Postoperative adhesion formation and reproductive outcome using Interceed after ovarian surgery: a randomized trial in the rabbit model

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Introduction

Pelvic adhesions may cause bowel obstruction, pelvic pain and infertility. Even when surgery is performed in strict adherence to microsurgical principles, postoperative adhesion formation occurs in 51–100% of cases (Diamond et al., 1987a).

Although a variety of agents have been employed to reduce de-novo adhesion formation and adhesion reformation after surgery, the use of many of these agents is rather empirical and not consistently supported by laboratory or clinical investigation (di Zerega, 1994). Controlled studies have failed to identify a universally accepted agent. Therefore, as yet, there is no standard adjuvant treatment for adhesion prevention.

Recently, surgical barriers which mechanically separate opposing surfaces during tissue healing have been devised (Boyers et al., 1988; Interceed Adhesion Barrier Study Group, 1989; Steinleiter et al., 1991; Best et al., 1992; Haney and Doty, 1992; Surgical Membrane Study Group, 1992; DeIaco et al., 1994; Hill-West et al., 1994; Evrard et al., 1996). Interceed is an absorbable oxidized regenerated cellulose barrier that adheres to the site of injury, converts into a gel, spontaneously maintains its position and does not necessitate sutures. The aim of the present study was to evaluate the efficacy of Interceed in the prevention of adhesion formation and also the reproductive outcome following ovarian surgery in a randomized trial in the rabbit model.

Materials and methods

Twenty-nine New Zealand white female rabbits of reproductive age, weighing 2800–3300 g, were anaesthetized using a single i.m. injection of ketamine hydrochloride 65 mg/kg and diazepam 3 mg/kg of body weight. The surgical procedures were performed in sterile conditions; no perioperative antibiotics were administered. Microsurgical principles were applied. The rabbits were submitted to a mid-line laparotomy and a standardized surgical incision, running for the whole length of the antimesial side of the ovary, was made on both ovaries using a monopolar microneedle delivering pure cutting current at a tissue power density of 66 666 W/cm². No sutures were applied to the ovarian cortex. Before closure of the abdomen, a sheet of Interceed was wrapped around the entire surface of the ovary on one side, chosen at random in accordance with a computer-generated sequence, and moistened with a few drops of normal saline in order to achieve adherence to the ovarian surface. The contralateral ovary was left uncovered. All excess fluid was aspirated from the abdominal cavity at the end of the procedure so as to prevent displacement of the barrier. The abdominal wall was closed in two layers, the first, peritoneum and muscle, using a 4–0 polygactin running suture, and the second, fascia and skin, using a 0 polygactin running suture. Four weeks after surgery, the rabbits were mated with a male of proven fertility, and 2 weeks later, a second-look laparotomy was performed by a blinded observer who evaluated the incidence and score of adhesions, the number of corpora lutea in each ovary, the number of embryos in the ipsilateral uterine horn and also calculated the nidation index for each side. Adhesions were observed in 66% of Interceed-covered and in 97% of control ovaries (P < 0.0001). The adhesion score on the Interceed side was significantly lower than on the control side. The nidation index for the Interceed side was significantly higher than for the control side. The authors conclude that, in the rabbit model, Interceed significantly reduces the incidence and score of postoperative ovarian adhesions and significantly improves reproductive outcome.

Key words: adhesions/Interceed/rabbit/reproductive outcome
Therefore, as yet, there is no standard adjuvant treatment for adhesion prevention. Barrier methods, Gore-Tex, and Interceed in particular, have been recently introduced for postoperative adhesion prevention (Boyers et al., 1988; Interceed Adhesion Barrier Study Group, 1989; Best et al., 1992; Haney and Doty, 1992; Surgical Membrane Study Group, 1992; Myomectomy Adhesion Study Group, 1995). However, evidence from both the experimental and clinical settings is inconclusive, and positive and negative results have been reported in the literature (diZerega, 1994).

In particular, as to the experimental setting, Interceed proved efficacious in reducing postoperative adhesion formation in seven studies on the rabbit model, either after uterine horn or sidewall surgery (Diamond et al., 1987b, 1991a,b; Linsky et al., 1987, 1988; Steinleiter et al., 1992; Wiseman et al., 1992) and in one study on the pig model after radical pelvic surgery (Montz et al., 1993). On the other hand, no efficacy for Interceed was demonstrated in two studies on the rabbit (Maxson et al., 1988; Best et al., 1992), in two on the rat model (Pagidas and Tulandi, 1992; Montgomery Rice et al., 1993) after uterine surgery in one study on the rabbit after ovarian surgery (Hill-West et al., 1994), in one study on the mouse sidewall model (Haney et al., 1992), or in one study on the hamster model after uterine surgery and suture application (Best et al., 1991). Only one experimental study evaluated the role of Interceed in adhesion prevention after ovarian surgery in an animal model (Hill-West et al., 1994), with no significant efficacy when compared to a resorbable hydrogel barrier. In addition, all experimental studies published to date only deal with the problem of postoperative adhesion formation. As yet, no article dealing with the reproductive outcome following application of these barriers has been published in the literature.

Clinical studies, as opposed to experimental studies, more consistently show a positive effect of Interceed on adhesion prevention. Four randomized multicentre studies, with second-look laparoscopies for the evaluation of adhesion reformation after adhesiolysis by laparotomy, showed a significant reduction of adhesions at the pelvic sidewall covered by Interceed compared to the control pelvic sidewall [Interceed Adhesion Barrier Study Group, 1989; Aziz and The Interceed (TC7) Barrier Study Group II, 1993; Franklin and the Ovarian Study Group, 1995]. In another two randomized studies, the efficacy of Interceed applied to the pelvic wall or wrapped around ovaries and/or fimbriae after bilateral adhesiolysis by laparotomy was demonstrated for the side randomized to the barrier versus the contralateral side (Li and Cooke, 1994; Nordic Adhesion Prevention Study Group, 1995).

Uncontrolled case series demonstrated the feasibility of Interceed application by laparoscopy (Aziz et al., 1991; Pados et al., 1992). Five randomized studies have been published so far on adhesion prevention after laparoscopic application of Interceed (Greenblatt and Casper, 1993; Mais et al., 1995a,b; Keckstein et al., 1996; Saravelos and Li, 1996). In three studies, Interceed has been shown significantly to reduce

### Table I. Number of ovaries by adhesion stage for Interceed-covered versus control ovaries

<table>
<thead>
<tr>
<th>Adhesion stage</th>
<th>Interceed</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>I</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>II</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

### Table II. Adhesion stage and nidation index for Interceed-covered versus control ovaries

<table>
<thead>
<tr>
<th>Adhesion score</th>
<th>Pregnancies</th>
<th>Nidation index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interceed</td>
<td>0.83 ± 0.76a</td>
<td>4.21 ± 1.36b</td>
</tr>
<tr>
<td>Control</td>
<td>1.86 ± 0.83a</td>
<td>2.95 ± 1.61b</td>
</tr>
</tbody>
</table>

*P < 0.0001; **P < 0.005.

Data are presented as mean ± SD.

### Results

There were no intra- or post-operative complications.

At second-look laparotomy, no macroscopic evidence of residual material attributable to the surgical barrier was present on any ovary. The number of ovaries by adhesion stage for both the Interceed and control sides is reported in Table I. The adhesion formation rate was 19/29 (66%) for the Interceed-covered ovaries versus 28/29 (97%) for the control ovaries (P < 0.0001). The mean adhesion score for the Interceed side was significantly lower than for the control side (P < 0.0001); the mean number of corpus lutea for the Interceed side (4.45 ± 1.10) was not significantly different from that of the control side (4.05 ± 1.09; NS), whereas the mean number of embryos in the uterine horns on the Interceed side was significantly higher than that on the control side (P < 0.005). As a result, the mean nidation index, expression of the pick-up capacity of the fimbriae, was significantly higher for the Interceed side with respect to the control side (P < 0.005) (Table II).

### Discussion

Ovarian surgery, frequently performed in women of reproductive age for common benign pathological conditions, such as endometriotic or dermoid cysts, may constitute a threat to the reproductive potential of these patients, since the ovary is extremely sensitive to surgical trauma. Postoperative adhesion formation occurs in 51–100% of cases when conservative ovarian surgery is performed by laparotomy (Diamond et al., 1987a). Despite initial optimism regarding adhesion formation following laparoscopic surgery, experimental and clinical studies published to date report inconsistent data (Luciano et al., 1989; Nezhat et al., 1990; Operative Laparoscopy Study Group, 1991; Canis et al., 1992; Marana et al., 1994). In particular, the adhesion reformation rate following operative laparoscopy is rather high (Nezhat et al., 1990; Operative Laparoscopy Study Group, 1991; Canis et al., 1992).

Several methods of adhesion prevention have been employed with the aim of reducing both postoperative de-novo adhesion formation as well as adhesion reformation. However, the use of many of these agents is rather empirical and not consistently supported by laboratory or clinical investigation (diZerega, 1994). Therefore, as yet, there is no standard adjuvant treatment for adhesion prevention.

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postoperative adhesion formation after laparoscopic surgery for endometriosis (Mais et al., 1995a), myomectomy (Mais et al., 1995b), and ovarian cysts (both endometriotic and non endometriotic) (Keckstein et al., 1996). In two studies (Greenblatt and Casper, 1993; Saravels and Li, 1996), Interceed was not efficacious in reducing adhesion formation after laparoscopic electrosurgical treatment of polycystic ovarian syndrome.

In this series of experiments, a monopolar microneedle was used because it best imitates the technique of the reproductive surgeon, concerned with the post-operative reproductive potential of the patient. The same experimental model has been used in several experimental studies published by our group, and it always achieves a post-operative adhesion rate in the control ovary of at least 50% (Marana et al., 1994, 1996). Moreover, the appropriateness of such a model is confirmed by the 97% adhesion formation rate in the control side.

In the present experimental study, the adhesion score, as evaluated by a blinded observer, on the ovary wrapped in Interceed was significantly lower than that on the contralateral ovary. The number of corpora lutea on the ovary on which Interceed was applied was not significantly different to that on the control side. Of interest is the observation, new to the literature, that the number of embryos and consequently the nidation index on the Interceed side were significantly higher than on the contralateral side.

We do not feel that the higher number of stage I adhesions for the Interceed side versus the control side is inconsistent with the hypothesis of the efficacy of Interceed in adhesion prevention. In fact, the rate of adhesion formation on the Interceed side (66%) was significantly less than that observed on the control side (97%). When classifying the ovaries by adhesion stage, more ovaries were in stage II–III on the control side than on the Interceed side, whereas the number of stage I ovaries was approximately the same.

It is widely accepted that adhesions are a mechanical cause of reduced fertility. The fact that, in this study, the adhesion score on the Interceed side was lower than that on the control side confirms a role for this absorbable barrier in limiting adhesion formation. In this study the number of embryos as well as the nidation index on the Interceed side were also higher with respect to those on the contralateral uterine horn. This datum, for the first time, strongly suggests that ovum retrieval was more efficient on the side of application of the absorbable barrier.

In conclusion, this study demonstrates the efficacy of Interceed both in the prevention of postoperative adhesion formation and in enhancing subsequent fertility when used after ovarian surgery in an animal model.

References


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