

Clinical evaluation of endometriosis and differential response to surgical therapy with and without application of Oxiplex/AP* adhesion barrier gel

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Objective: To correlate parameters of endometriosis obtained during routine clinical evaluation with the subsequent formation of adhesions following surgical treatment by laparoscopy.

Design: Randomized, controlled, double-blind, clinical trial.

Setting: Tertiary referral centers for the treatment of endometriosis.

Patient(s): Thirty-seven patients (65 with adnexa) with stage I–III endometriosis; endometrioma-only patients were excluded.

Intervention: Laparoscopic surgical treatment of endometriosis, followed by randomization to Oxiplex/AP (FzioMed, Inc., San Luis Obispo, California) gel treatment (treated group) of adnexa, or surgery alone (control group); follow-up laparoscopy 6–10 weeks later.

Main Outcome Measure(s): Adnexal American Fertility Society score, correlated with color and location of endometriosis, as well as stage of disease determined by masked review of videotapes.

Result(s): Control patients with at least 50% red lesions had a greater increase in ipsilateral adnexal adhesion scores than patients with mostly black or white and/or clear lesions. Treated patients with red lesions had a greater decrease in adnexal adhesion scores than control patients. There was a correlation between baseline endometriosis stage and postoperative adhesion formation in control patients, but not treated patients.

Conclusion(s): Patients with red endometriotic lesions had greater increases in their adhesion scores than patients with only black, white, and/or clear lesions. Oxiplex/AP gel was effective in reducing adhesions, compared to surgery alone, in all groups. (*Fertil Steril*® 2007;87:485–9. ©2007 by American Society for Reproductive Medicine.)

Key Words: Adhesion prevention, Oxiplex/AP gel, endometriosis

Recent progress in the study and treatment of endometriosis has shown this disease to be heterogeneous in its clinical manifestations and response to therapy (1, 2). Peritoneal, ovarian, and rectovaginal endometriotic lesions clinically may behave as different entities (3). Further, the biology of endometriosis associated with pelvic pain may be different from that of endometriosis-associated infertility (1). Another variable in the evaluation of endometriosis is mapping red,

black, and white lesions. The distribution of endometriosis on the surface of the peritoneum and of deeply infiltrating lesions raises questions regarding the clinical heterogeneity of the disease (4–7).

The diagnosis of endometriosis is traditionally based on laparoscopic visualization. Several visual parameters of endometriosis have been reported. In addition to the typical “powder-burn” bluish-black lesions, red, clear, and white lesions have been reported on the peritoneal and ovarian surfaces (8–10). The location and size of lesions, as well as associated adhesions, form the basis for endometriosis staging (11). The relative contributions of the various-colored lesions to clinical presentations or response to surgery have not been reported. The disease and its treatment recommendations are based on visual assessment of the lesions. Subsequent histological analysis after laparoscopic therapy seldom alters treatment plans (8, 10, 12, 13).

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In this study, we report on the correlation of presumptive endometriotic lesions based on color with the patient's response to surgical treatment, measured by postoperative formation of adnexal adhesions. The results show that although increases in adnexal adhesion scores occurred following surgical treatment of endometriosis, the adhesion scores were highest in patients with red lesions at the time of surgical therapy. Further, coverage of the surgical treatment sites with Oxiplex/AP (FzioMed, Inc., San Luis Obispo, California) gel reduced adhesion scores.

MATERIALS AND METHODS

The objectives of this study were to correlate the preoperative characterization of endometriosis, i.e., the color and extent of endometriotic lesions, with postsurgical outcomes, using the adnexal adhesion scoring system of the American Society of Reproductive Medicine (14). In addition, the effectiveness of Oxiplex/AP gel in reducing the American Fertility Society (AFS) score following surgical treatment of endometriosis was determined.

The general characteristics of these patients, as well as their response to surgery, were previously published, in part, in reports of the patients studied in Europe (15) and the United States (16). This paper uses as its database a composite of those studies for patients with gross visual evidence of endometriosis, as determined at the time of initial laparoscopy. Patients having only endometriomas or revised AFS stage IV endometriosis were excluded from analysis (17–19).

Subjects were women of reproductive age ($N = 37$) who were undergoing surgical treatment by laparoscopy for endometriosis. All patients gave written, informed consent to participate in the study. Where appropriate, the informed consent was approved by local regulatory review. Patients were randomized to surgery only ($N = 17$, control patients, 30 adnexa) or surgery followed by Oxiplex/AP gel treatment ($N = 20$ patients, 35 adnexa).

The distribution of patients based on their AFS stage of endometriosis was as follows: treated stage I, $n = 7$; stage II, $n = 8$; and stage III, $n = 5$; and control stage I, $n = 5$; stage II, $n = 8$; and stage III, $n = 4$. Patients underwent treatment of their endometriosis by excision or fulguration of endometriotic lesions. Tissues from 18 patients were sent for histological evaluation, which confirmed the presence of endometriosis. A second-look laparoscopy was performed 6–12 weeks after the initial laparoscopic procedure. Videos of both procedures were scored by a reviewer masked to treatment assignment. The video reviewer determined the AFS score for adnexal adhesions, and the revised AFS score for endometriosis stage. In addition, the color, size, and locations of endometriotic lesions were determined.

Oxiplex/AP gel was applied by applicator over the medial and lateral aspect of the ovary, fallopian tube, mesosalpinx, ovarian fossa, pelvic sidewall, and lateral aspect of the uterus. There were no adhesion-prevention devices used in

control patients, and no instillates were left at the end of surgery.

Statistical Analysis

The AFS score is the total of the ovary and fallopian-tube AFS scores (14). Change from baseline was calculated as the second-look AFS score minus the baseline score, resulting in a positive value when the AFS score increased at second look, and a negative value when the AFS score decreased at second look. Repeated-measures methodology, using Bonferroni correction, was used to assess treatment-group differences in the means after blocking by site and controlling for within-patient correlations between left-side and right-side measurements.

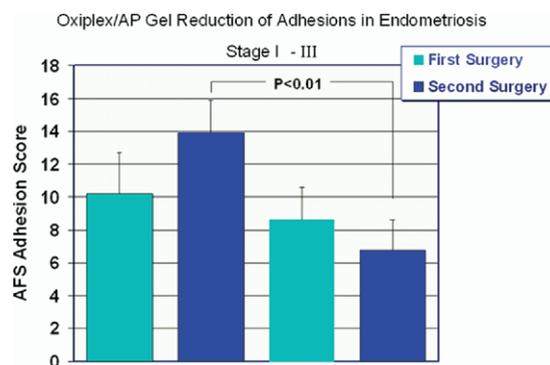
The stratified Kruskal-Wallis test was used to perform the analysis nonparametrically, after blocking by site. The paired t -test and the sign-rank test were the parametric and nonparametric tests, respectively, for the hypothesis H_0 : mean change from baseline = 0. The Cochran-Mantel-Haenszel chi-square test was used to assess treatment-group differences for categorical variables after controlling for site. Statistical significance with the use of a two-tailed t -test was set at $P < .05$.

RESULTS

All patients tolerated the surgical procedures well. There were no postoperative fevers or late-onset abdominal pain. Oxiplex/AP gel (approximately 12 mL; range, 4–60 mL) was easily applied over the adnexa in approximately 90 seconds.

FIGURE 1

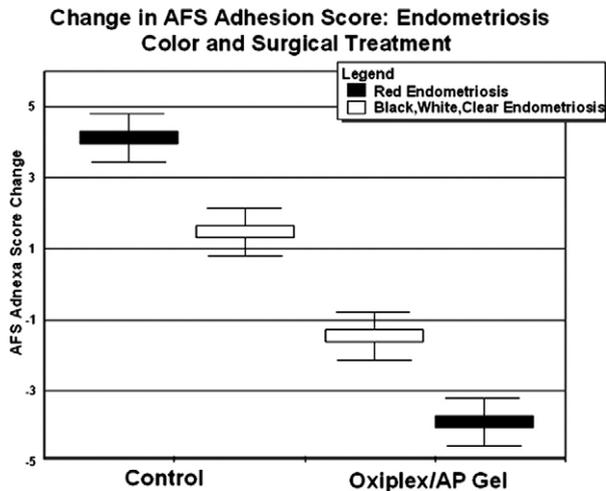
Reductions in adnexal AFS adhesion score between first-look and second-look laparoscopies in patients with endometriosis stages I–III. The AFS adhesion score increased between baseline and second-look surgeries in control patients. In contrast, AFS adhesion scores decreased in patients treated with Oxiplex/AP gel. These differences were statistically significant ($P < .01$).



diZerega. Red endometriosis and Oxiplex/AP gel. Fertil Steril 2007.

FIGURE 2

Patients with surgery alone had an increase in adhesion scores between first-look and second-look procedures. This increase in second-look adnexal adhesion score was significantly greater if the patient had endometriotic lesions that appeared red at the time of initial surgery ($P < .05$). Patients treated with Oxiplex/AP gel had a reduction in AFS adhesions scores, resulting in a significant change compared to surgery-only controls with ($P < .01$) or without ($P < .05$) red endometriotic lesions.



diZerega. Red endometriosis and Oxiplex/AP gel. *Fertil Steril* 2007.

The adnexa that underwent surgery alone had an increase in AFS score from 10 ± 2.5 to 14 ± 3 (\bar{X} or mean \pm SEM) at second-look laparoscopy. The adnexa that were covered by Oxiplex/AP gel had a decrease in AFS score from 8.4 ± 3 to 6.2 ± 2 (Fig. 1). This difference was statistically significant ($P < .01$). The change in AFS adhesion score in the adnexa in the control group without red lesions was 1.5 ± 1 , compared to 4 ± 1 for the adnexa with red lesions. This difference was statistically significant. For the Oxiplex/AP gel-treated adnexa, the change in AFS score in the adnexa without red lesions was -1.3 ± 0.8 and -3.8 ± 1 for adnexa with red lesions. Their relative reductions in AFS scores were also statistically different from the control adnexa ($P < .05$ and $P < .01$, respectively; Fig. 2).

A correlation between AFS score and revised AFS stage was expected, since an adhesion score is part of the endometriosis stage. The baseline AFS scores were similar for control and treated adnexa (Fig. 3). The second-look AFS scores increased in adnexa from both stage I and stage II groups in controls. In contrast, the AFS score either essentially stayed the same (stage I) or decreased (stage II) for the adnexa in the Oxiplex/AP gel-treated groups. The adnexa with at least 50% red endometriotic lesions had an increased AFS score at second-look laparoscopy in the control group,

and a decreased AFS score in the Oxiplex/AP gel-treated group. Similar patterns were observed in adnexa that had no red lesions, as well as those that had red lesions in the adjacent pelvic sidewalls.

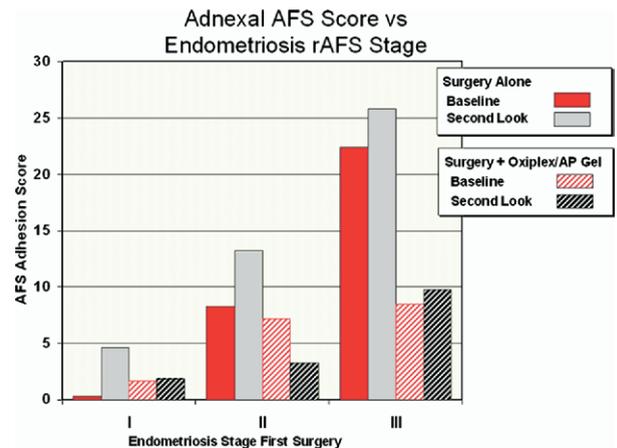
Correlation of the change in AFS score with the percentage of red lesions in each adnexa showed that control adnexa had greater increases in AFS scores when the red component of the endometriosis exceeded 30%–40%. Confidence in this “breakpoint” is limited by the distribution of observations, especially in the control group with <30%–40% red endometriosis. The Oxiplex/AP gel-treated adnexa had a more uniform response to surgical therapy, irrespective of the relative percentage of red lesions (Fig. 4).

DISCUSSION

Formation of adhesions is a major complication of surgical treatment for endometriosis. Recent evidence suggests that peritoneal inflammation, which may lead to adhesions, is enhanced in the presence of active endometriosis (20–27). This study correlated parameters of endometriosis obtained during routine clinical evaluations with the subsequent formation of adhesions following surgical treatment by laparoscopy. Patients with endometriosis have more adnexal adhesions following surgical therapy if their endometriosis is red in color. Adnexa with red endometriotic lesions had greater changes in adhesion scores than comparable areas with black or white and/or clear endometriotic lesions.

FIGURE 3

Adnexal AFS adhesion scores at first-look and second-look laparoscopy in patients with endometriosis stages I–III. Adhesion scores in all patients who had surgery alone increased at second look. In contrast, patients who received Oxiplex/AP gel had either a reduction in adhesion scores (stage II endometriosis) or essentially no change.

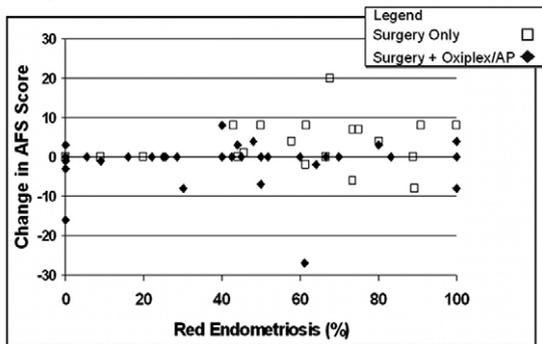


diZerega. Red endometriosis and Oxiplex/AP gel. *Fertil Steril* 2007.

FIGURE 4

Examination of change in AFS adnexal adhesion score as a function of the percentage of red endometriosis showed that control patients with >30% red endometriosis generally had increased adhesion scores at second-look surgery. In contrast, in patients who received Oxiplex/AP gel, adhesion scores generally decreased or stayed the same, irrespective of percentage of red endometriosis.

Correlation Between Red Endometriosis, Surgical Treatment, and AFS Adhesion Score



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Oxiplex/AP gel was effective in reducing adhesion formation compared to surgery alone in all subgroups. However, the persistence of adhesions, especially in cases of red endometriosis, suggests that incorporation of an antiendometriotic therapeutic into the gel may provide additional benefits.

Morphologic and morphometric data show similarities between eutopic endometrium and red peritoneal lesions, suggesting that these lesions are the first stage of early implantation of endometrial glands and stroma (3). Red peritoneal lesions are characterized by numerous proliferative glands with a columnar or pseudostratified epithelium, similar to what is observed in proliferative eutopic endometrium. Hyperplastic areas, characterized by an increase in the number of endometrial glands in relation to the stroma, were observed in 12% of red lesions (3). The glandular proliferation index and stromal vascularization are similar for eutopic endometrium and red peritoneal implants. An increase in stromal vascularization is observed during the secretory phase in both tissues (3, 12, 28).

In red endometriotic lesions, extensive vascularization was reported, in contrast to black lesions, which have reduced vascularization (3, 17, 28). The high stromal vascularization induced by red lesions is consistent with the presence of cytokines and angiogenic growth factors. Vascular endothelial growth factor (VEGF) was shown to be present in red lesions and eutopic endometrium in substantial excess, compared to black or other colored lesions (29, 30). Donnez et al. also reported that

VEGF levels in red peritoneal implants and eutopic endometrium increased in the late secretory phase of the cycle, whereas there was no cyclic variation found in black or other endometriotic lesions (29). Kokorine et al. (31) detected the presence of matrix metalloproteinases (MMP) in red peritoneal implants demonstrating ongoing biological activity.

Brosens (3, 32), as well as Donnez et al. (29), regarded red endometriotic lesions as indicative of early endometriosis, and black lesions as indicative of advanced endometriosis. White lesions are thought to be latent or quiescent, which is consistent with the relatively reduced adhesion formation that followed their treatment compared to red lesions in this study (33). This hypothesis is consistent with clinical reports that red lesions precede others lesions and that, with time, their presence decreases, and they are replaced by black and ultimately white lesions (8, 12, 32–34).

This spectrum of putative biological activity, correlated with the morphological appearance of endometriotic lesions, leads to the clinical question of surgical therapy. When should endometriotic lesions be surgically treated? Perhaps the tissue response and subsequent formation of adhesions would be less pronounced if red lesions were resected in the midproliferative phase of the cycle, or when the activity of the lesions was reduced by medical therapy. Gonadotropin-releasing hormone agonist has indeed been efficacious in reducing the vascularity and mitotic activity of red lesions (1). Should red lesions be removed by wide excision? In contrast, should white and clear lesions be left alone?

Oxiplex/AP gel was effective in reducing adhesion formation compared to surgery alone in all subgroups. However, the persistence of adhesions, especially in cases of red endometriosis, suggests that the incorporation of an antiendometriotic therapeutic into the gel may provide additional benefits. Should gels with pharmacologic agents which decrease the tissue response associated with removal of red lesions be used in selective cases? Conversely, the comparative lack of biological activity questions the need for surgical treatment of white or clear lesions.

A limitation of this study is the lack of histological confirmation of the endometriotic implants. Endometriosis was confirmed in the 18 patients who had biopsies taken. It is well-known that visual inspection alone may result in overdiagnosis of lesions (10, 12, 13, 35). In routine clinical practice, diagnosis of endometriosis is typically made by visual inspection, and is not confirmed by histological evaluation prior to initiation of treatment. Importantly, the correlation between histological diagnosis and visual impression was clearest with colored lesions such as red or black (9, 12, 13, 33, 36). Excision-biopsy sampling can provide histological confirmation; however, it increases the likelihood of injury to, or destruction of, underlying structures (37).

In conclusion, surgical treatment alone of red endometriotic lesions resulted in greater adnexal adhesions than did endometriotic lesions of other colors. The surgical treatment of

endometriosis composed of >30% red lesions led to increased AFS adhesion scores. The use of Oxiplex/AP gel significantly reduced adnexal adhesion formation in patients with endometriosis, including red endometriosis. The color, extent, and locations of endometriotic lesions should be considered when planning surgical therapy. Oxiplex/AP gel is a useful adjuvant to good surgical technique in treating endometriosis in patients who have disease at stages I–III. (36, 37).

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