

Hyaluronic acid fluid agents for the prevention of adhesions after fertility-preserving gynecological surgery: a meta-analysis of randomized controlled trials

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Objective: To investigate the role of hyaluronic acid–based fluid agents in the prevention of adhesions after fertility-preserving gynecological surgery.

Design: Meta-analysis.

Setting: The authors searched the Cochrane Menstrual Disorders and Subfertility Group Specialized Register of Controlled Trials, The Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE for randomized controlled trials of hyaluronic acid fluid agents compared with no treatment or placebo.

Patient(s): Women undergoing fertility-preserving gynecological surgery.

Intervention(s): Hyaluronic acid fluid agents.

Main Outcome Measure(s): [1] Prevalence and change in adhesion severity at second-look laparoscopy and [2] live birth rate.

Result(s): Four studies were included in the meta-analysis. The use of hyaluronic acid agents was associated with a decrease in the prevalence of adhesions at second-look laparoscopy (odds ratio, 0.31; 95% confidence interval, 0.19 to 0.51) and a lesser chance of deterioration of preexisting adhesions (odds ratio, 0.28; 95% confidence interval, 0.12 to 0.66). There was, however, no evidence for improvement in the adhesion score (odds ratio, 1.55; 95% confidence interval, 0.82 to 2.92).

Conclusion(s): There is evidence that hyaluronic acid agents may decrease the prevalence of adhesions and prevent the deterioration of preexisting adhesions. However, because of the limited number of studies available, this evidence should still be interpreted with caution. (*Fertil Steril*® 2007;87:1139–46. ©2007 by American Society for Reproductive Medicine.)

Key Words: Meta-analysis, adhesions, hyaluronic acid

Intraperitoneal adhesions are an important cause of postoperative intestinal obstruction, abdominal discomfort, and infertility (1). Despite careful attention to minimize tissue trauma and ensure hemostasis, pelvic surgery is associated with both de novo adhesion formation and reformation. Adhesions occur after approximately 80% of gynecological surgical procedures, and reformation after surgical lysis occurs postoperatively in 85% of patients (2, 3).

Despite improvement in the success of IVF, reproductive surgery remains an important component of assisted repro-

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ductive technologies (ART) for many couples. In addition, many pelvic operations are performed on women of reproductive age for indications unrelated to fertility. Adhesion formation after these procedures may compromise future fertility of the patient.

A study investigating the effect of tubal and ovarian adhesiolysis on subsequent fertility found that the cumulative pregnancy rate in the group that underwent salpingo-ovariolysis was three times higher than that in the nontreated group (4, 5); hence, adhesion preventive measures are important. Numerous substances have been used experimentally in animal models, including many that have been advocated for use during surgery in human beings (6).

Hyaluronic acid–containing solutions or fluid-like agents, including ferric hyaluronate (Intergel; Gynecare Worldwide, Ethicon Inc., Somerville, NJ), autocross-linked hyaluronic

acid gel (Hyalobarrier gel; Baxter, Pisa, Italy), and Sepracat (Genzyme Corporation, Cambridge, MA), are among those investigated.

This meta-analysis forms part of a Cochrane review (7) on fluid and pharmacological agents that are used for the prevention of adhesions after fertility-preserving gynecological surgery. The aim is to evaluate the impact of hyaluronic acid-containing fluid agents that are used as adjuvants during pelvic surgery on the prevalence and/or severity of postoperative adhesion formation after fertility-preserving gynecological surgery.

MATERIALS AND METHODS

Criteria for Study Inclusion

Randomized controlled trials of hyaluronic acid-containing fluid agents compared with either no treatment or placebo.

Participants

Participants included women in their reproductive period who were undergoing fertility-preserving pelvic surgery (laparoscopy or laparotomy). Patients in whom fertility was not conserved, such as in the case of hysterectomy, were not included.

Search Strategy

The review drew on the search strategy that was developed for the Menstrual Disorders and Subfertility Group. We searched the Cochrane Menstrual Disorders and Subfertility Group Specialized Register of Controlled Trials (last searched November 2005), The Cochrane Central Register of Controlled Trials (last searched November 2005), MEDLINE (1966 to week 2 of November 2005), and EMBASE (1980 to week 47 of 2005).

Data Extraction

Only randomized controlled trials were included (Fig. 1). Further information was sought from investigators whose articles

contained insufficient information to make a decision regarding eligibility. Surgery performed included both open and laparoscopic procedures. For each trial, information was collected regarding the location of the study, methodology, the participants (age and eligibility criteria), the nature of the interventions, and data related to the specified outcomes.

Where continuous data were presented graphically and exact figures could not be obtained, the data were not included in the meta-analysis (8).

Quality Assessment

Two of the reviewers (M.M. and A.W.) independently assessed the quality of all studies that were deemed eligible for the review, on the basis of the method of randomization, quality of allocation concealment, use of blinding, intention-to-treat analysis, and power calculation. Quality assessment of the included studies is seen in Table 1.

Outcome Measures

These included the following: prevalence of adhesions at second-look laparoscopy, improvement or deterioration of adhesion score at second-look laparoscopy, change in mean adhesion score or extent (cm²), and live birth rate.

Quantitative Data Analysis

Statistical analysis was performed in accordance with the guidelines developed by the Cochrane Collaboration (9). Heterogeneity between studies was determined by examining the results of the χ^2 and I^2 statistics. A χ^2 statistic that was larger than its degree of freedom or an I^2 statistic with a value of >50% provided evidence of heterogeneity of treatment effects. Where appropriate, the outcomes were pooled statistically.

Dichotomous data extracted from the individual studies were expressed as an odds ratio with 95% confidence intervals (CIs) and were combined for meta-analysis by using the RevMan software (Review Manager, Version 4.2 for Windows; Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark).

Because of the use of different scoring systems to describe the severity and extent of adhesions, we used the standardized mean difference to compare continuous data. The standardized mean difference was calculated by using the mean and SD. Where the SEM was given, it was converted to SDs by multiplying SEM by the square root of the number of patients.

RESULTS

Study Details

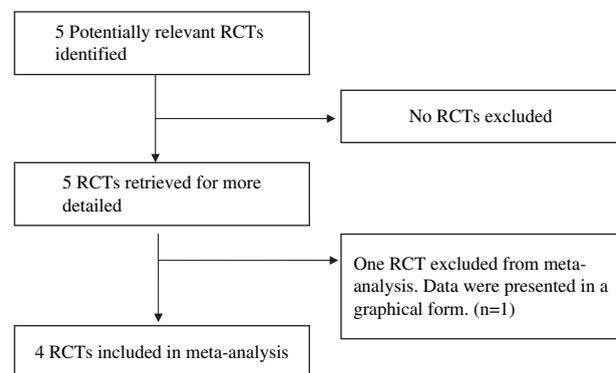
All studies investigating hyaluronic acid-containing fluids were combined. Statistical analysis of the data was possible only from four of five studies identified.

In the studies measuring the prevalence and change in adhesion severity, there was no evidence of significant

FIGURE 1

Flow chart for data extraction and analysis.

RCT = randomized controlled trial.



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TABLE 1**Quality assessment of included studies.**

Study	Pellicano et al. (12)	Lundorff et al. (11)	Johns et al. (10)	Diamond (13)
Allocation concealment clear	Yes	No	No	Yes
Randomization	True	True	True	True
Blinding	Yes	Yes	Yes	Yes
Intention-to-treat analysis	Yes	No	No	No
Power calculation	No	No	No	No

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heterogeneity detected between the studies, as determined by the overlapping of the CIs and by the I^2 and χ^2 statistics (Figs. 2 and 3). Three studies investigated the role of 0.5% ferric hyaluronate gel (Intergel; 365 total patients in all three studies) (8, 10, 11), with lactated Ringer's solution used as the control.

One study with 36 women investigated autocross-linked hyaluronic acid gel (Hyalobarrier) and used no treatment for the control group (12). The final study by Diamond (13) investigated the role of dilute hyaluronic acid solution (Sepracoa) and included 245 women with phosphate-buffered saline as the placebo control. Only the study by Pellicano et al. (12) stated infertility as an inclusion criterion, and none of the five studies evaluated pregnancy as an outcome.

Only one study (14) performed laparoscopy as the primary procedure (laparoscopic myomectomy); the remaining stud-

ies involved a laparotomy and peritoneal surgery for a variety of conditions (Table 2).

Prevalence of Adhesions

Four studies commented on the prevalence of adhesions at second-look laparoscopy (10–13) (Fig. 2) and showed evidence for a decreased prevalence of adhesions in patients who were treated with hyaluronic acid, compared with those given placebo or no treatment (odds ratio, 0.31; 95% CI, 0.19–0.51).

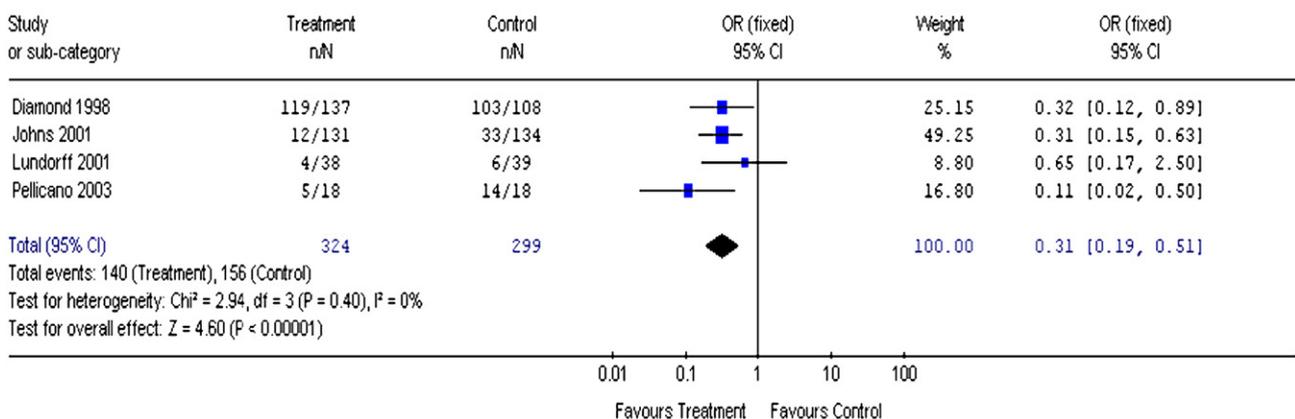
Change in Adhesion Score

Lundorff et al. (11) and Johns et al. (10) recorded the change in the adhesion score at second-look laparoscopy. Both studies used the American Fertility Society score. In the meta-analysis, change in adhesion scores was treated as a binary outcome with two levels; deterioration, defined as a higher

FIGURE 2

Prevalence of adhesions at second-look laparoscopy. There is a significant decrease in the prevalence of adhesions at second look. OR = odds ratio.

Review: Fluid and pharmacological agents for adhesion prevention after gynaecological surgery (confrimed for publication)
 Comparison: 09 Hyaluronic acid versus no hyaluronic acid
 Outcome: 05 Prevalence of adhesions at second-look laparoscopy



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TABLE 2**Characteristics of included studies.**

Study	Pellicano et al. (12)	Lundorff et al. (11)	Johns et al. (10)	Diamond (13)
Method of randomization	Central computer generated	Computer-generated schedule	Randomization schedule	Randomization list
Multicenter	No	Yes	Yes	Yes
Participants	Age: 28 y (mean) Inclusion criteria: 1. History of infertility or recurrent miscarriages. 2. Lack of pedunculation of the main myoma. 3. Presence of ≤ 4 myomas. 4. Absence of submucosal fibroids as screened by hysteroscopy. 5. No calcification of the main myoma. 6. Absence of abnormal cervical smear.	Age: 14–42 y Inclusion criteria: Female patients undergoing laparotomy Exclusion criteria: Any patient with systemic disease, inflammatory pelvic condition, or receiving any other form of adhesion prevention	Age: 18–46 y Inclusion criteria: Female patients undergoing laparotomy Exclusion criteria: patients with diabetes, hemochromatosis, hepatic or renal impairment, lymphatic, coagulation, or hematological abnormalities. Patients receiving cancer treatment, thrombogenic agents, anticoagulants or other adhesion prevention agents. Patients in whom the gastrointestinal or urinary tract were opened or patients undergoing tubal implantation, sterilization, or sterilization reversal.	Age: ≥ 18 y Inclusion criteria: Females of ≥ 18 y undergoing gynecological surgery Exclusion criteria: pregnancy, cancer, pelvic inflammatory disease.

TABLE 2**Continued.**

Study	Pellicano et al. (12)	Lundorff et al. (11)	Johns et al. (10)	Diamond (13)
	7. Negative urine pregnancy test. Exclusion criteria: Patients who did not fulfill the inclusion criteria.			
Surgery	Laparoscopic myomectomy	Laparotomy	Laparotomy	Laparotomy
Intervention	Autocross-linked hyaluronic acid gel vs. no treatment	Intergel vs. lactated Ringer's	Intergel vs. lactated Ringer's	Sepracoa vs. placebo
Outcomes	[1] Presence of adhesions at second-look laparoscopy. [2] Incidence of adhesions with regards to the site of the primary myoma	[1] Presence of adhesions at second look. [2] Improvement or deterioration of adhesion. scores at second look. [3] Change in mean adhesion score. [4] Severity and extent of adhesions. [5] Modified AFS score categorized by surgical procedure.	[1] Adhesions present at second-look laparoscopy. [2] Improvement of adhesion score [3] Deterioration of adhesion score [4] Shift in modified AFS adhesion score. [5] Percentage reduction in modified AFS score [6] Severity and extent of adhesions	[1] Adhesions present at second-look laparoscopy [2] Mean adhesion score [3] Mean extent of adhesion score [4] Mean incidence of de novo adhesions at second-look laparoscopy [5] Mean extent of adhesion score at second-look laparoscopy.
Sample size	36	77	281	277
Follow-up (time at which second-look laparoscopy was performed)	60–90 d	6–12 wk	6–12 wk	40 d (average)

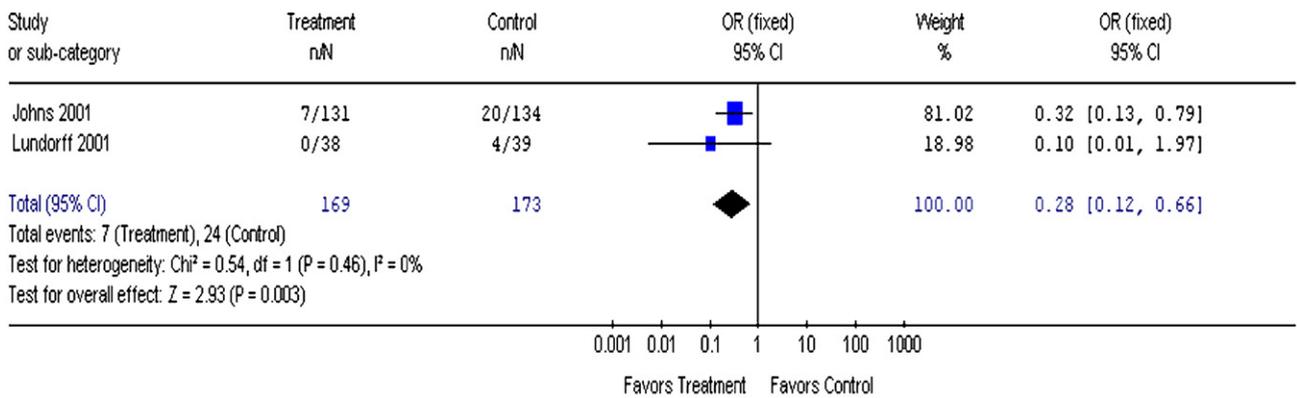
Note: AFS = American Fertility Society.

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FIGURE 3

Deterioration of adhesion score at second-look laparoscopy. Patients in the control group had significantly worse adhesion scores on second-look laparoscopy, compared with those who received hyaluronic acid. OR = odds ratio.

Review: Fluid and pharmacological agents for adhesion prevention after gynaecological surgery (Version 01)
 Comparison: 09 Hyaluronic acid versus no hyaluronic acid
 Outcome: 07 deterioration of adhesion score



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adhesion score, or improvement, defined as a lower adhesion score. Although there was no evidence for improved adhesion scores in the treatment group (odds ratio, 1.55; 95% CI, 0.82–2.92), there was a significant deterioration in the adhesion score in the control group (odds ratio, 0.28; 95% CI, 0.12–0.66; Fig. 3).

Mean Adhesion Score

The mean adhesion score was calculated from two studies (11, 13); the result showed no significant difference between treatment and control groups (standardized mean difference, 39.76; 95% CI, –114.6–35)

DISCUSSION

Hyaluronic acid is a linear polysaccharide with repeating disaccharide units that are composed of sodium D-glucuronate and N-acetyl-D-glucosamine. It is a major component of many body tissues and fluids, in which it provides mechanically protective and physically supportive roles (10).

Hyaluronic acid solutions have been shown in both laboratory animals (15) and clinical trials (13) to prevent adhesion formation after abdominopelvic surgery. Intergel, Sepracoat, and Hyalobarrier are all solutions that contain hyaluronic acid as the active component, and accordingly, this study has combined all these agents in one meta-analysis. We believed it appropriate to combine the effect of different agents, all sharing the common basic component, hyaluronic acid, because of the absence of heterogeneity when the studies were combined; that is, a similar effect for all hyaluronic acid agents was observed.

Hyalobarrier is a crosslinked derivative of hyaluronic acid that is characterized by its high viscosity (14). Intergel (0.5% hyaluronic acid) is a sterile, nonpyrogenic gel of highly purified sodium hyaluronate that is ionically crosslinked with ferric ion and adjusted to isotonicity with sodium chloride (11). Crosslinking between carboxylate groups on the hyaluronic acid molecule with ferric ions results in a marked increase in viscosity (11).

Intergel was approved for use in the United States on November 16, 2001 and was intended to be used in open, conservative gynecological surgery as an adjunct to good surgical technique. After off-license use in laparoscopic surgery, side effects were reported, namely pelvic pain and allergic reactions. Accordingly, Intergel was removed from the market in 2003, pending further investigation.

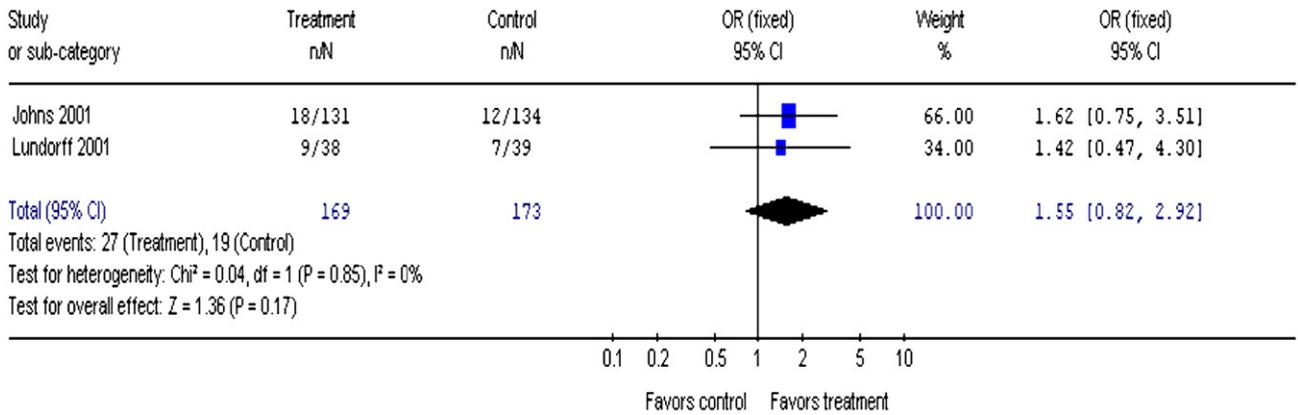
Finally, Sepracoat (0.4% solution of sodium hyaluronate) failed to gain Food and Drug Administration approval in 1998 as a result of a lack of significant evidence from studies in human beings. Despite the fact that some of the products mentioned in this article have been withdrawn from the market, they all draw on a common chemical structure and are therefore worthy of investigation.

Four of five studies were included in the meta-analysis; all four of these studies evaluated the prevalence of adhesions at second-look laparoscopy and showed a significant reduction in the prevalence of adhesions. When one evaluates the other outcomes, it is important to note that the number of studies included in the meta-analysis was limited (Figs. 3–5). The evidence therefore is less robust regarding the change in adhesion scores. This only serves to highlight the need for more

FIGURE 4

Improvement of adhesion score at second-look laparoscopy. There is no evidence for a significant improvement in adhesion scores with the use of hyaluronic agents. OR = odds ratio.

Review: Fluid and pharmacological agents for adhesion prevention after gynaecological surgery (Version 01)
 Comparison: 09 Hyaluronic acid versus no hyaluronic acid
 Outcome: 06 improvement of adhesion score



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studies. Nevertheless, the available data suggest a decreased chance of deterioration of the adhesion score when hyaluronic acid agents were used.

Data were represented graphically in the study by Thornton et al. (8) and were excluded from the meta-analysis because exact numerical data could not be obtained. The results of this study nevertheless agreed with the result of

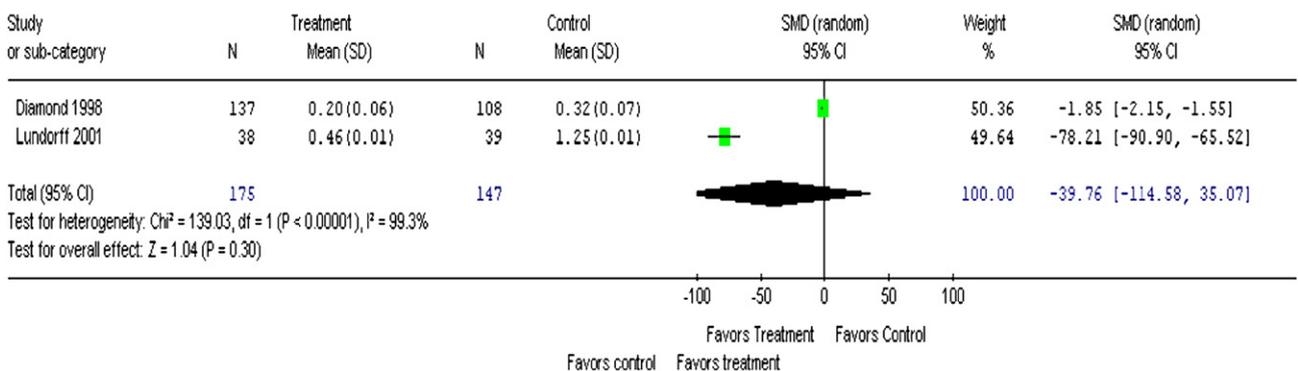
the meta-analysis, showing a lower prevalence of adhesions at second-look laparoscopy in patients who were treated with hyaluronic acid; when adhesions did occur, they were significantly less extensive and severe.

Three of the four studies (10, 11, 13) included patients undergoing laparotomy, whereas the remaining study by Pellicano et al. (12) included patients undergoing

FIGURE 5

Mean adhesion score. There is no evidence of a significant difference in the mean adhesion score between the two groups.

Review: Fluid and pharmacological agents for adhesion prevention after gynaecological surgery (Version 01)
 Comparison: 09 Hyaluronic acid versus no hyaluronic acid
 Outcome: 08 mean adhesion score



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laparoscopy. Even though the method of surgery was not consistent, the same effect for hyaluronic acid was observed across the studies.

None of the studies reported pregnancy rates. Because an attempt to decrease adhesions after fertility-preserving pelvic surgery aims mainly at preserving fertility, future studies should focus on live birth rate as a primary outcome.

In conclusion, hyaluronic acid has been used in several agents for adhesion prevention. This meta-analysis shows that hyaluronic acid may have the potential to help decrease adhesion formation. However, as a result of the limited number of studies available, this evidence should be interpreted with caution. Ideally, severity of adhesions should not be used as a surrogate marker for future fertility potential, and therefore, future studies should include live birth rate as a primary outcome measure and have adequate follow-up periods.

REFERENCES

1. Nehez L, Vodros D, Axelsson J, Tingstedt B, Lindman B, Andersson R. Prevention of postoperative peritoneal adhesions: effects of lysozyme, polylysine and polyglutamate versus hyaluronic acid. *Scand J Gastroenterol* 2005;40:1118–23.
2. Diamond MP, Freeman L, eds. Incidence of postsurgical adhesions. New York: Springer-Verlag, 2000.
3. Verco SJ, Peers EM, Brown CB, Rodgers KE, Roda N, diZerega G. Development of a novel glucose polymer solution (icodextrin) for adhesion prevention: pre-clinical studies. *Hum Reprod* 2000;15:1764–72.
4. Lok F, Ledger WL, Li TC. Surgical intervention in infertility management. *Hum Fertil* 2003;6.
5. Tulandi T, Collins JA, Burrows E, Jarrell JF, McInnes RA, Wrixon W, et al. Treatment-dependent and treatment-independent pregnancy among women with periadnexal adhesions. *Am J Obstet Gynecol* 1990;162:354–7.
6. diZerega G. Contemporary adhesion prevention. *Fertil Steril* 1994;61:219–35.
7. Metwally M, Watson A, Lilford R, Vandekerckhove P. Fluid and pharmacological agents for adhesion prevention after gynaecological surgery. *Cochrane Database Syst Rev* 2006;3:CD001298.
8. Thornton MH, Johns DB, Campeau JD, Hoehler F, DiZerega GS. Clinical evaluation of 0.5% ferric hyaluronate adhesion prevention gel for the reduction of adhesions following peritoneal cavity surgery: open-label pilot study. *Hum Reprod* 1998;13:1480–5.
9. Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions* 4.2.5. Chichester, United Kingdom: Wiley and Sons, 2005.
10. Johns BD, Keyport GM, Hoehler F, diZerega G. Reduction of postsurgical adhesions with Intergel adhesion prevention solution: a multicenter study of safety and efficacy after conservative gynecologic surgery. *Fertil Steril* 2001;76:595–604.
11. Lunderoff P, Geldorp H, Tronstad SE, Lalos O, Larsson B, Johns DB, et al. Reduction of postsurgical adhesions with ferric hyaluronate gel: a European study. *Hum Reprod* 2001;16:1982–8.
12. Pellicano M, Bramante S, Cirillo D, Palomba S, Bifulco G, Zullo F, et al. Effectiveness of autocrosslinked hyaluronic acid gel after laparoscopic myomectomy in infertile patients: a prospective, randomized, controlled study. *Fertil Steril* 2003;80:441–4.
13. Diamond MP. Reduction of de novo postsurgical adhesions by intraoperative precoating with Sepracoat (HAL-C) solution: a prospective, randomized, blinded, placebo-controlled multicenter study. The Sepracoat Adhesion Study Group. *Fertil Steril* 1998;69:1067–74.
14. Acunzo G, Guida M, Pellicano M, Tommaselli GA, Di Spiezio Sardo A, Bifulco G, et al. Effectiveness of auto-cross-linked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic adhesiolysis: a prospective, randomized, controlled study. *Hum Reprod* 2003;18:1918–21.
15. Kramer K, Senninger N, Herbst H, Probst W. Effective prevention of adhesions with hyaluronate. *Arch Surg* 2002;137:278–82.