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REVIEW ARTICLE

Adhesions after abdominal surgery: a systematic review of the incidence, distribution and severity

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Abstract Abdominal adhesions are associated with increased postoperative complications, cost and workload. We performed a systematic review with statistical pooling to estimate the formation rate, distribution and severity of postoperative adhesions in patients undergoing abdominal surgery. A literature search was carried out for all articles reporting on the incidence, distribution and severity of adhesions between January 1990 and July 2011. Twenty-five articles fulfilled the inclusion criteria. The weighted mean formation rate of adhesions after abdominal surgery was 54 % (95 % confidence interval [CI] 40–68 %), and was 66 % (95 % CI 38–94 %) after gastrointestinal surgery, 51 % (95 % CI 40–63 %) after obstetric and gynaecological surgery and 22 % (95 % CI 7–38 %) after urological surgery. The mean overall severity score was 1.11 ± 0.98 according to the Operative Laparoscopy Study Group classification. Laparoscopic surgery reduced the adhesion formation rate by 25 % and decreased the adhesion severity score (laparoscopic; 0.36 ± 0.69 vs. open; 2.14 ± 0.84) for gastrointestinal surgery. Our results demonstrate that the incidence and severity of abdominal adhesions varies between surgical specialties and procedures. An increased awareness of adhesions can help in identifying the underlying mechanisms of adhesion formation and novel therapeutic approaches, while also improving the surgical consent process.

Keywords Adhesion · Postoperative · Laparoscopic · Surgery · Abdominal

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Introduction

Abdominal adhesions are abnormal fibroid bands that bind between organ surfaces or the walls in the abdominal cavity. Surgery on the abdomen via laparotomy is the primary cause of adhesions, and the development of adhesions is considered to be the most common physiological reaction following abdominal surgical exposure. Some studies have reported a 93 % incidence of adhesions in patients with prior laparotomy undergoing a second laparotomy [1].

The mechanism underlying the formation of adhesions [2, 3] includes an initial surgical injury to the peritoneal epithelium, which results in the deposition of fibrin matrix gel between damaged intra-abdominal surfaces. Fibrinolysis by plasmin can degrade these deposits, but postoperatively, the fibrinolysis is typically inadequate, and non-degraded deposits are reorganized to form fibrous adhesions. The formation and location of adhesions are currently unpredictable in abdominal surgery due to the complex interplay of the many factors that regulate fibrinolysis.

The complications of adhesions, include chronic abdominal pain, small bowel obstruction (SBO), female infertility and inadvertent bowel injury at adhesiolysis. Adhesions account for up to 96 % of patients with chronic abdominal and/or pelvic pain at diagnostic laparoscopy [4], 60–70 % of patients with SBO [5] and 20–40 % of those

with female infertility [6]. Inadvertent bowel injury at adhesiolysis occurs in approximately 19 % of patients undergoing abdominal re-operations [7]. In addition, 37 % of patients with adhesive bowel obstruction need surgical management [8]. These complications typically require increased hospital visits, readmission, reintervention and further surgical management [8, 9]. The total treatment cost per admission for adhesive small bowel obstruction was £4677.41 for surgically treated admissions and £1606.15 for conservatively treated admissions [8]. The impact of adhesions on surgeon workload and the overall healthcare costs is, therefore, significant and continues to increase, with the financial cost of adhesions in the US for 1994 being estimated at $1.3 billion [10].

Surgeons typically underestimate the incidence and consequences of adhesions. Both trainees and experts score approximately 35–40 % on adhesion knowledge [11], and one study revealed that adhesions are listed in only 9 % of consent forms [12]. The current evidence base regarding surgical abdominal adhesions does not clearly identify the incidence, distribution, severity and complications of this postoperative condition. This is due to two reasons: first, the pattern of adhesion formation is anatomically and pathologically heterogeneous, and is therefore difficult to report. As a result, there is a large variation in the design and quality of studies relating to adhesions. Second, the diagnosis of adhesions requires confirmation at a "second-look" laparotomy or laparoscopy. Performing repeat surgery purely to assess the postoperative adhesion formation in all patients undergoing an abdominal procedure is unethical, rendering the knowledge regarding the incidence of postoperative adhesions biased toward the disease load in patients, who had clinical grounds to undergo these secondary procedures.

In this systematic review, we aimed to estimate the incidence, distribution and severity of postoperative adhesions in patients undergoing abdominal surgery. Our objective was to identify the distribution of this condition by procedure and clinical speciality to increase awareness, improve the consent process and highlight possible mechanistic patterns in the formation of abdominal adhesions.

Methods

Search strategy

We systematically searched the EMBASE, MEDLINE and PsychINFO databases for articles reporting the incidence, distribution and the severity of adhesions without language restriction between January 1, 1990 and July 1, 2011. Our search was performed using the following words: "adhesi*" AND "surg*" OR "operati*" OR "laparotomy" OR "postoperati*" OR "relaparotomy" OR "reoperati*" AND "abdom*" OR "bowel" OR "pelv*". All studies were assessed individually by two authors (KO and HA).

Criteria for considering studies in this review

Inclusion criteria

This review included randomized control trials, cohort studies and observational studies. The outcome measurements of the included studies are defined as the "incidence", "distribution" and "severity" of adhesions at a second-look operation. All participants were adults (more than 16 years old) and underwent either open or laparoscopic surgery for abdominal diseases or a caesarean section.

Exclusion criteria

Papers, including patients with Crohn's disease, endometriosis, peritoneal metastasis of cancer, and those treated with pre- or postoperative radiation therapy were excluded, because these diseases and procedures potentially have an impact on the formation of adhesions and bowel obstruction without abdominal surgery. Furthermore, patients, who underwent repair of incisional and inguinal hernias using biomaterials, such as polypropylene mesh, were excluded. This is because these biomaterials induce a similar fibrous tissue reaction that can be indistinguishable from surgical adhesions, so that differentiating the origin of adhesions in these cases would not be possible or accurate. Papers dealing with minor surgery, such as salpingopexy and ovarian drilling, were excluded, because these procedures need little or no intra-abdominal manipulation.

Data extraction

The extracted data consist of the authors, departments, institutes, year of publication, type of study (single centre or multicentre), study period, procedure used to assess adhesions, timing of assessment, follow-up program, follow-up period, patient number, age, gender, pathology, location of disease, type of procedure, treatment in the control arm of randomized control trials, incidence, distribution and severity of adhesions and measurement scale of the adhesion severity (Supplementary Table 1).

Risk of bias in individual studies

To assess the risk of bias in eligible studies, we used self-produced checklists, which consisted of seven categories, including the study design, details of participants, assessment of adhesions, underlying pathology, anatomy, type of

procedure and outcomes (Supplementary Table 1). Moreover, we assessed the quality of the included studies according to the Newcastle–Ottawa scale, which was developed as a risk assessment tool for non-randomized studies in a meta-analysis (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) [13].

Statistical analysis

The quantitative data from the studies were pooled using inverse variance weighting and random-effect methods. The standard error was calculated on the sample proportion of adhesions in each study and was used to compute the corresponding 95 % confidence intervals (CI), which were subsequently applied to create an overall pooled result. The percentage of heterogeneity between studies not attributable to random noise was estimated using the Higgins' I^2 statistic. Statistical calculations were performed with the Review Manager Software Program (Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). The severity of adhesions, which had a mean and standard deviation, was generated using Microsoft Excel 2010 (Microsoft, Redmond, Washington, USA) as follows: each standard deviation was individually squared to get each variance, and all the variances were then added and divided by the number of variances minus 1, and then the square root of that sum was determined.

Results

Overview of the search strategy

This review and meta-analysis was written according to the guidelines for systematic reviews and meta-analysis, the PRISMA statement, to ensure validity and transparency [14]. The overview of our search strategy is shown in Fig. 1. Of the 8,130 titles identified through our search and cross-reference manual search, we reviewed the full text of 71 studies. Twenty-five [15–39] of these 71 studies met our inclusion and exclusion criteria as outlined above. These 25 papers consisted of 10 nested cohorts from randomized control studies, 10 cohort studies and five observational studies. The overall median Newcastle–Ottawa score of all included studies was 4 (range 3–5), indicating a relatively low overall study quality (Table 1 and Supplementary Table 1).

Description and quality of studies

The quality of the studies and the details of the adhesion-specific outcomes in each included study are summarized in Table 1. Of the 25 studies, 19 addressed the incidence of adhesions [16, 17, 19–23, 26–28, 30, 31, 33–39], 16 assessed the distribution of adhesions [15–19, 21, 22, 25–29, 34–36, 39] and 20 examined the severity of adhesions [16–18, 20, 21, 24–32, 34–39]. Twenty studies examined more than one outcome [16–22, 25–31, 34–39]. The study quality was heterogeneous. Ascertainment of adhesions was provided by "second-look" laparoscopy or laparotomy in all 25 studies. The postoperative timing of assessment was not consistent, with the second-look procedure taking place 1 month to 3 years after the initial laparotomy.

Formation of adhesions

A total of 19 studies [16, 17, 19–23, 26–28, 30, 31, 33–39], which consisted of 7 in gastrointestinal surgery [17, 20, 22, 26, 27, 33, 35], 11 in obstetric and gynaecological surgery [16, 19, 23, 28, 30, 31, 34, 36–39] and 1 in urological surgery [21], reported the incidence of adhesions after abdominal surgery. Fifteen studies were eligible for evidence synthesis; the results of statistical pooling are presented in Fig. 2. Of all the 2,825 patients, 1,041 (37 %) developed adhesions. The overall weighted mean formation rate of adhesions after abdominal surgery was 54 % (95 % CI 40–68 %) (Fig. 2). There was large heterogeneity between the studies ($I^2 = 98$ %, $p < 0.00001$).

The development of adhesions by speciality

We also performed a subgroup analysis according to surgical speciality. Adhesions occurred in 288 (64 %) of 451 patients, who underwent gastrointestinal surgery, 747 (32 %) of 2,347 patients, who underwent obstetric and gynaecological surgery and six (22 %) of 27 patients, who underwent urological surgery. The weighted mean formation rate of adhesions was 66 % (95 % CI 38–94 %) in the gastrointestinal surgery cases, 51 % (95 % CI 40–63 %) in the obstetric and gynaecological surgery cases and 22 % (95 % CI 7–38 %) in the urological surgery cases.

The development of adhesions by procedure

The studies that were eligible for inclusion in the analysis by procedure consisted of one study of cholecystectomy, six total colectomy studies, six caesarean section studies and five studies of uterine surgery. Fourteen of these studies were eligible for evidence synthesis. The results and details of the statistical pooling are presented in Fig. 3. Adhesions occurred in 16 (62 %) of the 26 patients, who underwent cholecystectomies, 50 (100 %) of 50 patients, who underwent left sided colectomies, 222 (59 %) of the 375 patients, who underwent total colectomy, 613 (31 %) of 1,988 patients, who underwent a caesarean section and 134 (37 %) of 359 patients, who underwent myomectomy.

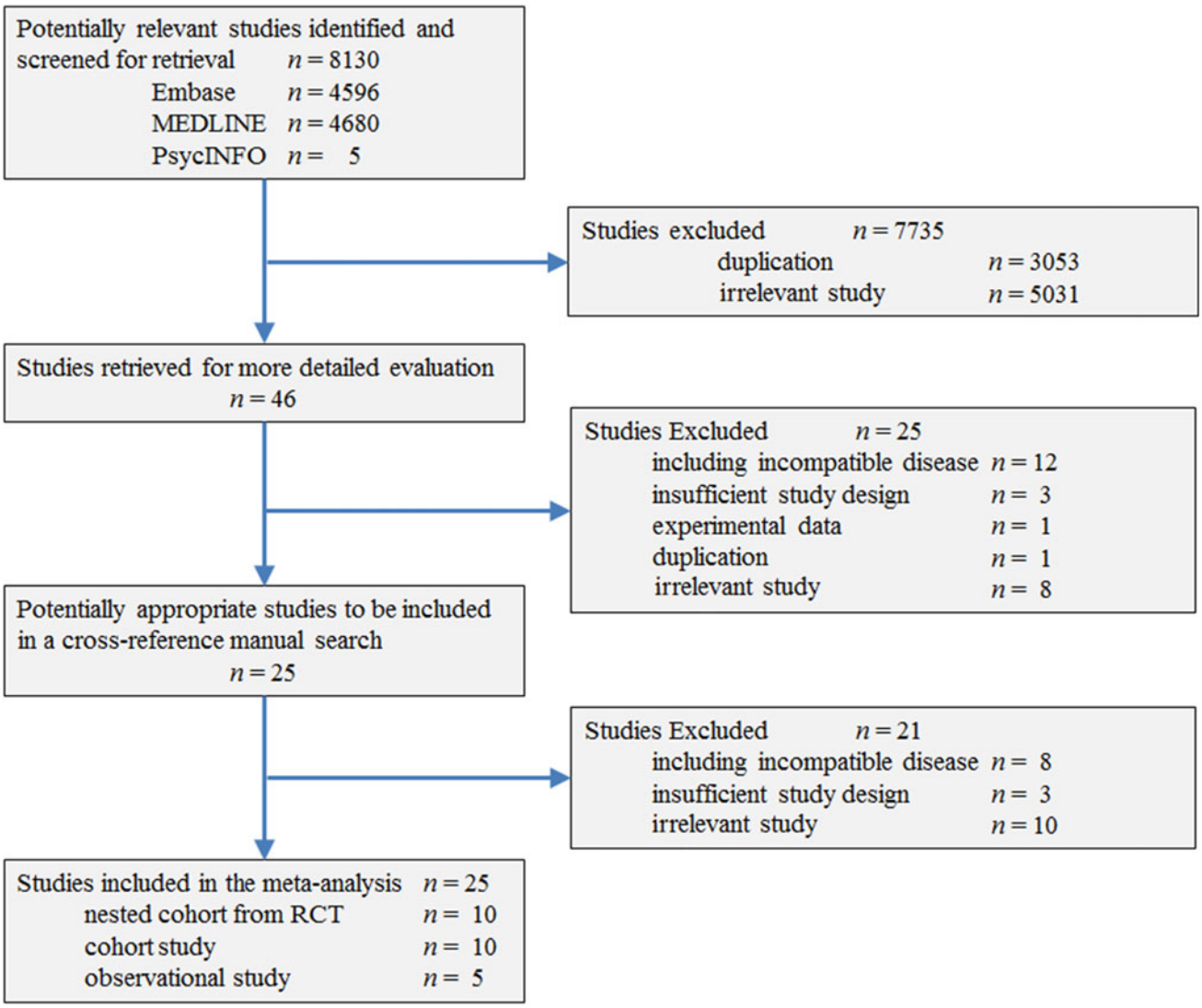

Fig. 1 A flow chart of the search process

The weighted mean formation rate of adhesions was 61 % (95 % CI 43–80 %) for cholecystectomy, 67 % (95 % CI 35–99 %) for total colectomy, 41 % (95 % CI 29–53 %) for caesarean section and 64 % (95 % CI 31–98 %) for myomectomy.

Impact of laparoscopic surgery

Nine studies reported on laparoscopic surgery and nine reported on open surgery. Adhesions occurred in 115 (38 %) of the 304 patients, who underwent laparoscopic surgery and in 914 (36 %) of the 2,508 patients, who underwent open surgery. The pooled weighted mean formation rate of adhesions was 49 % (95 % CI 27–72 %) in the laparoscopic surgery studies and 50 % (95 % CI 32–68 %) in the open surgery studies. In the cases of gastrointestinal surgery, the pooled weighted mean adhesion formation rates were 48 % (95 % CI 34–62 %) for laparoscopic surgery and 73 % (95 % CI 38–109 %) for open surgery (Fig. 4). In the patients, who underwent obstetric and gynaecological surgery, the weighted mean adhesion formation rates were 57 % (95 % CI 20–94 %) in those who underwent laparoscopic surgery and 39 % (95 % CI 29–49 %) in those who underwent open surgery (Fig. 5). However, all of the listed laparoscopic obstetric and gynaecological procedures were myomectomies, and did not include caesarean sections.

Three studies compared the incidence of adhesions between laparoscopic and open surgery; these considered cholecystectomy, total colectomy and myomectomy. All three studies reported a lower incidence of adhesion formation after laparoscopic surgery compared to open

Table 1 Characteristics of included studies

Author	Gender (M/F)	Procedure	Lap/Open	No anti-adhesive agent used				Anti-adhesive agent used			
				Incidence (%)	Distribution	Severity tool/score	Quality score	Type of anti-adhesive agent	Incidence	Distribution	Severity tool/score
Mais	0/25	myo	L	88	Adnexal: 64 %	OLSG/1.64 ± 0.95	4	Interceed	40 %	Adnexal: 40 %	OLSG/0.52 ± 0.71
Becker	42/40	TC	O	94	Midline: 94 % Midline–omentum: 79 % Midline–bowel: 63 % Midline–bladder: 12 % Midline–peristoma: 17 % Midline–stomach: 13 % Midline–ileal pouch: 6 % Midline–liver: 8 %	OLSG/2.42 ± 0.82	4	HA	49 %	Midline: 49 % Midline–omentum: 39 % Midline–bowel: 25 % Midline–bladder: 4 % Midline–peristoma: 7 % Midline–stomach: 5 % Midline–ileal pouch: 1 % Midline–liver: 7 %	OLSG/1.00 ± 1.15
Ugur	0/48	myo	L	–	Uterus: 83 % Uterus–adnexa: 65 %	AFS/7.4 ± 8.1	5	–	–	–	–
Assaf	0/17	myo	L	41	Uterus–bowel: 35 % Uterus–adnexa: 18 %	–	5	–	–	–	–
Polymeneas	6/20	chole	L/O	62	–	OLSG/open: 3 ± 0 Lap: 0.44 ± 0.5	3	–	–	–	–
Pattaras	N.S	various	L	22	AW: 19 % Pelvis: 4 %	OLSG/0.26 ± 0.53	3	–	–	–	–
Vrijland	11/10	Hart	O	100	Midline: 100 % Pelvis: 90 %	–	4	HA	90 %	Midline: 90 % Pelvis: 76 %	–
Mettler	0/13	myo	N.S	92	–	–	5	SprayGel	72.2 %	–	–
Tang	49/41	RS	N.S	–	–	SP/phase I: 7.28 ± 0.4 Phase II: 7.82 ± 0.6	4	HA	–	–	SP/phase I: 7.42 ± 0.5 Phase II: 5.81 ± 0.5

Table 1 continued

Author	Gender (M/F)	Procedure	Lap/ Open	No anti-adhesive agent used				Anti-adhesive agent used			
				Incidence (%)	Distribution	Severity tool/score	Quality score	Type of anti-adhesive agent	Incidence	Distribution	Severity tool/ score
Swank	2/22	lysis	L	–	AW–stomach: 4 % AW–small bowel: 21 % AW–colon: 21 % AW–omentum: 50 % AW–female organs: 5 % AW–bladder: 0 % AW–liver: 8 % Stomach: 0 % Small bowel: 54 % Colon: 25 % Omentum: 17 % Female organs: 9 % Bladder: 25 % Liver: 4 %	Zühlke/abdominal wall: 4.04 Their system: 5.33	3	–	–	–	–
Cohen	34/27	TC	O	89	–	OLSG/1.98 ± 0.97	4	HA	67 %	–	OLSG/ 1.19 ± 1.02
Kusunoki	21/9	RS	O	100	Midline: 86 % Peristoma: 100 %	OLSG/1.34 ± 0.72	4	HA	87 %	Midline: 13 % Peristoma: 87 %	OLSG/ 0.13 ± 0.35
Myers	0/191	CD	O	27	–	SP/	4	–	–	–	–
Takeuchi	0/32	myo	L	75	Uterus–colon: 53 % Uterus–omentum: 9 % Uterus–bladder: 13 % Adnexa: 13 %	OLSG/1.46 ± 1.08	3	Fibrin Gel Fibrin Sheet	Fibrin Gel 35 % Fibrin Sheet 80 %	Fibrin Gel uterus–colon: 31 % Uterus–omentum: 0 % Uterus–bladder: 3 % Adnexa: 7 % Fibrin Sheet terus–colon: 47 % Uterus–omentum: 23 % Terus–bladder: 10 % Adnexa: 8 %	Fibrin Gel OLSG/ 0.58 ± 0.91 Fibrin Sheet OLSG/ 1.43 ± 1.00

Table 1 continued

Author	Gender (M/F)	Procedure	Lap/ Open	No anti-adhesive agent used				Anti-adhesive agent used			
				Incidence (%)	Distribution	Severity tool/score	Quality score	Type of anti-adhesive agent	Incidence	Distribution	Severity tool/ score
Tsuji	0/63	CD	O	–	AW: 69 % Uterus: 77 % Adnexal: 92 %	AFS/8.53 ± 8.79	4	HA/Dextran/ Beriplast	–	HA AW: 14 % Uterus: 14 % Adnexal: 14 % Dextran AW: 29 % Uterus: 53 % Adnexal: 71 Beriplast AW: 42 % Uterus: 75 % Adnexal: 17 %	AFS/ 8.53 ± 8.79
Zareian	0/31	CD	O	32	–	SP/	3	–	–	–	–
Hamel	0/62	CD	O	58	–	SP/	3	–	–	–	–
Mettler	0/23	myo	L/O	–	–	mAFS/2.6 ± 2.2	4	Hydrogel	–	–	mAFS/ 0.8 ± 2.0
Sileri	131/ 159	TC	L/O	35	–	–	4	–	–	–	–
Fatusic	0/362	CD	O	25	AW: 26 % AW: 17 % AW: 35 %	Bristow/Misgav: 0.43 ± 0.79 Pfannestiel: 0.71 ± 1.27 Low midline: 0.99 ± 1.49	3	–	–	–	–
Indar	13/21	TC	L	50	AW: 32 % Adnexa: 29 %	AFS/0.32 ± 0.47	4	HA	33 %	AW: 66 % Adnexa: 29 %	AFS/ 1.15 ± 1.00
Tulandi	0/1283	CD	O	29	AW–omentum: 4 % AW–uterus: 19 % Uterus–bowel: <1 % Uterus–bladder: 3 % Adnexa–omentum: 4 %	SP 2nd: 1.8 ± 0.1 3rd: 2.1 ± 0.1 >3rd: 1.9 ± 0.1	3	–	–	–	–

Table 1 continued

Author	Gender (M/F)	Procedure	Lap/Open	No anti-adhesive agent used			Anti-adhesive agent used			
				Incidence (%)	Distribution	Severity tool/score	Quality score	Type of anti-adhesive agent	Incidence	Distribution	Severity tool/score
Blumenfeld	0/127	CD	O	–	Uterus–bowel: 1 % AW–uterus: 24 % Uterus–omentum: 17 % AW–omentum: 15 % Uterus–pelvis: 36 % Uterus–bladder: 7 %	–	4	–	–	–	–
Chapa	0/59	CD	O	78	Uterus–wall: 59 % Uterus–bladder: 19 %	OLSG/1.64 ± 1.06	3	Interceed	26 %	Uterus–wall: 16 % Uterus–bladder: 10 %	OLSG/ 0.38 ± 0.69
Tinelli	0/272	myo	L/O	25	–	AFS/	4	Interceed	19 %	–	AFS/

Author: add footnotes to indicate what your abbreviations indicate (e.g. myo)

Lap (*or L*) laparoscopic, *O* open, *TC* total colectomy, *Myo* myomectomy, *Chole* cholesystectomy, *Hart* Hartmanns procedure, *RS* rectal surgery, *CD* caesarean section, *AFS* American Fertility Society score, *mAFS* modified American Fertility Society score, *HA* hyaluronate, *AW* abdominal wall, *SP* self-proposed scoring system, *OLSG* Operative Laparoscopic Study Group score, *NS* not specified

procedures; this difference was marginally significant (risk ratio: 0.58, 95 % CI 0.32–1.05, $p = 0.07$).

Distribution of adhesions

Sixteen studies [15–19, 21, 22, 25–29, 34–36] reported the distribution of adhesions. These included six studies in the field of gastrointestinal surgery [17, 22, 25–27, 35], nine in obstetric and gynaecological surgery [15, 16, 18, 19, 28, 29, 34, 36, 39] and one in urological surgery. Owing to the heterogeneity in these 16 studies, we herein report the results of these studies qualitatively.

One study was an analysis of a 12 centre study in the US and Canada, and demonstrated that the percentage of initial midline incision length associated with adhesions was 65 % in 120 patients with a primary diagnosis of ulcerative colitis and familial polyposis [26]. Three studies identified that in colorectal patients who had midline incisions, adhesions were found arising from the midline incision to any location within the abdomen in from 86 to 100 % of postoperative cases [17, 22, 27]. Only one of these studies mentioned the organs adherent to the midline incision [17]. Midline adhesions developed to the omentum in 71 (79 %), to the small bowel in 57 (63 %) and to the left abdominal side wall in 19 (21 %) of the 90 patients. Indar et al. mentioned the possibility of laparoscopic surgery to reduce the postoperative adhesions and demonstrated that the occurrence of adhesions to the abdominal wall was found in 11 (32 %) of 34 patients and in 6 (29 %) of 21 female patients to the adnexa after laparoscopic surgery for ulcerative colitis [35]. Swank et al. evaluated the distribution of adhesions after laparoscopic adhesiolysis, and reported that they developed between the small bowel loops in 13 (54 %) of 24 postoperative patients [25].

The studies in obstetric and gynaecological surgery consisted of four studies of caesarean section and five of myomectomy. In the case of caesarean section, all three papers mentioned midline incision adhesions [15, 34, 36]. After caesarean section, 19–59 % of patients developed abdominal wall adhesions to the uterus and 19 % of those developed adhesions to the omentum. All five studies of myomectomy mentioned adnexal adhesions, one of which included patients who underwent open surgery [29] and the remaining four focused on laparoscopic surgery [16, 18, 19, 28]. When compared with laparoscopic surgery, patients undergoing open myomectomy developed adnexal adhesions more frequently (laparoscopic 13–65 % vs. open 92 %). In addition, 35–53 % of patients developed adhesions between the bowel and uterus [19, 28].

Although only one study considered urological surgery, it involved various operations, and demonstrated that adhesions to the abdominal wall occurred in five (19 %) of the 27 patients [21].

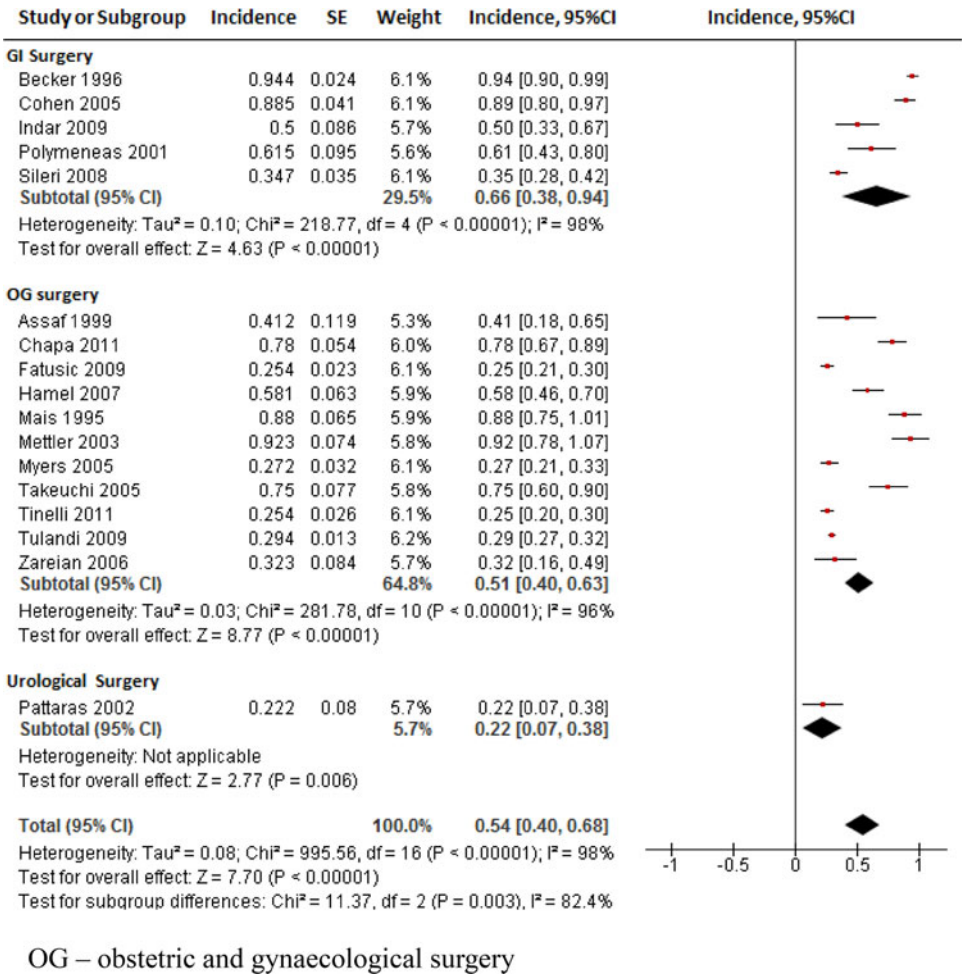

Fig. 2 The weighted mean formation rate of adhesions by speciality. The weighted mean formation rate was calculated using a random-effects model. *Squares* indicate the point estimates of the incidence of adhesions, and *diamonds* show the summary estimate from the pooled studies; the 95 % CIs are indicated by *horizontal bars* and are shown in *parentheses*. *OG* obstetric and gynaecological surgery

Severity of adhesions

Seven main types of severity scoring were utilized in 20 studies. The scoring systems utilized (Table 2) were the Operative Laparoscopic Study Group classification [40] in 10 studies[16, 17, 20, 21, 26–28, 35, 39, 41], the American Fertility Society score [42] in five [18, 29, 32, 35, 38], the Bristow adhesion scoring system in one [34], the scoring system proposed by Zühlke [25] in one and a self-developed scoring system in three studies [30, 36, 37]. Most of these contained common components, including tenacity, extent, vascularity and surgical findings. However, we cannot synthesize evidence from these studies in view of the large reporting heterogeneity.

We were able to synthesize data from nine studies which were assessed using the Operative Laparoscopic Study Group classification. They included five in the field of gastrointestinal surgery, four in obstetric and gynaecological surgery and one in urological surgery. The mean overall score of the severity was 1.11 ± 0.98. The severities by specialty were 1.75 ± 0.72 for gastrointestinal surgery, 0.85 ± 1.38 for obstetric and gynaecological surgery and 0.26 ± 0.53 for urological surgery. The score of severity by procedure was 1.22 ± 0.5 for cholecystectomy, 1.34 ± 0.72 for rectal surgery, 1.89 ± 0.96 for total colectomy, 0.77 ± 1.67 for caesarean section and 1.54 ± 1.44 for myomectomy. In patients, who underwent gastrointestinal surgery, the severity score was 0.36 ± 0.69 for laparoscopic surgery and was 2.14 ± 0.84 for open surgery. In patients, who underwent obstetric and gynaecological surgery, the severity was 1.54 ± 1.44 for laparoscopic surgery and it was 0.77 ± 1.67 for open surgery.

One study demonstrated that the severity of adhesions at the adnexa after total colectomy was 0.33 ± 0.58 using the American Fertility Society score [35]. Tsuji et al. [29] and Ugar et al. [18] presented the adhesion severity in the uterus using the American Fertility Society score, and noted that the scores were 8.53 ± 8.79 and 7.1 ± 8.1, respectively. Swank et al. showed that the severity of adhesions was reduced between the first and second laparoscopic adhesiolysis using a scoring system proposed by Zühlke [25].

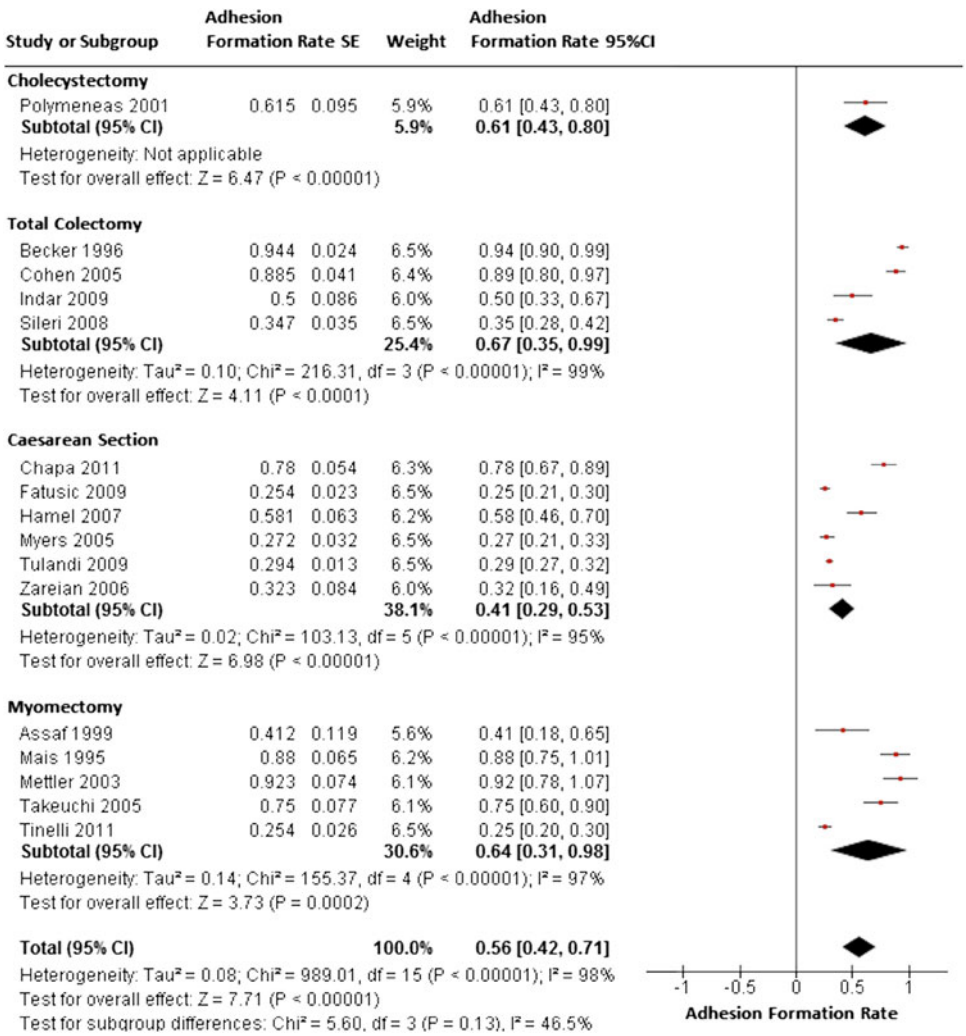

Fig. 3 The weighted mean formation rate of adhesion by procedure. The weighted mean formation rate was calculated using a random-effects model. *Squares* indicate the point estimates of the incidence of adhesions and *diamonds* show the summary estimate from the pooled studies; the 95 % CIs are indicated by *horizontal bars* and are shown in *parentheses*

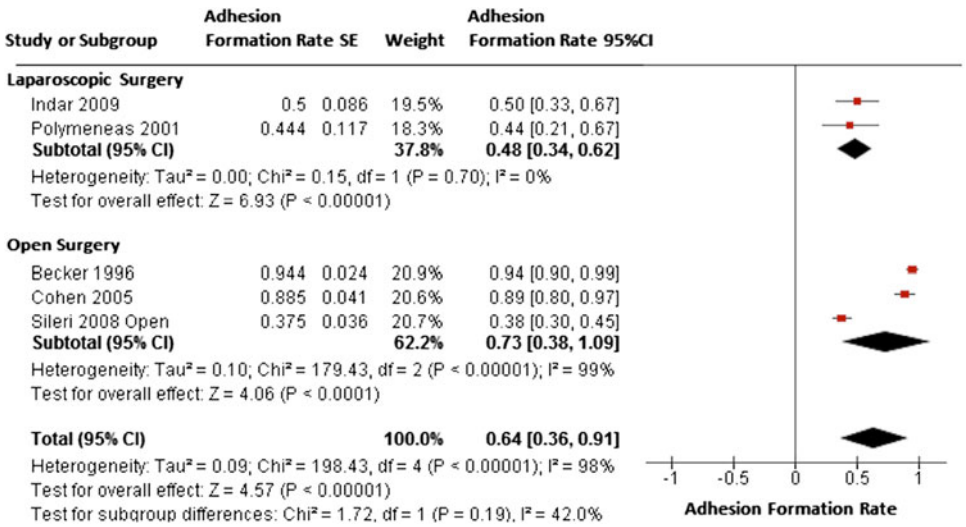

Fig. 4 The weighted mean formation rate of adhesions by procedure in the field of gastrointestinal surgery. The weighted mean formation rate was calculated using a random-effects model. *Squares* indicate the point estimates of the incidence of adhesions and *diamonds* show the summary estimate from the pooled studies; the 95 % CIs are indicated by *horizontal bars* and are shown in *parentheses*

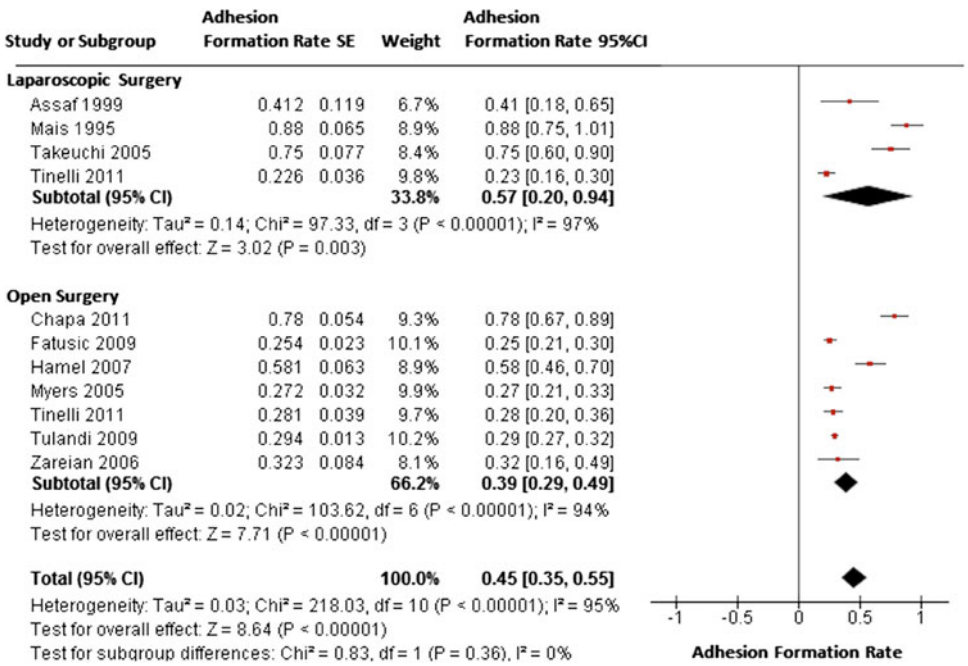

Fig. 5 The weighted mean formation rate of adhesion by procedure in the field of obstetric and gynaecological surgery. The weighted mean formation rate was calculated using a random-effects model. Squares indicate the point estimates of the incidence of adhesions and diamonds show the summary estimate from the pooled studies; the 95 % CIs are indicated by *horizontal bars* and are shown in *parentheses*

Discussion

The results of this systematic review suggest that the weighted mean formation rate of adhesions after abdominal surgery was approximately 54 %. As we expected, there are differences in the incidence and severity of adhesions between surgical specialties and procedures. Adhesions occurred most frequently after total colectomy and myomectomy, and this was associated with higher severity scores for these procedures. Laparoscopic surgery reduced the overall incidence of adhesions after GI surgery by 25 %, and the severity by 1.7 points, according to the Operative Laparoscopic Study Group (OSLG) classification as compared to open surgery. The Surgical and Clinical Adhesions Research (SCAR) group reported that 6 % of all surgical readmissions were directly associated with adhesions, with 4 % of these readmissions requiring adhesiolysis [43]. The results of our analysis can be utilized in conjunction with the previous data from other studies (such as the SCAR group) to enhance patient risk counselling and consent preoperatively.

The rate of adhesion formation was comparable between surgical specialties. The particularly low incidence of adhesions identified in urological surgery may result from the small number of adhesion studies published for this speciality. The overall results of modern adhesion studies compare favourably with those published three decades ago, where Weibel et al. [44] reported that the incidence of postoperative adhesions was 74 % in gastrointestinal surgery and 71 % in obstetric and gynaecological surgery without caesarean delivery [44]. The approximate 20 % reduction in the incidence of adhesions in the past two decades from our analysis could represent a possible improvement in modern surgical practice or performance. This includes minimising peritoneal foreign body exposure, careful tissue handling, meticulous hemostasis [45, 46], specific closure of the peritoneum in caesarean sections (reducing adhesion rates by 40 %) [30, 31, 37] and modern surgical techniques, such as minimally invasive procedures. The few urological studies included in our search strategy may be explained by our inclusion criteria, which focused on operations utilising a peritoneal approach. In urological operations, both extraperitoneal and retroperitoneal approaches are frequently utilized, which could further decrease the overall adhesion rate in this speciality. The overall incidence of adhesions is still remarkably high, and adhesions occur after more than half of abdominal operations. Further research is required to develop novel technological and pharmaceutical strategies to decrease surgical adhesions and their associated complications.

The adhesions were widely distributed throughout the abdominal cavity. They were most commonly identified between the midline incision and omentum (79 %), or between the midline incision and small bowel (63 %) [17]. However, the evidence for the overall distribution of adhesions is limited, as there are no classification systems designed to describe the pattern of adhesion formation. One of the most significant sequelae of adhesions, includes bowel obstruction and pain. Demco et al. [47] reported that filmy adhesions between movable structures, such as the ovaries and the peritoneum, had the highest pain scores,

Table 2 The current scoring systems used to classify the severity of the adhesions (OLSG = Operative Laparoscopy Study Group, AFS = American Fertility Society); these scoring systems are not directly comparable, as their definitions of adhesion severity are based on the characteristics that are not equivalent

Score	OLSG	AFS		Bristow	Zühlke
		Severity	Extent		
0	None	None	None	None	None
1	Filmy/avascular	Mild	Localized	Avascular; easily lysed and failing to bleed	Filmy adhesion; easy to separate by blunt dissection
2	Dense/vascular	Mild	Moderate		Stronger adhesion blunt dissection possible, partly sharp dissection necessary; beginning of vascularization
3	Binding			Vascular; easily lysed, but bleeding of time of lysis	Strong adhesion; lysis possible by sharp dissection only; clear vascularization
4		Mild severe	Extensive localized		Very strong adhesion; lysis possible by sharp dissection only, organs strongly attached with severe adhesions; damage of organs hardly preventable
5				Thick; requiring extensive sharp surgical dissection	
8		Severe	Moderate		
16		Severe	Extensive		

whereas fixed or dense adhesions had the lowest pain scores [47]. Swank et al reported that 71 % of patients who underwent adhesiolysis for chronic abdominal pain had adhesions between small bowel loops, and that these were reduced in terms of their incidence and severity after a second adhesiolysis [25].

The severity of adhesions was comparable between surgical specialties, and was milder for caesarean section as compared to other procedures. However, the overall evidence regarding the severity of adhesions was limited due to a lack of standardized severity scoring systems. Recent histological studies have identified adhesion characteristics, such as the presence of sensory nerves, clusters of smooth muscle cells and the development of new blood vessels, which can contribute to adhesion formation and severity [48, 49]. Establishing a standard adhesion severity scoring system would be helpful to determine the relationship between these pathological findings and adhesion-specific complications.

Laparoscopic surgery is considered to be an effective modality for reducing the incidence and severity of adhesions. This has been explained by smaller incisions, less tissue trauma, reduced bleeding, prevention of desiccation, less tissue trauma, early recovery of bowel function and a reduction of contamination by foreign bodies [50]. In patients who underwent gastrointestinal surgery, laparoscopic surgery reduced the incidence of adhesions by 25 % and the severity of the adhesions by 1.7 points by the OLSG classification as compared to open surgery. These results are supported by several animal and human studies demonstrating a reduction of adhesion formation after laparoscopic surgery as compared to open surgery [50]. Although there is some opposing evidence in the literature demonstrating that the use of a pneumoperitoneum increases hypoxia and vascular endothelial growth factor release, which enhance adhesion formation [51, 52], these effects are likely to represent only one aspect of laparoscopy that is usually outweighed by the greater benefits of laparoscopic adhesion reduction. Our contradictory finding that laparoscopic surgery may be associated with a higher adhesion formation rate than open surgery in obstetrics and gynaecology may be influenced by the unique endocrine, immunological and physiological environment in female patients, which may have contributed to some of the results in this speciality. This may increase the pro-adhesion effects of laparoscopy, and warrants further research and robust studies assessing the incidence of adhesion rates in laparoscopic surgery. Randomized controlled trials may not be feasible to directly assess adhesion formation as a primary outcome due to their cost and the lack of quantifiable end points for adhesion imaging. As a result, the appropriate study design to assess the adhesion formation rate would include prospective studies with follow-up cohorts.

There were no studies that identified the ideal time to perform reoperations with regard to postoperative adhesions. Fifteen studies reported their results according to a planned second-look laparotomy or laparoscopy performed between one and four months postoperatively. However in 10 of the 25 studies without a scheduled second-look laparotomy or laparoscopy, the assessment of adhesions was performed more than 1 year after the operation. One study reported that there were no differences in the mortality, morbidity or anastomotic leakage after Hartmann's

reversal between early operated (range 4–15 weeks) and late operated patients (range 16–100 weeks), although the length of hospital stay was longer and the difficulty of the operation was greater in the early operated patients [53]. Further prospective studies identifying the development and optimal management of adhesions according to a specifically designed time scale could enhance surgical decisions regarding re-operations in patients with adhesions. These studies would offer increased levels of evidence to support clinical decisions made for the management of adhesions.

The results of this study demonstrated that overall, more than half of all abdominal procedures result in adhesion formation (54 %). This high rate is associated with significant morbidity and mortality that warrant the consideration of anti-adhesion strategies. Two recent meta-analyses have reported the results using intraperitoneal prophylactic agents, such as hyaluronic acid/carboxymethylcellulose membranes, oxidized regenerated cellulose and expanded polytetrafluoroethylene sheets, for reducing the incidence, severity and extent of peritoneal adhesions [54, 55]. Further investigations into the overall reduction of adhesion-specific complications by anti-adhesion agents and an assessment of their cost-effectiveness are required to better understand their clinical efficacy.

There is increasing evidence that can be used to identify and decrease the effects of adhesion-inducing elements in the context of any abdominal operation. These include the presence of latex or powder on surgical gloves [56–58], the operation time, blood loss [59] and development of abdominal infections [60], which have all been demonstrated to induce adhesions in animal models. Conversely, the use of steroids [61, 62] and non-steroidal anti-inflammatory drugs [63–65] have been demonstrated to reduce postoperative adhesion formation by decreasing the inflammatory activity, whereas cytotoxic agents, such as mitomycin C, can reduce adhesion formation via the inhibition of fibroblast proliferation [66, 67]. An increased awareness of these anti-adhesion strategies in a practical setting may help decrease the long-term complications of surgical adhesions.

Interestingly, the incidence and severity of adhesions were higher in myomectomies as compared to caesarean section, despite a similar tissue exposure associated with both procedures. During normal pregnancy, there is a marked increase in pro-coagulant activity and a reduction in fibrinolytic activity [68, 69]. This conflicts with our results showing decreased adhesions in this patient group, and further research is necessary to identify the mechanisms underlying adhesion formation in the physiological environment of pregnancy.

There were several limitations to the present study. The statistical pooling of observational studies is vulnerable to the bias and confounding factors inherent in these studies [70]. Most of the included studies were not comparative studies, and were retrospective in origin and had a small sample size, large heterogeneity and low scientific quality due to a lack of validated adhesion scoring systems; we suggest that an ideal scoring system for adhesions should include the specific anatomical distribution, severity, clinical complications and a quantified volume of intra-abdominal adhesions. In our analysis, the various procedures were pooled, because there were few published studies classified by surgical procedure. Although laparoscopy was used as a technique to assess adhesions in 68 % (17/25) of the included studies (a "second-look" surgery), this method may underestimate the occurrence of adhesions deep in the abdominal cavity due to the limited field of view. Furthermore, these results do not account for the formation of adhesions in patients, who do not undergo a follow-up laparotomy or laparoscopy. Consequently, our results do not reflect the overall rates of formation of adhesion after surgery (as this data is not available), but represent the adhesion formation in patients, who underwent a repeat diagnostic operation. Our results are also biased to procedures that have reported postoperative adhesion data in the literature. Considering the large heterogeneity of the data sources, a formal subgroup analysis by disease or symptoms from adhesions was not possible.

Of the 25 studies included in our analysis, 15 (60 %) reported the results of postoperative adhesions after a planned "second-look" procedure, seven studies (28 %) identified the postoperative adhesion formation at a caesarean operation that followed previous abdominal surgery and three studies (12 %) identified adhesions during an unplanned abdominal procedure where patients had clinically significant abdominal symptoms. In the latter group, the abdominal symptoms may or may not have been due to their postoperative adhesions. Our results, therefore, likely underestimated the actual adhesion rate, as patients with non-symptomatic adhesions may not have undergone diagnostic exploration of their abdomens postoperatively. Furthermore, the studies analysed had variable follow-up periods, so that there was a bias related to the length of follow-up, and there was limited information on the formation of adhesions over time. As a result, there is currently inadequate evidence available to predict which patients will develop adhesions, where they will be located and whether they will lead to postoperative complications.

Conclusions

The development of postoperative adhesions is an increasingly recognized cause of postoperative complications ranging from pain to bowel obstruction. Typically,

adhesions are diagnosed at a "second-look" laparotomy, which is frequently inadequate and delayed. The incidence and severity of postoperative adhesions vary by surgical speciality and procedure. Gastrointestinal surgery and myomectomy have the highest rates of postoperative adhesion formation, whereas urological surgery and caesarean section have the lowest rates. Laparoscopic gastrointestinal surgery is currently the only surgical modality used to minimize the incidence and severity of adhesions that can offer decreased complications and enhanced recovery. Furthermore, the results of modern surgery have revealed an improvement in the overall incidence of adhesions as compared to surgery 30 years ago, which may reflect the improvements in surgical practice and education in addition to the development of minimally invasive surgery. These results can be further enhanced by the application of anti-adhesive films and pharmacological therapies, such as hyaluronic acid/carboxymethylcellulose membranes, oxidized regenerated cellulose and expanded 0.5 % ferric hyaluranate gels. Further experimental research in adhesion biology may provide an increased understanding of the molecular mechanisms underlying the formation of adhesions, which may lead to novel strategies for adhesion prevention and treatment, while also improving adhesion awareness and the surgical consent process. Future studies should apply well-designed comparative designs (such as prospective studies with follow-up cohorts) in the context of internationally approved and standardized scoring systems for the adhesion location and severity. These should also consider the cost of adhesions and the cost-effectiveness of their treatments. The high rate of postoperative adhesions warrants the introduction of increasingly innovative strategies for the reduction in surgical adhesions to improve patient morbidity and mortality and the cost of abdominal surgeries.

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References

1. Menzies D, Ellis H. Intestinal obstruction from adhesions—how big is the problem? Ann Roy Coll Surg Engl. 1990;72:60–3.
2. Holmdahl L. The role of fibrinolysis in adhesion formation. Eur J Surg Suppl Acta Chir Suppl 1997;24–31.
3. Holmdahl L, Eriksson E, Eriksson BI, Risberg B. Depression of peritoneal fibrinolysis during operation is a local response to trauma. Surgery. 1998;123:539–44.
4. Swank DJ, Jeekel H. Laparoscopic adhesiolysis in patients with chronic abdominal pain. Curr Opin Obstet Gynecol. 2004; 16:313–8.
5. Menzies D. Peritoneal adhesions. Incidence, cause, and prevention. Surg Ann. 1992;24(Pt 1):27–45.
6. Hershlag A, Diamond MP, DeCherney AH. Adhesiolysis. Clin Obstet Gynecol. 1991;34:395–402.
7. Van Der Krabben AA, Dijkstra FR, Nieuwenhuijzen M, Reijnen MM, Schaapveld M, Van Goor H. Morbidity and mortality of inadvertent enterotomy during adhesiotomy. Br J Surg. 2000;87: 467–71.
8. Menzies D, Parker M, Hoare R, Knight A. Small bowel obstruction due to postoperative adhesions: treatment patterns and associated costs in 110 hospital admissions. Ann Roy Coll Surg Engl. 2001;83:40–6.
9. Prichayudh S, Sriussadaporn S, Samorn P, Pak-Art R, Sriussadaporn S, Kritayakirana K, et al. Management of open abdomen with an absorbable mesh closure. Surg Today. 2011;41:72–8.
10. Ray NF, Denton WG, Thamer M, Henderson SC, Perry S. Abdominal adhesiolysis: inpatient care and expenditures in the United States in 1994. J Am Coll Surg. 1998;186:1–9.
11. Schreinemacher MH, ten Broek RP, Bakkum EA, van Goor H, Bouvy ND. Adhesion awareness: a national survey of surgeons. World J Surg. 2010;34:2805–12.
12. Rajab TK, Wallwiener M, Talukdar S, Kraemer B. Adhesion-related complications are common, but rarely discussed in preoperative consent: a multicenter study. World J Surg. 2009;33: 748–50.
13. Stang A. Critical evaluation of the Newcastle–Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603–5.
14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
15. Blumenfeld YJ, Caughey AB, El-Sayed YY, Daniels K, Lyell DJ. Single-versus double-layer hysterectomy closure at primary caesarean delivery and bladder adhesions. BJOG. 2010;117: 690–4.
16. Mais V, Ajossa S, Piras B, Guerriero S, Marongiu D, Melis GB. Prevention of de-novo adhesion formation after laparoscopic myomectomy: a randomized trial to evaluate the effectiveness of an oxidized regenerated cellulose absorbable barrier. Hum Reprod. 1995;10:3133–5.
17. Becker JM, Dayton MT, Fazio VW, Beck DE, Stryker SJ, Wexner SD, et al. Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double-blind multicenter study. J Am Coll Surg. 1996;183:297–306.
18. Ugur M, Turan C, Mungan T, Aydogdu T, Sahin Y, Gokmen O. Laparoscopy for adhesion prevention following myomectomy. Int J Gynaecol Obstet. 1996;53:145–9.
19. Assaf A. Adhesions after laparoscopic myomectomy: effect of the technique used. Gynaecol Endosc. 1999;8:225–9.
20. Polymeneas G, Theodosopoulos T, Stamatiadis A, Kourias E. A comparative study of postoperative adhesion formation after laparoscopic vs open cholecystectomy. Surg Endosc. 2001;15: 41–3.
21. Pattaras JG, Moore RG, Landman J, Clayman RV, Janetschek G, McDougall EM, et al. Incidence of postoperative adhesion formation after transperitoneal genitourinary laparoscopic surgery. Urology. 2002;59:37–41.
22. Vrijland WW, Tseng LN, Eijkman HJ, Hop WC, Jakimowicz JJ, Leguit P, et al. Fewer intraperitoneal adhesions with use of hyaluronic acid–carboxymethylcellulose membrane: a randomized clinical trial. Ann Surg. 2002;235:193–9.
23. Mettler L, Audebert A, Lehmann-Willenbrock E, Schive K, Jacobs VR. Prospective clinical trial of SprayGel as a barrier to adhesion formation: an interim analysis. J Am Assoc Gynecol Laparosc. 2003;10:339–44.
24. Tang CL, Seow-Choen F, Fook-Chong S, Eu KW. Bioresorbable adhesion barrier facilitates early closure of the defunctioning

ileostomy after rectal excision: a prospective, randomized trial. Dis Colon Rectum. 2003;46:1200–7.
25. Swank DJ, Hop WC, Jeekel J. Reduction, regrowth, and de novo formation of abdominal adhesions after laparoscopic adhesiolysis: a prospective analysis. Dig Surg. 2004;21:66–71.
26. Cohen Z, Senagore AJ, Dayton MT, Koruda MJ, Beck DE, Wolff BG, et al. Prevention of postoperative abdominal adhesions by a novel, glycerol/sodium hyaluronate/carboxymethylcellulose-based bioresorbable membrane: a prospective, randomized, evaluator-blinded multicenter study. Dis Colon Rectum. 2005;48:1130–9.
27. Kusunoki M, Ikeuchi H, Yanagi H, Noda M, Tonouchi H, Mohri Y, et al. Bioresorbable hyaluronate-carboxymethylcellulose membrane (Seprafilm) in surgery for rectal carcinoma: a prospective randomized clinical trial. Surg Today. 2005;35:940–5.
28. Takeuchi H, Kitade M, Kikuchi I, Shimanuki H, Kumakiri J, Kinoshita K. Adhesion–prevention effects of fibrin sealants after laparoscopic myomectomy as determined by second-look laparoscopy: a prospective, randomized, controlled study. J Reprod Med. 2005;50:571–7.
29. Tsuji S, Takahashi K, Yomo H, Fujiwara M, Kita N, Takebayashi K, et al. Effectiveness of antiadhesion barriers in preventing adhesion after myomectomy in patients with uterine leiomyoma. Eur J Obstet Gynecol Reprod Biol. 2005;123:244–8.
30. Zareian Z, Zareian P. Non-closure versus closure of peritoneum during cesarean section: a randomized study. Eur J Obstet Gynecol Reprod Biol. 2006;128:267–9.
31. Hamel KJ. Incidence of adhesions at repeat cesarean delivery. Am J Obstet Gynecol. 2007;196:e31–2.
32. Mettler L, Hucke J, Bojahr B, Tinneberg HR, Leyland N, Avelar R. A safety and efficacy study of a resorbable hydrogel for reduction of post-operative adhesions following myomectomy. Hum Reprod. 2008;23:1093–100.
33. Sileri P, Sthory R, McVeigh E, Child T, Cunningham C, Mortensen NJ, et al. Adhesions are common and costly after open pouch surgery. J Gastrointest Surg. 2008;12:1239–45.
34. Fatusic Z, Hudic I. Incidence of post-operative adhesions following Misgav Ladach caesarean section—a comparative study. J Matern Fetal Neonat Med. 2009;22:157–60.
35. Indar AA, Efron JE, Young-Fadok TM. Laparoscopic ileal pouch-anal anastomosis reduces abdominal and pelvic adhesions. Surg Endosc. 2009;23:174–7.
36. Tulandi T, Agdi M, Zarei A, Miner L, Sikirica V. Adhesion development and morbidity after repeat cesarean delivery. Am J Obstet Gynecol 2009;201:56e51–56.
37. Myers SA, Bennett TL. Incidence of significant adhesions at repeat cesarean section and the relationship to method of prior peritoneal closure. J Reprod Med. 2005;50:659–62.
38. Tinelli A, Malvasi A, Guido M, Tsin DA, Hudelist G, Hurst B, et al. Adhesion formation after intracapsular myomectomy with or without adhesion barrier. Fertil Steril. 2011;95:1780–5.
39. Chapa HO, Venegas G, Vanduyne CP, Antonetti AG, Sandate JP, Silver L. Peritoneal adhesion prevention at cesarean section: an analysis of the effectiveness of an absorbable adhesion barrier. J Reprod Med. 2011;56:103–9.
40. Operative Laparoscopy Study Group. Postoperative adhesion development after operative laparoscopy: evaluation at early second-look procedures. Fertil Steril. 1991;55:700–4.
41. Tang CL, Jayne DG, Seow-Choen F, Ng YY, Eu KW, Mustapha N. A randomized controlled trial of 0.5% ferric hyaluronate gel (Intergel) in the prevention of adhesions following abdominal surgery. Ann Surg. 2006;243:449–55.
42. The American Fertility Society classifications of Adnexal Adhesions. Distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Mullerian anomalies and intrauterine adhesions. Fertil Steril. 1988;49:944–55.
43. Ellis H, Moran BJ, Thompson JN, Parker MC, Wilson MS, Menzies D, et al. Adhesion-related hospital readmissions after abdominal and pelvic surgery: a retrospective cohort study. Lancet. 1999;353:1476–80.
44. Weibel MA, Majno G. Peritoneal adhesions and their relation to abdominal surgery. A postmortem study. Am J Surg. 1973;126:345–53.
45. Monk BJ, Berman ML, Montz FJ. Adhesions after extensive gynecologic surgery: clinical significance, etiology, and prevention. Am J Obstet Gynecol. 1994;170:1396–403.
46. Dijkstra FR, Nieuwenhuijzen M, Reijnen MM, van Goor H. Recent clinical developments in pathophysiology, epidemiology, diagnosis and treatment of intra-abdominal adhesions. Scand J Gastroenterol Suppl 2000;52–59.
47. Demco L. Pain mapping of adhesions. J Am Assoc Gynecol Laparosc. 2004;11:181–3.
48. Herrick SE, Mutsaers SE, Ozua P, Sulaiman H, Omer A, Boulos P, et al. Human peritoneal adhesions are highly cellular, innervated, and vascularized. J Pathol. 2000;192:67–72.
49. Sulaiman H, Gabella G, Davis MC, Mutsaers SE, Boulos P, Laurent GJ, et al. Presence and distribution of sensory nerve fibers in human peritoneal adhesions. Ann Surg. 2001;234:256–61.
50. Gutt CN, Oniu T, Schemmer P, Mehrabi A, Buchler MW. Fewer adhesions induced by laparoscopic surgery? Surg Endosc. 2004;18:898–906.
51. Molinas CR, Campo R, Elkelani OA, Binda MM, Carmeliet P, Koninckx PR. Role of hypoxia inducible factors 1alpha and 2alpha in basal adhesion formation and in carbon dioxide pneumoperitoneum-enhanced adhesion formation after laparoscopic surgery in transgenic mice. Fertil Steril. 2003;80(Suppl 2):795–802.
52. Molinas CR, Mynbaev O, Pauwels A, Novak P, Koninckx PR. Peritoneal mesothelial hypoxia during pneumoperitoneum is a cofactor in adhesion formation in a laparoscopic mouse model. Fertil Steril. 2001;76:560–7.
53. Keck JO, Collopy BT, Ryan PJ, Fink R, Mackay JR, Woods RJ. Reversal of Hartmann's procedure: effect of timing and technique on ease and safety. Dis Colon Rectum. 1994;37:243–8.
54. Ahmad G, Duffy JM, Farquhar C, Vail A, Vandekerckhove P, Watson A et al. Barrier agents for adhesion prevention after gynaecological surgery. Cochrane Database Syst Rev. 2008;CD000475.
55. Kumar S, Wong PF, Leaper DJ. Intra-peritoneal prophylactic agents for preventing adhesions and adhesive intestinal obstruction after non-gynaecological abdominal surgery. Cochrane Database Syst Rev. 2009;CD005080.
56. Dwivedi AJ, Kuwajerwala NK, Silva YJ, Tennenberg SD. Effects of surgical gloves on postoperative peritoneal adhesions and cytokine expression in a rat model. Am J Surg. 2004;188:491–4.
57. Numanoglu V, Cihan A, Salman B, Ucan BH, Cakmak GK, Cesur A, et al. Comparison between powdered gloves, powder-free gloves and hyaluronate/carboxymethylcellulose membrane on adhesion formation in a rat caecal serosal abrasion model. Asian J Surg/Asian Surg Assoc. 2007;30:96–101.
58. van den Tol MP, Haverlag R, van Rossen ME, Bonthuis F, Marquet RL, Jeekel J. Glove powder promotes adhesion formation and facilitates tumour cell adhesion and growth. Br J Surg. 2001;88:1258–63.
59. Ordonez JL, Dominguez J, Evrard V, Koninckx PR. The effect of training and duration of surgery on adhesion formation in the rabbit model. Hum Reprod. 1997;12:2654–7.
60. van Goor H, Bom VJ, van der Meer J, Sluiter WJ, Bleichrodt RP. Coagulation and fibrinolytic responses of human peritoneal fluid and plasma to bacterial peritonitis. Br J Surg. 1996;83:1133–5.
61. Hockel M, Ott S, Siemann U, Kissel T. Prevention of peritoneal adhesions in the rat with sustained intraperitoneal dexamethasone

delivered by a novel therapeutic system. Ann Chir Gynaecol. 1987;76:306–13.
62. Kucukozkan T, Ersoy B, Uygur D, Gundogdu C. Prevention of adhesions by sodium chromoglycate, dexamethasone, saline and aprotinin after pelvic surgery. ANZ J Surg. 2004;74:1111–5.
63. Guvenal T, Cetin A, Ozdemir H, Yanar O, Kaya T. Prevention of postoperative adhesion formation in rat uterine horn model by nimesulide: a selective COX-2 inhibitor. Hum Reprod. 2001;16: 1732–5.
64. De Leon FD, Toledo AA, Sanfilippo JS, Yussman MA. The prevention of adhesion formation by nonsteroidal antiinflammatory drugs: an animal study comparing ibuprofen and indomethacin. Fertil Steril. 1984;41:639–42.
65. Nishimura K, Nakamura RM, diZerega GS. Ibuprofen inhibition of postsurgical adhesion formation: a time and dose response biochemical evaluation in rabbits. J Surg Res. 1984;36:115–24.
66. Liu Y, Li H, Shu XZ, Gray SD, Prestwich GD. Crosslinked hyaluronan hydrogels containing mitomycin C reduce postoperative abdominal adhesions. Fertil Steril. 2005;83(Suppl 1): 1275–83.
67. Cubukcu A, Alponat A, Gonullu NN, Ozkan S, Ercin C. An experimental study evaluating the effect of mitomycin C on the prevention of postoperative intraabdominal adhesions. J Surg Res. 2001;96:163–6.
68. Brenner B. Haemostatic changes in pregnancy. Thromb Res. 2004;114:409–14.
69. Holmes VA, Wallace JM. Haemostasis in normal pregnancy: a balancing act? Biochem Soc Trans. 2005;33:428–32.
70. Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. BMJ. 1998;316:140–4.