgical histories with multiple laparotomies. Another explanation might be that gynaecological patients with pelvic pain have a more extensive differential diagnosis of chronic pain. Unfortunately, a subgroup analyses of men and women was not possible. Because men have a less complex differential diagnosis of chronic pain, causality between adhesions and pain might be more evident.

We systematically analysed outcomes related to both benefit and harm, and graded for clinical relevance. Relatively few data are available for the outcomes deemed to be critical for decision-making (improvement of pain and quality of life at long-term follow-up). There were two trials identified, only one of which had a low risk of bias and long-term follow-up (Swank *et al.*, 2003).

The trial of Cheong *et al.* (2014a) had a potential source of bias from premature termination of the trial. The trial was prematurely ended because funding for the study stopped after a relatively slow recruitment process (Cheong *et al.*, 2014a). Reasons for this slow recruitment were not further specified. A potential reason may be the high rate of negative laparoscopies (36%) in the study, causing a large number of patients to be excluded at a late stage of the trial after use of scarce resources such as operating room time. Another reason might be scepticism of referring physicians towards adhesiolysis, resulting in a relatively low referral rate of potential candidates for the trial (Swank *et al.*, 2003; Meuleman *et al.*, 2013; Cheong *et al.*, 2014a).

Most studies did not report on the prevalence of chronic pain at the index operation. If chronic pain was present prior to the index operation causing the adhesions, chronic pain sensitization rather than the adhesions might have caused chronic pain (Bouwense *et al.*, 2013). The data presentation did not allow subgroup analysis of the efficacy of adhesiolysis in patients with prior chronic pain. Nevertheless, the trial of Cheong *et al.* (2014a) showed positive effect of adhesiolysis despite a relative high number of patients with prior chronic pain (40%).

No firm conclusions could be drawn regarding the impact of new developments in the field of adhesion treatment, such as non-invasive imaging modalities for diagnosis and use of adhesion barriers. Non-invasive imaging was not applied in the work-up of patients with chronic pain. Only three studies applied an adhesion barrier following adhesiolysis for pain, one of which evaluated results beyond 6 months (Nezhat *et al.*, 2000; Khaitan *et al.*, 2003; Cheong *et al.*, 2014a).

Comparison with previous research

We deliberately limited the scope of this review to post-operative adhesions. Adhesions in patients without previous surgery are often the result of inflammatory conditions, endometriosis or adenomyosis, all of which with purportedly different pain mechanisms (Wiseman, 2008; Fortin *et al.*, 2015). Studies that included patients without a history of surgery tended to have higher incidences of negative laparoscopy for adhesions and lower overall success rates. Hebbar *et al.* found pelvic adhesions in only 20.9% of patients with chronic pelvic pain (Hebbar and Chawla, 2005). In a trial by Peters *et al.* (1992), in which only half of the patients had previous surgery, adhesiolysis was effective in only 45.8% of patients—primarily the subset of patients with dense adhesions. Keltz *et al.* (2006) reported on adhesiolysis in a cohort in which 40% of patients had previous surgery and 60% had endometriosis. No subgroup analysis of patients with previous surgery was performed. In this study, adhesiolysis only had a limited impact on pain in the right lower quadrant. Patients with a history of surgery have a higher *a priori* chance of finding adhesions at laparoscopy, and might benefit more from operative intervention because of a lower incidence of concomitant/confounding pelvic pathologies. Indeed, patients with endometriosis were excluded in the randomized trials cited in this paper (Swank *et al.*, 2003; Cheong *et al.*, 2014a).

Even with this selection of patients with history of prior surgery, the results are equivocal. There was a marked difference in the results of the only two randomized trials (Swank *et al.*, 2003). The long-term results of adhesiolysis without an adhesion barrier in the trial of Swank compared unfavourably with those reported in other studies. In the trial of Swank *et al.,* only 56% of patients had improved of pain, compared with an average of almost 70% in other studies (Swank *et al.*, 2003; Cheong *et al.*, 2014a). In contrast, positive results were found in the other trial of Cheong *et al.* after performing adhesiolysis with application of an adhesion barrier (Swank *et al.*, 2003; Cheong *et al.*, 2014a).

Striking differences between the trial of Cheong *et al.* and that of Swank *et al.* are the use of an adhesion barrier and the duration of follow-up (6 months vs. 12 months) (Swank *et al.*, 2003; Cheong *et al.*, 2014a). Adhesion barriers can reduce adhesion reformation and there is some evidence that adhesion reformation indeed is associated with recurrence of pain (Nezhat *et al.*, 2000; Khaitan *et al.*, 2003). However, the choice of barrier in the trial of Cheong *et al.*, Icodextrin 4%, is somewhat controversial. Evidence for efficacy in adhesion prevention for this barrier in gynaecological surgery is scarce (Trew *et al.*, 2011; Ahmad *et al.*, 2015; Hindocha *et al.*, 2015). Icodextrin has been popularized because of its relatively low cost and easy application compared with other commercially available adhesion barriers. Compared with other barriers, it appears to be one of the least efficacious barriers, especially in the setting of adhesion reformation, which is usually more difficult to prevent than *de novo* adhesions (Ten Broek *et al.*, 2014a; Ahmad *et al.*, 2015). However, in one trial with adhesion reformation, the use of icodextrin in surgery for adhesive small bowel obstruction reduced the incidence of clinical recurrences (Catena *et al.*, 2012).

In addition, the follow-up period in Cheong's trial may be too short for a definitive conclusion. There is some debate on the length of follow-up required to assess the efficacy of adhesiolysis. Although reformation of adhesions begins quickly after surgery (and no significant changes in adhesions are expected after a few months of maturation), the follow-up period should also extend beyond the period of time that any placebo effect of surgery could plausibly be expected to interfere with results. It remains uncertain how long the placebo effect of a sham operation for chronic pain can last, but there is evidence that a placebo effect from invasive treatments tends to be significant and have a long duration (Kaptchuk *et al.*, 2000, 2006; Harris, 2016).

It is not possible to draw firm conclusion from literature on placebo effects of surgery on the follow-up period that is required to evaluate results of adhesiolysis. We judged a period of at least 1 year to be the most appropriate for long-term follow-up. There was little data available on the efficacy of adhesiolysis with an adhesion barrier beyond 1 year. Only Khaitan *et al.* (2003), using a carboxy methylcellulose barrier in 19 patients, had a follow-up period of 1 year after adhesiolysis with an adhesion barrier (Khaitan *et al.*, 2003). In this study, there was no decline in efficacy when comparing between 6 months and 1 year (Khaitan *et al.*, 2003).

Learning curve and expertize might also impact results of adhesiolysis. Both of the included trials had been performed by research groups with expertize in this area. Prior to the trial, the group of Swank *et al.* reported on a retrospective case series of 157 adhesiolysis procedures for pain with few complications. Although this report did not meet our strict inclusion criteria, it demonstrates the clinical expertize of this group in this field. In this series, the short-term relief after adhesiolysis was 80%, consistent with the results seen in studies included in this review (Swank *et al.*, 2002). Additionally, the group of Cheong *et al.* inarguably has substantial expertize with treatment of chronic pelvic pain (Cheong and William, 2006; Cheong *et al.*, 2014b).

The aim of adhesiolysis is to improve symptoms and quality of life, not to prolong life. As such, it is important that the decision to perform the procedure be guided by a carefully considered decision-making process. Although the overall incidence of complications associated with the procedure was relative low, a number of serious complications were reported, including inadvertent bowel injury. In the included studies, no mortality was reported. Nevertheless, bowel injuries are fatal in ~8% of cases (Swank *et al.*, 2002; Ten Broek *et al.*, 2013a,b). Although the sample sizes were too small to reach significance, there was a trend towards an increased rate of complications in the general surgery cohorts compared with the gynaecological cohorts. These findings probably represent differences in patient selection: patients in the general surgery cohorts often had extensive surgical histories with multiple laparotomies (Ten Broek *et al.*, 2014b). With an increasing number of repeat operations, the *a priori* risk of having denser and more numerous adhesions rises (Strik *et al.*, 2015). Dense adhesions harbour a higher risk of organ injury upon adhesiolysis.

Implications for future research

Over a decade after the trial conducted by Swank *et al.*, scant progress has been made towards the proper management of chronic abdominal

and pelvic pain caused by adhesions. The recent progress made in both the diagnosis and treatment of adhesions suggests that renewed investigation of adhesiolysis may be worthwhile (Ten Broek *et al.*, 2016). Long-term follow-up was lacking in most included studies. Future studies should obtain long-term results to prevent biases in the results from placebo effects of surgery. More research is needed to also investigate whether non-invasive diagnostic techniques can be used to guide clinical decision-making in patients with pain from adhesions.

Over recent years, non-invasive techniques for diagnosing adhesions using the 'visceral slide' principle have become available (Lienemann *et al.*, 2000; Minaker *et al.*, 2015; Ha *et al.*, 2016; Randall *et al.*, 2016). Adhesions are not directly visible on imaging with non-invasive diagnosis; however, with movement of the abdominal wall amid increasing intra-abdominal pressure, intra-peritoneal organs should move without restriction. Aberrant movement patterns on dynamic imaging studies could indicate the presence of adhesions. This non-invasive diagnostic tool has shown promise in diagnosing adhesions to the abdominal wall (Lienemann *et al.*, 2000; Kirchhoff *et al.*, 2010; Randall *et al.*, 2016).

Several adhesions barriers are commercially available, although none seem to have ideal properties for the indication of chronic pain (Schreinemacher *et al.*, 2010; Tsuruta *et al.*, 2015). Hyaluronic acid-carboxy methylcellulose is the most extensively investigated barrier at present. Although techniques for placing this barrier have been described, most surgeons consider its placement to be inconvenient (Wiseman *et al.*, 1998; Ten Broek *et al.*, 2014a). Icodextrin 4% solution is more easily placed in laparoscopy, but has low viscosity and is absorbed relatively quickly, which may reduce its efficacy in preventing long-term adhesion reformation (Ten Broek *et al.*, 2014a).

Development of a next-generation barrier for chronic pain should therefore focus on ease of laparoscopic use and efficacy in adhesion reformation after adhesiolysis. Such barriers needs to be tested for their long-term results.

Implications for clinical practice

Even after selecting only patients with a history of previous surgery, the efficacy of adhesiolysis for chronic pain remains inconclusive. Reasonable concerns regarding long-term efficacy, the relatively high number of negative laparoscopies and the risk of serious inadvertent visceral injuries warrant a restrictive policy towards elective adhesiolysis for chronic pain. More evidence on this topic is needed, especially on novel techniques for diagnosis and prevention of adhesion reformation. To avoid such risks, clinicians should first attempt to control pain by conservative treatments. Unfortunately, evidence for conservative treatment options is similarly lacking. Consequently, chronic abdominal and pelvic pain is a driver of long-term use of analgetics and opioid dependency, and frequently incurs high-cost multidisciplinary or complementary treatments which lack sufficient evidence for efficacy (Cheong *et al.*, 2014b; Volkow and McLellan, 2016). In a recent Cochrane review of non-surgical interventions for chronic pelvic pain, none of the studies was dedicated to patients with adhesions (Cheong *et al.*, 2014b). Moreover, the quality of evidence for different pharmacological, psychological, dietary and lifestyle interventions was poor (Cheong *et al.*, 2014a). Silverman *et al.* (2012) performed a trial with pregabalin in a cohort of patients with adhesion-related pain, but the study was underpowered. Based on expert opinion, we suggest a 'team approach' to the patient with chronic pain, to target all possible factors that might contribute to pain. Anxiety, for example, is a common feature in patients with chronic pain that may need further attention (Miller-Matero *et al.*, 2016).

Adhesiolysis should preferably be performed in the setting of clinical studies. Evidence for adhesion barriers in the specific indication of chronic pain is low. Nevertheless, we believe that in cases where operative treatment is considered, there is merit to the application of adhesion barriers, given the increasing evidence for their efficacy in other clinically relevant outcomes (Ten Broek *et al.*, 2014a). The harms reported in this review relate to the procedure of adhesiolysis itself, rather than to the placement of a barrier.

Conclusion

Laparoscopic adhesiolysis reduces pain from adhesions in ~70% of patients in the initial phase after treatment. While the number of reported complications was low, such complications did include severe adverse events such as bowel injuries. Adhesiolysis without application of an adhesion barrier was not efficacious in a trial with long-term follow-up. The long-term efficacy of adhesiolysis with an adhesion barrier is still unclear. No study used novel non-invasive techniques to diagnose adhesions in the work-up phase. At present, there is little evidence to support routine use of adhesiolysis as a treatment for chronic pain. Further research is needed to investigate whether the results of adhesiolysis can be improved by new techniques for diagnosis and prevention of adhesion reformation.

Supplementary data

Supplementary data is available at *Human Reproduction Update* online.

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Authors' roles

B.A.B.: search strategy, data extraction, data analysis, drafting of manuscript, final approval; R.R.: data extraction, data analysis, drafting of manuscript, final approval; S.L.: search strategy, critical review of manuscript, final approval; E.A.B., C.S. and H.G.: study design, critical review of manuscript, final approval; R.P.G.B.: study design, supervision of search strategy and data extraction, data interpretation, supervision of drafting of the manuscript, final approval.

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Conflict of interest

B.A.B., R.R., S.L., E.A.B., C.S. and R.P.G.B. reports no conflict of interest. H.G. reports grants from Atrium Maquet, outside the submitted work.

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