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Meta-analysis

Using different surgical techniques and ideas to reduce post-operative adhesion formation: a systematic review and meta-analysis

Rekha Rani*, Shikha Singh, Urvashi, Ruchika Garg

Department of Obstetrics and Gynaecology, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India

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***Correspondence:**
Dr. Rekha Rani,
E-mail: drrekha.gynae@gmail.com

ABSTRACT

Adhesion development is the most common sequelae of intra-abdominal and pelvic surgery. Using a good surgical technique is advocated as a first step in preventing adhesions. However, the evidence for different surgical techniques to reduce adhesion formation needs confirmation. This review contributed to the growing knowledge pool by elucidating factors that potentially predispose to the development of adhesions. A literature search was performed using the PubMed database for all relevant English language articles and were reviewed with particular attention to predisposing factors to post-operative adhesion development. In addition, the reference lists of each article were reviewed to identify additional relevant articles. Various factors have been shown to directly increase the risk of post-operative adhesion development; namely, certain genetic polymorphisms in the interleukin-1 receptor antagonist, increased estrogen exposure, and endometriosis. There were 28 papers with 27 studies included for a systematic review. Of these, 17 studies were eligible for meta-analysis and 11 for qualitative assessment only. None of the techniques that were compared significantly reduced the incidence of adhesive small bowel obstruction. In a small low-quality trial, the pregnancy rate increased after subserous fixation of suture knots. However, the incidence of adhesions was lower after laparoscopic compared with open surgery (relative risk (RR): 0.14; 95% confidence interval (CI): 0.03-0.61) and when the peritoneum was not closed (RR: 0.36; 95% CI: 0.21-0.63). None of the specific techniques that were compared reduced the two main adhesion-related clinical outcomes, small bowel obstruction and infertility.

Keywords: Tissue adhesions, Laparoscopy, Peritoneal closure, Infertility, Small bowel obstruction

INTRODUCTION

Adhesion development is the most common sequelae of intra-abdominal and pelvic surgery and represents a significant cause of morbidity among post-operative patients. The incidence of adhesive small bowel obstruction (SBO) was 2%. Among patients with a known cause of SBO, adhesions were the single most common cause. Using a good surgical technique is advocated as a first step in preventing adhesions. However, the evidence for different surgical techniques to reduce adhesion formation needs confirmation.

Adhesion formation following pelvic surgery is also common and is a major cause of infertility in women. The mechanism by which adhesions cause infertility includes distortion of the normal ability of the fallopian tube to achieve ovum pickup following ovulation, which can be due to ovarian encapsulation by adhesions or limitations in tubal/fimbral potential for movement.

It has been estimated that 22% of all infertility cases are attributable to adhesions. In one study, adhesions were found in 37% of infertile patients. In 15% of these cases, adhesions were the only factor identified as the cause of

infertility.[1] Interestingly, pregnancy rates have been shown to increase by 38 to 52% among previously infertile patients following laparotomy with adhesiolysis, demonstrating the potential value of adhesiolysis.

Another major consequence of adhesion development is chronic pelvic or abdominal pain, likely the result of increased tension on internal organs at sites stretched as a consequence of anomalous attachments. Another major consequence of adhesion development is chronic pelvic or abdominal pain, likely the result of increased tension on internal organs at sites stretched as a consequence of anomalous attachments . Upon laparoscopic adhesiolysis, 74% of these patients had either a reduction or a complete resolution of their pain, indicating that adhesions were the sole contributor to their pain.[2] Meta-analysis show an increase in operative time by 15 min in patients with previous surgery, as well as a reduction in operative time with the placement of an anti-adhesion barrier.[3]

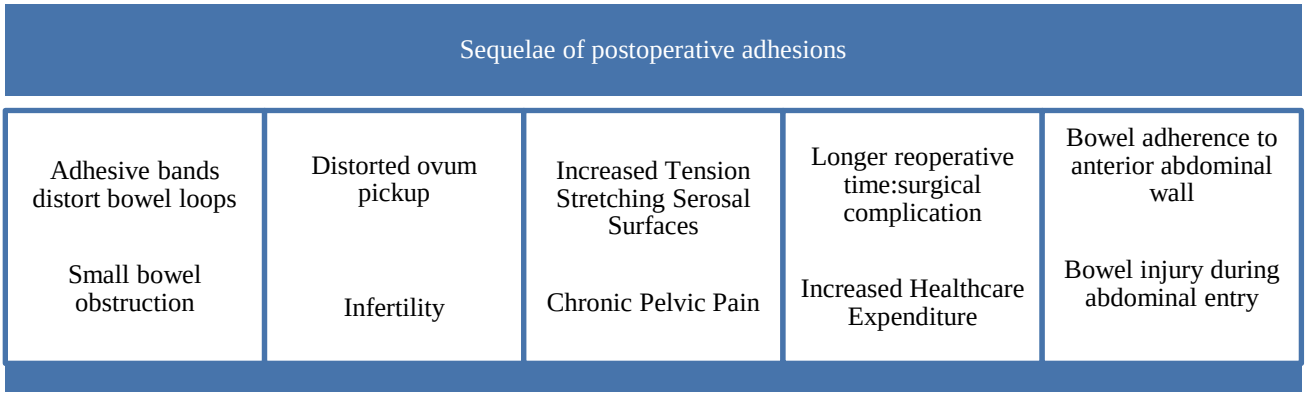

Figure 1: Common clinical sequelae of post-operative adhesion.

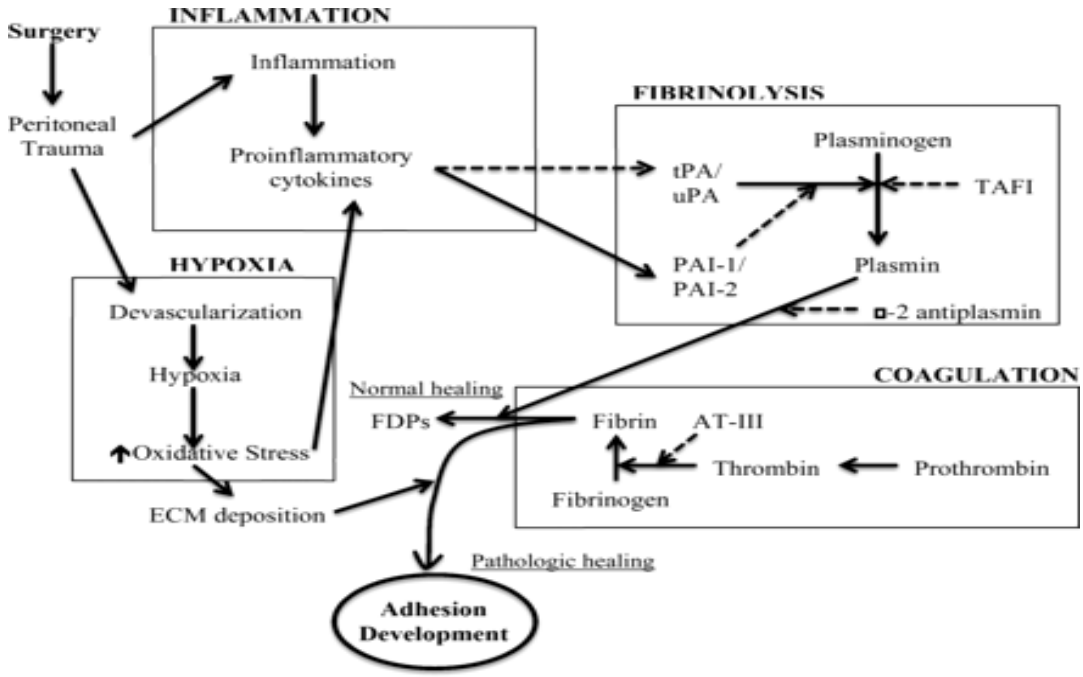

Figure 2: Interconnected processes.

Pathophysiology

The peritoneum is an extensive layer of mesothelial cells that functions to protect the abdominal organs and reduce friction between their viscera.[4] The peritoneum is exquisitely delicate and highly susceptible to trauma due to the loose interconnection between mesothelial cells. Damage to the peritoneum can be secondary to inflammatory or surgical causes. Inflammatory damage occurs as a result of intra-abdominal inflammatory

processes, including pelvic inflammatory disease, possibly past use of an intrauterine contraceptive device. There are a handful of factors that can damage the peritoneum perioperatively. These include trauma, ischemia, infection, exposure to intestinal contents and foreign bodies (e.g. talcum and powders from gloves, fibers from disposable paper items and lint from abdominal packs). Postsurgical adhesions are the most common subtype of adhesions and will be the focus of this review.

Hypoxia and the subsequent oxidative stress is believed to play a significant role in the pathogenesis of post-operative adhesions. In support of this concept, studies suggested that acute oxidative stress in the peritoneum subsequently induces mesothelial cell loss or dysfunction, peritoneal fibrosis and intra-abdominal adhesion formation. During the first 5 min of ischemia, there is already a significant production of free radicals, either through an increase in reactive oxygen species (ROS) formation or by decreasing ROS scavengers.[5,6] The enhanced production of ROS is associated with phenotypic changes such as enhanced expression of cytokines, growth factors and extracellular matrix as well as genotypic changes such as alterations in DNA sequence of NAPH oxidase.[7]

Once the peritoneum is damaged, the coagulation cascade is set in motion. The coagulation cascade involves the conversion of a series of inactive proenzymes to active enzymes, ultimately resulting in the formation of a clot. Intrinsic and extrinsic pathways lead to the activation of factor X, which then triggers the conversion of prothrombin (factor II) to thrombin (factor IIa). Thrombin serves as the final enzyme of this cascade and converts fibrinogen into fibrin monomers. These fibrin monomers then polymerize to form an insoluble fibrin clot.

This cascade is a normal hemostatic response to tissue injury and is targeted at repair of the damage. However, if two damaged peritoneal surfaces come in contact with each other, the healing process can in essence result in fusion to form a connection, an adhesion.

Research indicated that the coagulation cascade was altered in response to tissue hypoxia. Studies have demonstrated a marked reduction of the tPA/PAI-1 (tissue plasminogen activator/plasminogen activator inhibitor-I) mRNA expression ratio as well as decreased tPA activity in response to tissue hypoxia. Thus the likelihood that fibrinous collections at surgical sites would undergo fibrinolysis was markedly reduced. Subsequent fibroblast migration into the fibrinous mass and deposition of extracellular matrix resulted in adhesion development. Figure 2 depicts the interconnected processes of inflammation, hypoxia, coagulation, and fibrinolysis and their role in the development of post-operative adhesion formation.

Inflammation, hypoxia, coagulation and fibrinolysis and their role in the development of post-operative adhesion formation. Dashed lines represent inhibition. AT-III, antithrombin III; ECM, extracellular matrix; FDPs, fibrin degradation products; PAI, plasminogen activator inhibitor; TAFI, thrombin-activatable fibrinolysis inhibitor; tPA, tissue plasminogen activator; uPA, urokinase-type plasminogen activator.

METHODS

Search

A comprehensive literature search was carried out in Pubmed, Embase and Central. A list of predefined search terms was combined with the Cochrane highly sensitive strategy for Pubmed (Table 1). Similar keywords were used for searching Embase and Central. The Embase search was combined with the sensitivity maximizing search strategy described by Wong et al in 2006. No language or date restrictions were applied. The latest search was carried out on 1 October 2011. A manual search of the bibliographies of relevant papers was carried out to identify additional studies for possible inclusion.

Various factors have been shown to directly increase the risk of post-operative adhesion formation. A summary of the factors associated with increased or decreased risk of adhesion development as well as with alterations in fibrosis, is depicted in Table 1. These factors have been grouped into five major categories: surgical and medical history (type of surgery, medications, diabetes mellitus, cancer, endometriosis); reproductive milieu (hormones, menstrual cycle, pregnancy); specific demographics (gender, age, genetics); lifestyle and nutritional factors (obesity, exercise, diet, alcohol, smoking) and psychological well-being (stress, mood). Figure 3 depicts the impact that each of these categories has on the coagulation and fibrinolytic systems with its consequential propensity for adhesion development, or for remesotheliazation and healing without adhesion development, respectively.

Factors associated with increased/decreased risk of fibrosis as well as post-operative adhesion formation

Hypothesized to increase risk of adhesions

Medical/surgical history of adhesiolysis, endometriosis, estrogen intake were hypothesized to increase risk of adhesions.

Hypothesized to increase risk of fibrosis

Anti-Parkinsonian drugs, diabetes mellitus, obesity, cancer, alcohol consumption, smoking were hypothesized to increase tisk of fibrosis.

Unclear or conflicting finding

Lower GI surgery, menstrual cycle, gender, age were the unclear or conflicting findings.

Hypothesized to decrease risk of fibrosis

Statin, low-saturated-fat diet, coffee, antioxidants, light to moderate consumption were hypothesized to decrease the risk of fibrosis.

Hypothesized to decrease risk of adhesions

Tamoxifen was hypothesized to decrease the risk of adhesions.

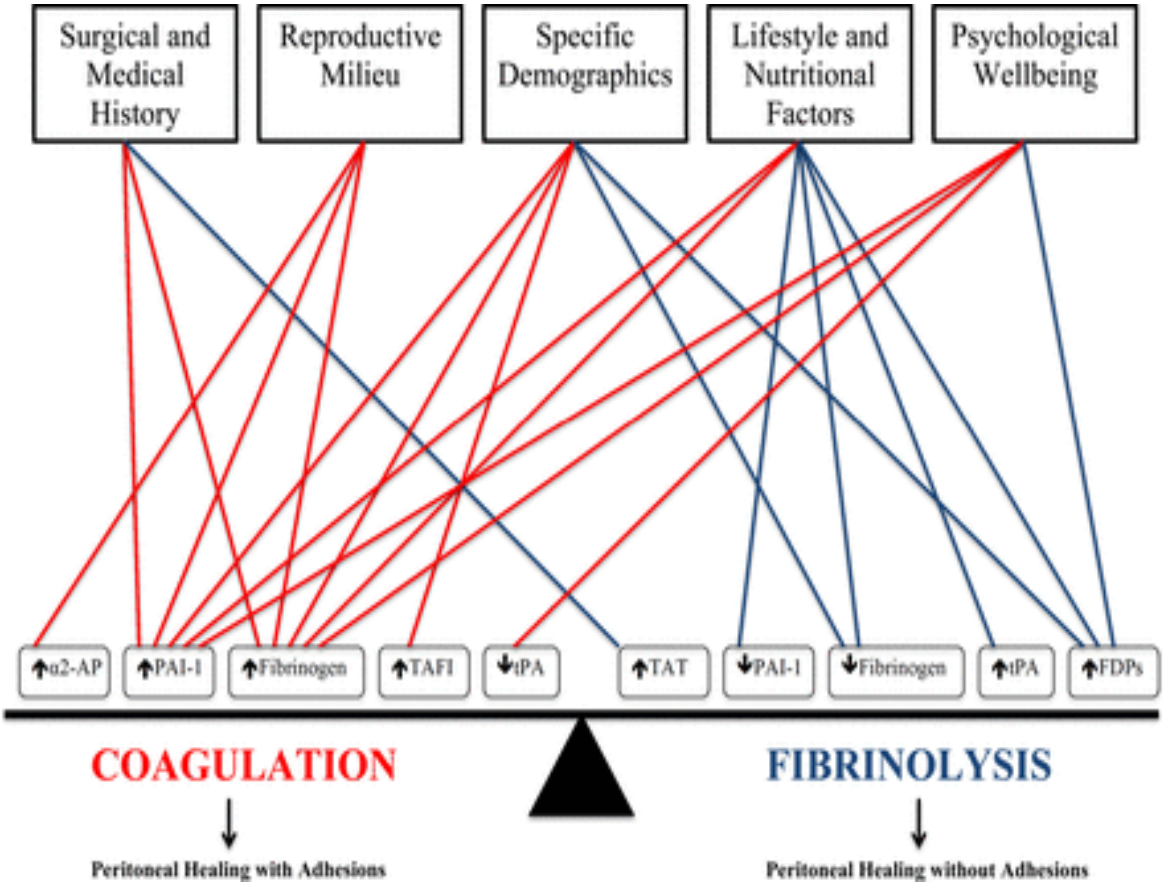

Figure 3: The impact of predisposing factors on key players of the coagulation and fibrinolytic systems; α2-AP, α2-antiplasmin; TAT, thrombin/antithrombin III complex.

Table 1: Predefined search terms used in Pubmed.

Sr. No.	Predefined search terms (title/abstract)
	Patients
1.	Abdo*
2.	Intraabdominal
3.	Peritoneal
4.	Intraperitoneal
5.	Laparoscop*
6.	Laparotom*
7.	Myomect*
8.	Gyne*
9.	Surgi*
10.	Surge*
11.	Color*
12.	Pelv*
13.	Cesarean section
14.	Caesarean section
15.	Combine 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
	Interventions

Continued.

Sr. No.	Predefined search terms (title/abstract)
16.	Electrocoag*
17.	Electrotherm*
18.	Ultrason*
19.	Harmonic scalpel
20.	Ultracision
21.	Periotneal
22.	Peritoneum
23.	Lavage
24.	Sutur*
25.	Closure
26.	Powder
27.	Foreign*
28.	Laparoscope
29.	Laparotom*
30.	Hydra
31.	Conditioning
32.	Antibio*
33.	Laser
34.	Combine 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
	Control
35.	–
	Outcome
36.	Adhesi*
37.	Tissue adhesions (mesh terms)
37.	Combine 37 or 38
	Total
38.	Combine 17 and 36 and 39

RESULTS

Description and quality of included studies

Searches identified 3912 publications. After removal of duplicates, abstracts and titles of 2854 publications were assessed. There were 59 potentially relevant papers were identified from title and abstract and 31 papers were excluded. One paper was written in Romanian language and full text could not be retrieved. The other 30 papers were excluded from analysis after reading the full text. There were 25 papers excluded because they did not compare different surgical techniques or did not report an adhesion-related outcome. Four papers encompassed studies already included and provided no additional information on outcomes or methodology. Only one paper described a study protocol

Finally, 28 papers describing 27 studies were included (Figure 4). Two papers of Lundorff et al in 1991 and 1992 reported results on different outcomes of the same trial.[7]

All 27 studies were published between 1986 and 2010 and addressed different topics of surgical technique. There were 23 studies performed in patients undergoing gynaecological surgery.

Two techniques of caesarean section

The study of Nabhan et al on caesarean section was separately analysed because the operative technique between the experimental and control group differed on more aspects than peritoneal closure alone. This study was not suitable for meta-analysis because 79.3% of patients were lost to follow up by Nabhan et al in 2008.

In the standard technique control group, caesarean section was performed using the traditional Pfannenstiel-Kerr technique, making a bladder flap and closing the peritoneum. In the modified technique group, the Joel-Cohen-Stark technique (based on the Misgav Ladach technique) was used, without making a bladder flap and without closing the peritoneum. The incidence of adhesions was significantly lower in the modified technique group (11.3 versus 35.5%; p=0.003) by Nabhan et al in 2008. Obviously, this reduction cannot solely be attributed to peritoneal non-closure.

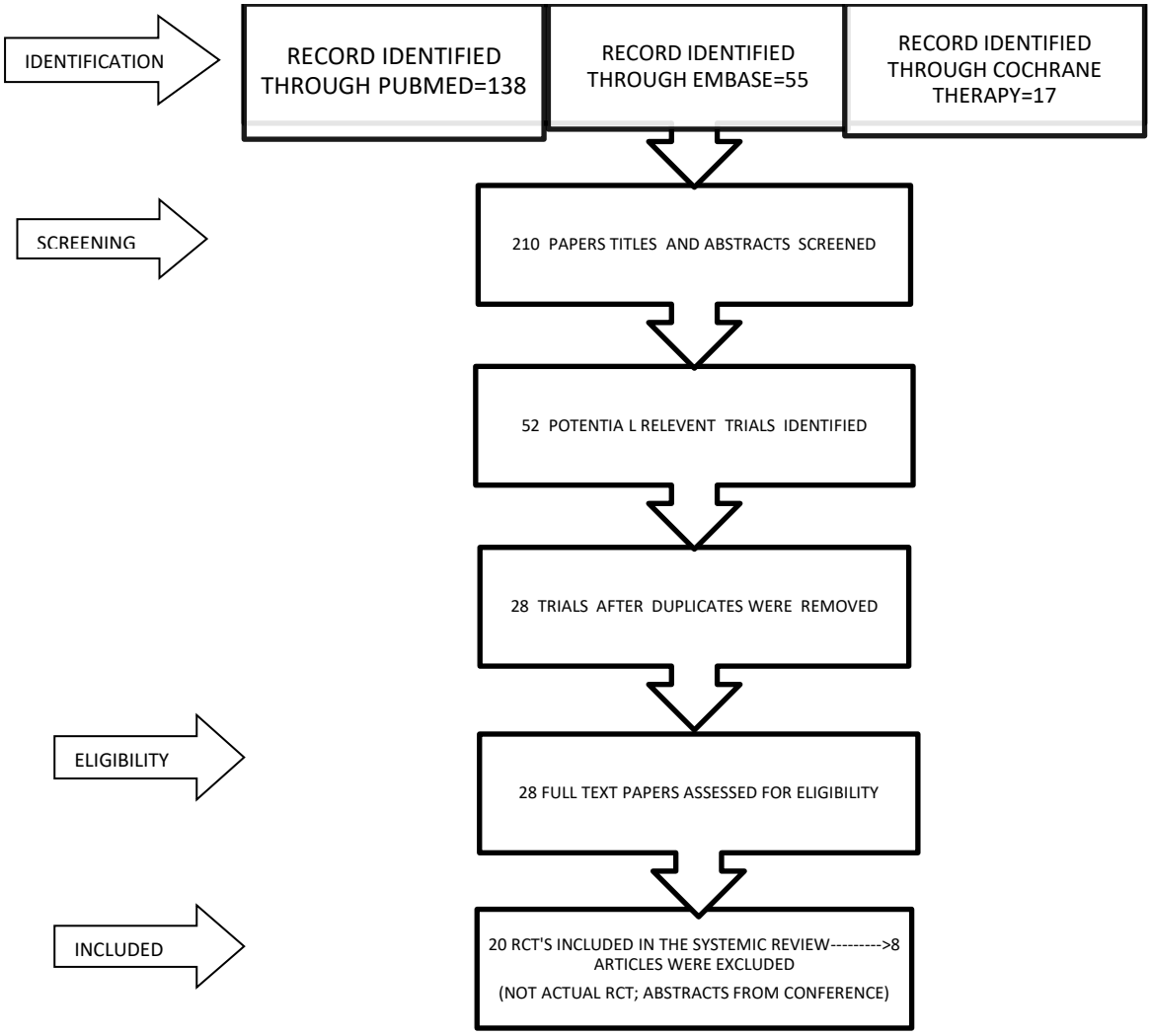

Figure 4: Flow diagram.

Table 2: Risk of bias assessment summary.

References	Adequate sequence generation	Allocation concealment	Blinding blinding (observer)	Adequate reporting on loss to follow up	Power analysis	Free of other sources of bias	Domains with low risk of bias (n)	Comment-other source of bias
Fujishita et al (2004)	Yes	Nr	No	No	NR	No	1	Not all randomized patients had pregnancy desire; no fertility analysis described
Franchi et al (1997)	Yes	NR	NR	Yes	Yes	Yes	4	
Gurgan et al (1991)	NR	NR	NR	NR	NR	NR	0	Randomization of patients not explicitly reported
Gurgan et al (1992)	Yes	NR	No	Yes	NR	NR	2	No assessment and comparison of adhesion in initial surgery

Continued.

References	Adequate sequence generation	Allocation concealment	Blinding blinding (observer)	Adequate reporting on loss to follow up	Power analysis	Free of other sources of bias	Domains with low risk of bias (n)	Comment-other source of bias
Kadanali et al (1996)	NR	Yes	Yes	Yes	NR	NR	3	Length till second look operation not described
Kapustian et al (2011)	Yes	NR	Yes	No	Yes	No	3	Repeat Caesarean section might introduce selection bias
Komoto et al (2006)	No	No	No	No	NR	No	0	Repeat Caesarean section might introduce selection bias
Lundorff (1991+1992)	Yes	Yes	No	No	NR	No	2	Second look not planned for all randomized patients; Not all randomized patients had pregnancy desire
Malvasi et al (2009)	No	No	No	Yes	NR	NR	1	Repeat Caesarean section might introduce selection bias
Mercorio et al (2008)	Yes	Yes	No	Yes	NR	Yes	4	
Nabhan et al (2008)	Yes	Yes	No	No	Yes	No	3	Repeat Caesarean section might introduce selection bias
Ng et al (2009)[a]	Yes	Yes	No	Yes	Yes	Yes	5	
Pellicano et al (2005)	No	NR	No	Yes	NR	No	1	No fertility analysis described
Pellicano et al (2008)	Yes	NR	Yes	Yes	NR	No	3	Problems with statistical analysis
Roy et al (2009)	NR	NR	NR	Yes	NR	No	1	Second look only in patients who failed to conceive, excluded for outcome second look
Sharma et al (2006)	Yes	NR	NR	Yes	NR	No	2	Fertility analysis described is incomplete; Pregnancy rate in abstract does not correspond to rate in full text.
Stocchi et al (2008)	NR	NR	NR	Yes	NR	No	1	No prospective follow-up; might have included some patients before start of randomization

Continued.

References	Adequate sequence generation	Allocation concealment	Blinding blinding (observer)	Adequate reporting on loss to follow up	Power analysis	Free of other sources of bias	Domains with low risk of bias (n)	Comment-other source of bias
Takahashi et al (2007)	NR	NR	No	Yes	NR	Yes	2	Randomization of patients not explicitly reported
Talwar et al (1997)	No	No	No	NR	NR	No	0	Criteria for clinical diagnosis of ASBO not given
Taskin et al (1999)	Yes	NR	NR	NR	NR	No	1	Inconsistencies in reported outcomes
Alborzi et al (2003)	Yes	NR	No	No	NR	No	1	Adhesion score used is highly subjective
Eshuis et al (2010)[a]	Yes	Yes	No	No	Yes	Yes	4	
Weerawetwat et al (2004)	NR	NR	Yes	No	NR	No	1	Repeat Caesarean section might introduce selection bias
Taylor et al (2010)	Yes	Yes	NR	No	Yes	No	3	No prospective follow-up
Zareian et al (2006)	Yes	Yes	NR	No	NR	No	2	Repeat Caesarean section might introduce selection bias

ASBO, adhesive small bowel obstruction; [a]primary powered outcome not adhesion related; NR: not reported or report insufficient for judgement.

Table 3: Characteristics of trials included in meta-analysis.

Study	Period	Patients	Interventions	N	Outcomes	Lost to follow up per outcome (%)	Follow up in months
Laparoscopy versus laparotomy							
Lundorff (1991+1992)	1987-1989	Patients with ectopic pregnancy	Laparoscopy	48	Pregnancy	18/105 (17.1)	1-36
			Laparotomy	57			
Takahashi (2007)	NR	Polycystic ovarian syndrome	Laparoscopy	39	Second look	0/76 (0)	1 week
			Laparotomy	37	Pregnancy	0/76 (0)	12
Peritoneal closure versus no peritoneal closure							
Kadanali (1996)	1992-1995	Lymphadenectomy in ovarian cancer	Peritoneal closure	50	Second look	0/102 (0)	NR
			No peritoneal closure	52			
Franchi (1997)	1991-1995	Hysterectomy and pelvic node dissection	Peritoneal closure	59	ASBO-reoperation	0/120 (0)	11-72
			No peritoneal closure	61			
Malvasi (2009)	2003-2007	Caesarean section	Peritoneal closure	54	Second look	0/112 (0)	NR
			No peritoneal closure	58			
Haemostasis							

Continued.

Study	Period	Patients	Interventions	N	Outcomes	Lost to follow up per outcome (%)	Follow up in months
Laser versus electrocautery							
Gürgan (1991)	NR	Poly cystic ovarian syndrome	Laser	10	Second look	0/17 (0)	3-4 weeks
			Electrocautery (unipolar)	7	Pregnancy	0/17 (0)	6
Tulandi (1986)	NR	Periadnexal adhesions	Laser	30	Pregnancy	0/63 (0)	NR
			Electrocautery (unipolar)	33			
Sutures versus electrocautery							
Pellicano (2008)	2004-2005	Ovarian endometrioma	Suturing	16	Second look	5/32 (15.6)	60-90 days
			Electrocautery (bipolar)	16			
Second look surgery versus no second look surgery							
Alborzi (2003)	NR	Adnexal adhesions	Second look	46	Pregnancy	0/90 (0)	12
			No second look	44			
Gürgan (1992)	NR	Poly Cystic ovarian syndrome	Second look	19	Pregnancy	0/39 (0)	6
			No second look	20			
Various techniques in laparoscopic surgery for polycystic ovarian syndrome							
Sharma (2006)	NR	Poly cystic ovarian syndrome	Unipolar electrocautery	10	Pregnancy	0/20 (0)	NR
			Bipolar electrocautery	10			
Mercorio (2008)	2002-2006	Poly cystic ovarian syndrome	12 punctures	96[a]	Second look	12/182[a] (6,3)	4-9 weeks
			6 punctures	96[a]			
Roy (2009)	2005-2007	Poly cystic ovarian syndrome	Bilateral	22	Pregnancy	0/44	12
			Unilateral	22			
Miscellaneous							
Pellicano (2005)	2001-2002	Laparoscopic myomectomy	Subserous sutures	18	Pregnancy	0/36	12
			Figure-eigth sutures	18			

NR: not reported; [a]randomization unit is ovary.

Table 4: Characteristics of studies included in qualitative assessment.

Study	Period	Patients	Interventions	N	Outcomes	Lost to follow up per outcome (%)	Follow up in months
Laparoscopy versus laparotomy							
Lundorff (1991-1993)	1987-1989	Patients with ectopic pregnancy	Laparoscopy	48	Second look	32/105 (27.8)	12 weeks
			Laparotomy	57	Pregnancy	18/105 (17.1)	1-36
Stocchi (2008)	NR	Ileocolic resection for Crohn's disease	Laparoscopy	27	ASBO-reoperation	0/27 (0)	120±38[a]
			Laparotomy	29		0/29 (0)	132±17[a]
Taylor (2010)	1996-2002	Colorectal cancer	Laparoscopy	526	ASBO-reoperation	246/526 (46.8)	36
			Laparotomy	268		131/268 (48.9)	
Peritoneal closure versus no peritoneal closure							
Kapustian (2011)	2004-2007	Caesarean section	Peritoneal closure	47	Second look	436/533 (81.8)	NR

Continued.

Study	Period	Patients	Interventions	N	Outcomes	Lost to follow up per outcome (%)	Follow up in months
			No peritoneal closure	50			
Komoto (2006)	1995-2000	Caesarean section	Peritoneal closure	70	Second look	74/124 (59.7)	NR
			No peritoneal closure	54			
Weerawetwat (2004)	1987-1991	Caesarean section	Peritoneal closure	240	Second look	295/360 (81.9)	NR
			No peritoneal closure	120			
Zareian (2006)	1999-2004	Caesarean section	Peritoneal closure	24	Second look	14/45 (31.1)	NR
			No peritoneal closure	21			
Techniques in cesarean section							
Nabhan (2008)	2002-2007	Caesarean section	Pfannenstiel-Kerr	300	Second look	476/600 (79.3)	NR
			Joel-Cohen-Stark	300			
Suturing versus no suturing following salpingotomy							
Fujishita (2004)	1996-2002	Salpingotomy for ectopic pregnancy	Sutures	32	Pregnancy	43/75 (57.3)	6-65
			No sutures	43			
Tulandi (1991)	NR	Salpingotomy for ectopic pregnancy	Sutures	19	Second look	8/19 (42.1)	24
			No sutures	15		8/15 (53.3)	
Taskin (1999)	NR	Poly cystic ovarian syndrome	Microlaparoscopy	9	Second look	?/9	2-3 weeks
			Laparoscopy	9		?/9	

Randomization unit is ovary; NR: not reported; median (range); [a]mean±SD.

DISCUSSION

Summary of evidence

Surgical techniques aiming to reduce adhesion formation included a large variety of technical aspects. None of the different techniques or approaches evidently showed a reduction of the main adhesion-related complications ASBO (adhesive small bowel obstruction) and infertility. The incidence of ASBO, established by reoperation was not significantly different in any comparison. The clinical suspicion of ASBO was lower following laparoscopy compared with open surgery in one study. The incidence of adhesions was lower following laparoscopy than laparotomy and when the peritoneum was left open compared with peritoneal closure. However, the evidence for a lower incidence of adhesions was limited to a single small RCT and conflicting results were found in the qualitative assessment of lower quality studies. The pregnancy rate was significantly higher in one study after subserous fixation of sutures compared with standard sutures in a small low-quality RCT.

Strengths and limitations of the review

The failure to demonstrate an effect on a relevant clinical end-point such as ASBO and pregnancy in this meta-analysis has several causes. Particularly in gynaecological studies, a substantial portion of patients were lost to follow up decreasing the number of evaluable patients. One single adhesive band may still cause a bowel obstruction.

The present study was the first systematic review and meta-analysis of the impact of different surgical techniques on adhesion formation. The available evidence was predominantly from surgery of gynaecologic origin, particularly related to fertility by Metwally et al 2006 and Ahmad et al 2008).[9,10] This type of surgery was often chosen in adhesion prevention research, because of the historical awareness of the adhesion problem within the European and the American fertility societies and because the surgery included a second-look procedure and prevention of local adhesion reformation corresponded with clinical success by Zerega 1993, Marana et al 1995 and Nappi et al 2007.[4,11,12]

A large number of studies had difficulty in achieving a complete follow up. As many as nine studies were excluded from meta-analysis because of an inadequate follow up. Especially, the repeat caesarean section model seems prone to high numbers of patients lost to follow up, a study done by Weerawetwat et al 2004, Komoto et al 2006, Zareian et al 2006, Nabhan et al 2008 and Kapustian et al 2011.[13-17] Further, the choice of a repeat caesarean section as a second-look procedure to study peritoneal closure bears the risk of selection bias towards patients with fewer adhesions because they had a higher chance of becoming pregnant again. Such study design also led to a large variation in the follow up period, as the timing of the next pregnancy and the need for another caesarean section were unpredictable.

Unpublished data from a large RCT revealed that every 30 min of adhesiolysis was correlated to an increase in hospital stay with 1 day, study done by Fazio et al 2006.[18]

Comparison with previous research

The reduction in adhesion extent and severity by limited electrocoagulation, subserous suture fixation and non-closure of the peritoneum emphasized the importance of limiting peritoneal ischaemia and foreign body material in surgery, study done by Kadanali et al 1996 and Pellicano et al 2003.[6,19] Contrastingly, current guidelines suggested that non-closure might be more favourable in terms of short-term complications, recovery and adhesion formation (Royal college of obstetricians and gynecologists, 2002; National institute of clinical excellence, 2004). A Cochrane review studying short-term complications and recovery after caesarean section found no difference between closure and non-closure of the peritoneum, a study done by Bamigboye et al 2009.[20] A recent large RCT of caesarean sections also demonstrated no difference in short-term complications. Long-term follow up results were still awaited by Caesar study collaborative group, 2010.[21] Six RCTs addressing peritoneal closure in general surgery and following hysterectomy have demonstrated a similar incidence of incisional hernia after closure or non-closure of the peritoneum, studies done by Ellis et al 1977; McFadden et al 1983; Gilbert et al 1987; Hugh et al 1990; Than et al 1994 and Lipscomb et al 1996).[22-27] Summarizing the results of suturing or not suturing the peritoneum in caesarean section, both techniques seemed acceptable considering short-term complications but non-closure might decreased incidence of adhesions. The question was why adhesions were not more effectively prevented despite the strong concept of minimal invasive surgery inducing less tissue damage and thus a lower risk of adhesion formation. A number of factors might explain the lack of difference between laparoscopic and open surgery. First, an abdominal incision was often needed after a laparoscopic procedure to extract the specimen by an open approach. Secondly, the extent of serosal wound surfaces was comparable between open and laparoscopic procedures. Thirdly, the CO_2 pneumoperitoneum, the higher intra-abdominal pressure and the light of the laparoscope being associated with peritoneal ischaemia, decreased fibrinolysis and increased adhesion formation, studies done by Binda et al 2003 and Brokelman et al 2006).[28,29] Fourth, the pneumoperitoneum potentially injured the whole peritoneal surface inducing adhesion formation at remote areas. More meticulous dissection and haemostasis, no retraction of the abdominal wall and no use of gauzes in the peritoneal cavity in laparoscopic surgery counterbalance the drawbacks mentioned.

Implications for future research

The poor quality of RCT's and the limited number of eligible patients illustrate the main difficulty in clinical adhesion research, the execution of a planned second-look operation, which was the gold standard for assessment of the incidence and severity of adhesions. The number of planned second procedures had declined over recent years in both female patients who underwent planned second-look laparoscopy following fertility surgery. The declining number of planned second procedures was a challenge for future research in adhesion prevention. Visceral slide and cine-MRI were non-invasive adhesion detection techniques that have the potential to replace a second-look operation. Cine-MRI especially holds promise identifying both adhesions to the abdominal wall and between abdominal viscera, studies done by Lienemann et al 2000; Kirchhoff et al 2010.[31,32]

Implications for clinical practice

None of the different techniques had a major impact on adhesion-related complications. This meta-analysis provided little evidence that less invasive techniques, less foreign body material and less ischaemic injury reduced the extent and severity of adhesions in humans. The total prevention of adhesion formation was the only means to prevent an adhesion-related complication. It was not expected that optimal surgical technique alone will achieve this goal, based on the inevitable peritoneal injury inflicted by any type of surgery. As a consequence, there continued to be a need for anti-adhesion barriers and agents in open and laparoscopic surgery, studies done by Diamond 1996; Zerega et al 2002; Fazio et al 2006 and Metwally et al 2006.[9,18,33,34]

CONCLUSION

Adhesion development is a significant, yet poorly understood cause of morbidity in post-operative patients. To date, it remains unknown exactly why adhesions form more frequently in certain tissues and/or patients, or at specific locations, as opposed to others. This review contributes to the growing knowledge pool by elucidating factors that potentially predispose to the development of adhesions. By identifying those factors shown to directly increase risk (genetic polymorphisms, estrogen exposure and endometriosis) in addition to those that might do so indirectly by way of altering the coagulation/fibrinolytic

profile in such a way that increases fibrosis (genetic polymorphisms, diabetes mellitus, metabolic syndrome, hyperglycemia, obesity, depression, binge alcohol consumption, anti-Parkinsonian medications, oral hormone therapy, pregnancy and cancer), this review can be a useful tool for surgeons to identify high-risk patients who might benefit from anti-adhesion agents. Furthermore, this review serves as a useful catalyst for inspiring future areas of investigation. Further research is necessary to understand the mechanisms that underlie the association of the factors identified in this review with adhesion formation. Future research should also investigate whether there exists a direct link between adhesion formation and any of the factors we have identified as potentially doing so indirectly by increasing fibrosis. This information will be crucial in the creation of adequate preventative and treatment strategies.

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