Introduction

Laparoscopic ovarian electro surgical injury is increasingly used for ovulation induction in clomiphene-resistant infertile women with polycystic ovarian syndrome (PCOS; Donesky and Adashi, 1995). This treatment may also reduce the high rate of miscarriage found in women with PCOS by normalizing the hormonal milieu (Balen et al., 1993). Although there are numerous studies reporting promising clinical results, only a few investigators have prospectively evaluated post-operative adhesion formation after laparoscopic electro surgical procedures (Lyles et al., 1989; Gurgan et al., 1991; Greenblatt and Casper, 1993; Naether, 1995). A systematic adnexal evaluation at second-looking is important because it can provide useful information that may explain the discrepancy between post-operative ovulation and pregnancy rates. Prospective studies assessing post-operative adhesions avoid the selection bias that is introduced by a sporadic evaluation at Caesarean section or at second-look laparoscopy for persistent infertility. This selection bias may be partly responsible for the wide variation in the rate of post-operative adnexal adhesions reported at second-

Materials and methods

In this study we tested the hypothesis that Interceed, an absorbable adhesion barrier, is of value in preventing de-novo adhesion formation following the laparoscopic treatment of PCOS. Assuming that the post-operative adhesion rate would be similar to that reported by recent prospective studies, i.e. 85-100% (Gurgan et al., 1991; Greenblatt and Casper, 1993), and that the use of Interceed may have halved this incidence, the minimum number of patients required in the study was 20, accepting a type 1 error (α) of 5% and type 2 error (β) of 25%. Following approval by the local hospital ethics committee, 28 women with PCOS were recruited from the gynaecological outpatient clinics at the Jessop Hospital for Women (Sheffield, UK). All the women recruited gave written informed consent and agreed to undergo laparoscopic ovarian treatment and a second-look laparoscopy 2-11 weeks after the initial procedure. Operations were carried out between 14 March 1994 and 19 June 1995. However, of the 28 women who were recruited, one underwent laparoscopic treatment of PCOS by laser drilling; this patient was not considered further in the analysis. Of the remaining 27 women who underwent laparoscopic treatment of PCOS, only 21 (78%) underwent a second-look procedure. Six patients (22%) did not undergo a second-look procedure, because either they became pregnant shortly after treatment (n = 4) or they...
decided to withdraw from the study (n = 2). Therefore, a total of 21 women were included in the data analysis.

In all, 15 women (71%) presented with anovulatory infertility (12 with primary infertility, three with secondary infertility), two women (10%) presented with recurrent miscarriages (three or more miscarriages) and four women (19%) presented with both subfertility and recurrent miscarriage. Inclusion criteria were age ≥18 years, the presence of both ovaries, bilateral tubal patency, the absence of adnexal adhesions at laparoscopy and the absence of any haematological or coagulation disorders. The diagnosis of PCOS was confirmed if two or three of the following criteria were met: (i) elevated follicular phase luteinizing hormone (LH) concentrations (>10 mIU/ml) or an elevated follicular phase LH:follicle stimulating hormone (FSH) ratio (>2.5); (ii) clinical or biochemical evidence of androgen excess; and/or (iii) the typical image of PCOS on ultrasound, with ovaries containing multiple small subcapsular cysts with a diameter <8 mm and increased stromal density.

Anovulation due to abnormal thyroid function and hyperprolactinemia was excluded in the subjects suffering from infertility. These women had failed to conceive despite increasing doses of clomiphene citrate (up to 150 mg from days 2-6 of the menstrual cycle). There were no associated infertility factors, e.g. endometriosis, tubal or male factor, in any of the infertility patients. Apart from endocrinological investigations, women suffering from recurrent miscarriages additionally underwent the following investigations: coagulation studies, auto-antibody screening, hysterosalpingography, karyotyping of both partners and LH-timed endometrial biopsy at the peri-implantation period. Of the subjects suffering from recurrent miscarriages, two had previously conceived with clomiphene ovulation induction but subsequently miscarried. One of the recurrent miscarriage patients had a bicornuate uterus and another had retarded endometrial development at the peri-implantation period.

The average age of the patients was 28 years (range 20–37). The mean body mass index (BMI) was 28 kg/m² (range 19–40), with 57% of patients classified as overweight (BMI >25). The mean duration of infertility for the anovulatory infertile patients was 39 months (range 24–84). Patients suffering from infertility had been treated previously with clomiphene ovulation induction but subsequently miscarried. One of the recurrent miscarriage patients had a bicornuate uterus and another had retarded endometrial development at the peri-implantation period.

Application of Interceed and randomization procedure
A sealed envelope disclosed the assignment of which side was to be treated with Interceed (Johnson and Johnson Medical Ltd, New Brunswick, NJ, USA). Following symmetrical bilateral ovarian electrosurgical treatment, a surgical fabric applicator (Johnson and Johnson Medical Ltd) was used to apply Interceed over the cautery output waveform of the current had a nominal frequency of 500 kHz, a duty cycle of 25% and a maximum output of 99 W at 300 Ohm resistance. Six (± two) injuries were inflicted on each ovary, depending on its size, and the duration of every insult was between 4 and 6 s. The craters created were ~3–4 mm in diameter and 6–8 mm in depth.

Evaluation of adhesions at second-look
All second-look video tapes were reviewed to assess post-operative adhesion development. Assessment was blinded regarding which of the two ovaries was wrapped with Interceed in each patient. The presence or absence of adhesions on each adnexum and the involvement of other pelvic structures with adhesions were noted. No residual Interceed was observed. Adhesions were classified according to severity into four categories: filmy, organized avascular, organized vascular and cohesive. Raw surfaces on every structure involved in the adhesions were measured after adhesiolysis in the following manner. For every raw surface in each structure involved in adhesions, the video image was frozen when the laparoscope was viewing the area directly, the axis of the laparoscope being perpen-
Location of adhesions

Incidence of adhesions

994

As 21 pairs of ovaries were treated, there were 42 sites available for the evaluation of adhesion development. The

Table I. Incidence of adhesions at second-look evaluation

<table>
<thead>
<tr>
<th>Paired incidence of adhesions (n = 21)</th>
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</thead>
<tbody>
<tr>
<td>Adhesions absent bilaterally</td>
<td>9 (43)</td>
<td></td>
</tr>
<tr>
<td>Adhesions present bilaterally</td>
<td>4 (19)</td>
<td></td>
</tr>
<tr>
<td>Adhesions present only on control side</td>
<td>3 (14)</td>
<td></td>
</tr>
<tr>
<td>Adhesions present only on treatment side</td>
<td>5 (24)</td>
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Site-specific incidence of adhesions (n = 42)

| Ovary                  | 15 (36) |
| Pelvic sidewall        | 13 (31) |
| Fallopian tube         | 3 (7)   |
| Omentum                | 2 (5)   |
| Bowel                  | 1 (2)   |

Values in parentheses are percentages.

diccular to the surface of interest. The image included a reference laparoscopic probe with marks at 1 cm distance, which was placed next to the surface to be measured. The probe was used to correct for differences in scale which occur as the laparoscope moves closer to or away from the surface of interest. A transparent plastic sheet was placed on the video screen and the area of interest was copied. The outline of this surface was then transferred onto a sectional graphic pad with squares measuring 1 mm². In this manner, a certain number of squares was outlined for every surface of interest. Counting of these squares corresponded to the actual size of the raw area of interest only if the scale, as controlled by the reference probe, was 1:1. However, on most occasions measurements had to be adjusted because the image was usually magnified. To adjust the surface area measured, the length of the 1 cm reference distance on the video screen was also measured. Subsequently, the number of squares measured on the sectional graphic pad was divided by the length of the 1 cm reference distance, squared. For example, if the area transferred on the sectional graphic pad measured 1000 mm² and the 1 cm reference distance measured 2 cm on the video screen, then the actual area of interest was 1000 divided by 2², i.e. 1000/4 = 250 mm². In this way, all raw surfaces involved in the adhesions were measured.

Statistics

The main outcome measures included the occurrence, severity and extent of adhesions. Adhesion formation on the treatment side (Interceed) was compared with adhesion formation on the control side. As patients were used as their own controls, matched-paired tests were employed for analysis. Adhesion severity was compared using Wilcoxon's non-parametric matched-pairs signed-rank test. Adhesion extent was compared using both Wilcoxon's non-parametric matched-pairs signed-rank test and the paired samples t-test.

Results

Incidence of adhesions

The incidence of adhesions in the 21 subjects was 33% on the control side (n = 7) and 43% on the Interceed-treated side (n = 9). As shown in Table I, adhesions were absent bilaterally in nine subjects (43%) and were present on both the Interceed and control side in four subjects (19%). In three subjects (14%) adhesions were present only on the control side, while in five subjects (24%) they were present only on the Interceed side.

Location of adhesions

As 21 pairs of ovaries were treated, there were 42 sites available for the evaluation of adhesion development. The ovaries were involved in all but one adhesion site (15 of 42 sites, 36%). In one site where the ovary was not involved, there was a small adhesion from the mid-portion of the tube to the omentum. Regarding other intra-abdominal locations, the pelvic sidewall was the one most commonly involved in adhesion formation (13 of 42 sites, 31%) both on the control (n = 5, 24%) and the Interceed side (n = 8, 38%). The Fallopian tube was involved in three cases (7%), two on the control (5%) and one on the Interceed side (2%), while the omentum was involved in two cases (5%) on the Interceed side. Finally, the large bowel was involved in one case (2%) on the Interceed side.

Severity and extent of adhesions

Table II summarizes the severity of adhesions at second-look laparoscopy. An analysis using Wilcoxon's matched-pairs signed-rank test showed no significant difference between the control and the Interceed side in the severity of adhesions following the bilateral laparoscopic electro-surgical treatment of PCOS. The mean raw areas following adhesiolysis at second-look laparoscopy on the control and the Interceed sides were 975 (range 150-1901) and 879 mm² (range 84-1090) respectively. The mean paired difference in the extent of ovarian adhesions between the control and the Interceed sides was 561 (range 129-1087) and 460 mm² (range 95% CI -195-120). There was no significant difference in the extent of ovarian adhesions between the control and the Interceed sides (Wilcoxon's matched-pairs signed-rank test, not significant).

Clinical outcome

Post-operatively, 16 patients (76%) initiated spontaneous ovulatory cycles, as confirmed by the spontaneous onset of menses after a biphasic temperature rise and/or luteal phase progesterone concentrations >25 nmol/l, whereas five patients (24%) remained anovulatory. Of these five patients, two
subsequently had successful ovulation induction with clomiphene. A total of 14 patients have now been followed up for >6 months after laparoscopic treatment of PCOS, and seven (50%) of these conceived. Of those who conceived, two had been treated for first trimester recurrent miscarriage and five had been treated for infertility. The two recurrent miscarriage patients are currently 28 and 32 weeks pregnant. Two of the infertility patients have delivered, and the remaining three are beyond 24 weeks of gestation. All conceptions have been singleton. There were no adverse events noted in any of the patients in our study.

Discussion
This prospective study was designed to examine post-operative adhesion formation at second-look after standardized electrosurgical laparoscopic treatment for PCOS. Most earlier studies on post-operative adhesion formation after laparoscopic treatment for PCOS were retrospective. Drawbacks of these retrospective studies include selection bias because of the sporadic evaluation of ovaries at second-look and the lack of standardization of ovarian injury. Without a systematic evaluation of all the patients, only limited inferences can be made for the incidence of post-operative adhesion formation. However, biases cannot be eliminated even in carefully designed prospective studies. For example, in our study a second-look was not performed in four patients who conceived shortly after treatment because it would have been unethical. This is a significant proportion of the total number investigated and may represent some natural bias.

In our study, 57% of patients and 38% of adnexa were found to have adhesions at second-look laparoscopy. Interceed could not be shown to have any significant protective effect on adhesion formation. Recently, Interceed has been shown to be effective in reducing adhesion reformation at various pelvic sites (Li and Cooke, 1994), and specifically the pelvic sidewall (Azziz and the Interceed Adhesion Barrier Study Group, 1993). These findings were also confirmed by studies involving adhesion reformation to the ovary (Keckstein et al., 1994; Franklin and the Ovarian Adhesion Study Group, 1995; Nordic Adhesion Prevention Study Group, 1995), but were not confirmed in our study. One explanation for the variation in results between these studies and ours may be the different ability of Interceed to reduce de-novo and reformed adhesions. Alternatively, the fact that only the treated ovarian surfaces and not the whole ovaries were wrapped with Interceed in our study may have accounted for these differences. In the studies involving adhesion reformation (Keckstein et al., 1994; Franklin and the Ovarian Adhesion Study Group, 1995; Nordic Adhesion Prevention Study Group, 1995), ovaries were completely wrapped with a single piece of Interceed. The size of fabric that can be placed using the applicator is limited (5.1X3.8 cm²). The use of several smaller pieces of fabric may be problematic because some areas may be left uncovered, while others may have double layers of fabric where two pieces overlap. Using a backloading technique (Azziz et al., 1991), a much larger piece (10.2X7.6 cm²) of Interceed can be placed through the trocar, thereby overcoming these potential difficulties.

Regarding the statistical power of the study, it has to be noted that the initial calculation assumed a high post-operative adhesion rate (85—100%), as reported by previous investigators (Gurgan et al., 1991; Greenblatt and Casper, 1993). However, in our study the adhesion rate in the control site was only 33%, probably because of differences in the operative technique. This means that the number of subjects required to obtain the initially calculated power is higher. For example, if the expected adhesion rate for the Interceed-treated site was to be reduced to 22%, then the minimum requirement would be 58 evaluable subjects with 80% statistical power at a 5% significance level. Nevertheless, the trend in this study was not in favour of Interceed, as the incidence of adhesions was higher on the Interceed-treated side (43%) than on the control side (33%).

In our study, when adhesions were present they were often of significant extent and severity. Peri-ovarian adhesions were filmy in only one case, and ovarian adhesion extent was >500 mm² in 50% of the ovaries with adhesions. These findings are in contrast to those of retrospective studies which often report minimal peri-ovarian adhesions (Gjonnaes, 1984; Keckstein, 1989). The lack of severe adhesions in these earlier studies may well be a result of the biased samples.

In three of four previous prospective studies, which examined adhesion formation after the laparoscopic electrosurgical treatment of PCOS, the incidence of post-operative adhesions (86—100%) seems to be higher than in our study (Lyles et al., 1989; Gurgan et al., 1991; Greenblatt and Casper, 1993). Combining these three studies accumulates a total of 19 subjects, of whom 18 (95%) were found to have adhesions. In only one study were adhesions examined separately on the right and left ovaries (Greenblatt and Casper, 1993). In this report by Greenblatt and Casper (1993), Interceed was randomly applied to one ovary in a similar study design to that reported here, and all 14 ovaries (100%) operated upon developed adhesions. These investigators were also unable to demonstrate that Interceed had a protective anti-adhesiogenic effect after laparoscopic electrosurgery for PCOS, although all patients did conceive. As in our study, three of the four previous prospective reports described adhesions that were often of significant extent and severity (minimal adhesions were found in 28% of cases). Lyles et al. (1989) did not describe the method used to treat the ovary, while Greenblatt and Casper (1993) used a monopolar electric current of 4 mA to create eight to 10 cautery points with laparoscopic scissors. Gurgan et al. (1991) did not describe their electrosurgical probe but used a monopolar intermittent current of 70 W to create 20—25 cautery points on each ovary, and left 150 ml of heparinized Ringer’s solution (5000 IU/L) in the pelvis at the end of the procedure. It is likely that the lower incidence of adhesions in our study is because the method used resulted in a reduced amount of ovarian surface injury. This was achieved by using monopolar needle electrodes that were insulated where they contacted the ovarian surface. Low power settings were used, and this may also have helped to reduce ovarian surface injury by avoiding sparking during penetration of the electrode. This method is similar to that described by Armar.
et al. (1990), who created four to eight cautery points and used varied power settings. Laparoscopic treatment of PCOS may also compromise ovarian function by destroying a great number of follicular units (Dabirbashrad, 1989). Therefore, the minimization of ovarian injury, as described in our study, is likely to have the additional benefit of a decreased destruction of follicular units. Preservation of the follicular units may reduce the chance of premature menopause, which is a potential consequence of this form of treatment.

More recently, Naether (1995) prospectively assessed post-operative adhesions after electrosurgical treatment for PCOS in 46 subjects. This was the largest prospective report to date, but in contrast to our study the operative technique was not standardized in these cases. Nevertheless, the incidence of adhesions in Naether’s series was significantly lower than that observed in our and previous prospective studies mentioned above (adhesions present in 11% of subjects and 5% of ovaries); furthermore, all adhesions observed were minimal. These favourable results are unlikely to be a result of less ovarian surface injury because treatment involved the creation of up to 20 cautery points with coagulation forces (power settings 400 W/s). The authors attribute the low incidence of adhesions to the instillation of 300–500 ml saline solution in the peritoneal cavity at the end of the procedure.

Advances in electrosurgical technology include, amongst others, newly developed bipolar cautery forceps with computer-based monitoring of the temperature in the tissue (Kato et al., 1995). Tissue temperature control may reduce the risk of complications and also help with the standardization of surgical treatment for PCOS. However, although bipolar electrosurgery is safer than monopolar electrosurgery, there are several drawbacks when it is used for surgical ovulation induction. First, the currently available electrodes may cause excessive undesired superficial ovarian injury. Secondly, even if suitable needle electrodes were available, the concentrated current flowing between the active and return electrodes within the ovary may cause non-selective follicular and stromal damage. In contrast, because of the differences in the electrical resistance of ovarian tissue, it is possible that the monopolar electrical current could selectively cause more stromal than follicular damage as it disperses from the active electrode through the ovary to the return plate. In this way, more follicular units may be preserved, while the beneficial effect resulting from the destruction of androgen-producing stroma could be enhanced. However, evidence to support this theory is lacking.

Our study was not designed to determine the possible beneficial effect of second-look adhesiolyis. Nevertheless, ovulation (86%) and pregnancy rates (50%) (for subjects followed up for >6 months) were similar to the average ovulation (85%) and pregnancy rates (56%) calculated in a recent review of laparoscopic ovulation induction studies where no second-look adhesiolyis was performed (Donesky and Adashi, 1995). However, wider ranging conclusions regarding the role of second-look adhesiolyis must remain guarded for two reasons: (i) there may be significant differences in case selection between the populations compared, and (ii) most of the patients participating in our study have yet to be followed up for an adequate time period (only three subjects have been followed up for 1 year). In addition, preliminary data suggest that second-look adhesiolyis after the laparoscopic treatment of women with PCOS using the Nd:YAG laser may not be associated with an increase in pregnancy rates compared with laser treatment alone (Gurgan et al., 1992). However, the laser effect is not necessarily the same as the electrosurgical effect, and therefore a cautious approach is required in the extrapolation of results from laser to electrosurgery.

An interesting preliminary observation was made during the course of this study. In a significant number of patients without any adhesions at second-look (6/9), the ovaries appeared to have maintained the typical PCOS appearance. None of these patients has conceived so far. In contrast, in most patients with adhesions (11/12), normal ovarian morphology appeared to have been restored. When follow-up is completed, it would be interesting to relate pregnancy rates to initial adhesion formation. In general, women with fewer adhesions should have better chances of conception, provided the normal hormonal milieu has been restored and they have become ovulatory. However, if the lack of adhesions is associated with a lack of response to treatment, then adhesion formation may be an indicator of successful treatment. The explanation for this finding may be that the response of the ovary to ovarian injury leads to a local cascade of growth factors, which results in the stimulation of follicular growth (Adashi et al., 1988) and the production of gonadotrophin surge-attenuating/inhibitory factor (Balen and Jacobs, 1991). It is possible that the local production of these growth factors is also responsible for peri-ovarian adhesion formation. To test this hypothesis, more cases would be required.

In conclusion, minimal electrosurgical ovarian injury, as described here, is successful in restoring the normal ovulatory pattern and achieving pregnancy. Previously, Interceed has been reported to be of value in reducing post-operative adhesion formation, but its effects on the incidence, extent and severity of de-novo adhesions following laparoscopic ovarian electrosurgical treatment in women with PCOS could not be detected in our study.

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References


Adhesions after laparoscopic surgery for PCOS


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