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Original Article

Intercoat (Oxiplex/AP Gel) for Preventing Intrauterine Adhesions After Operative Hysteroscopy for Suspected Retained Products of Conception: Double-Blind, Prospective, Randomized Pilot Study

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ABSTRACT **Study Objective:** To evaluate the safety and effectiveness of Oxiplex/AP gel (Intercoat) in reducing intrauterine adhesion formation after hysteroscopic treatment because of retained products of conception (RPOC).

Design: Prospective double-blind, randomized, controlled pilot study (Canadian Task Force classification I).

Setting: Tertiary medical center.

Patients: All women who underwent hysteroscopic treatment because of RPOC at our institution between September 2009 and June 2012 were invited to participate. After operative hysteroscopy, participants were randomized to either have their uterine cavity filled with Oxiplex/AP gel (study group, n = 26) or not (control group, n = 26).

Interventions: Diagnostic office hysteroscopy to assess for adhesion formation was performed after 6 to 8 weeks. Findings were graded according to the American Fertility Society classification. Rates of subsequent pregnancy in the 2 groups were assessed.

Measurements and Main Results: Intraoperative complication rates were similar between the 2 groups. There were no postoperative complications after Oxiplex/AP gel application. Moderate to severe adhesions developed in 1 woman (4%) in the study group and 3 (14%) in the control group (p = .80). During follow-up of 20 months (range, 2–33 months), 7 women (27%) in the treatment group conceived, compared with 3 (14%) in the control group (p = .50).

Conclusion: Intrauterine application of Oxiplex/AP gel after hysteroscopic removal of RPOC is safe. In this small sample, the difference in the rate of intrauterine adhesions was not statistically significant. A larger study would enable further establishment of the safety and efficacy of use of this gel. Journal of Minimally Invasive Gynecology (2014) 21, 126–130 © 2014 AAGL. All rights reserved.

Keywords: Asherman syndrome; Hysteroscopy; Intercoat (Oxiplex/AP gel); Intrauterine adhesions; Retained products of conception

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Asherman syndrome is a combination of intrauterine adhesions and clinical manifestations including menstrual abnormalities, secondary infertility, and substantial obstetric morbidity [1–3]. The underlying pathophysiology of Asherman syndrome is trauma to the vascular basal endometrium [4]. Such trauma could be induced by uterine curettage in the postpartum period, after spontaneous miscarriage, during termination of pregnancy, or by cesarean section [1]. Anticipated recovery may be further disrupted, in particular in a state of hypoestrogenemia, which is common in lactating women [5]. It has been suggested that a local or systemic infection also contributes to this process [1,6]. However, it seems that the primary cause is retained

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products of conception (RPOC) combined with surgical interventions to remove them [1,6].

Asherman syndrome may be treated via operative hysteroscopy; however, recurrence of adhesions is common [7], and pregnancy rates remain low in the case of severe adhesions [8]. Thus, primary prevention of intrauterine adhesions after treatment because of RPOC is important. To date, strategies of primary prevention have concentrated on the use of operative hysteroscopy as opposed to traditional curettage for treatment of RPOC [1]. Studies have shown the efficacy of this approach [1]; however, other methods of prevention may be of use. Systemic estrogen combined with prophylactic antibiotic therapy has been used, although the efficacy of this approach has yet to be established [9]. Another common method involves distancing the uterine walls using an intrauterine device or a Foley catheter balloon immediately after treatment [10]; however, this approach may be associated with risk of perforation, infection, and compromise of the local vascular supply to the endometrium [2].

A novel approach is to use a biologic barrier immediately after surgical treatment, to prevent direct contact between opposing uterine walls. Such barriers were originally developed to minimize adhesion formation in the abdominal and pelvic cavity after surgery. The mode of action is creation of an inert layer between the area of excision and the surrounding environment. The ideal barrier should be non-immunogenic, unaffected by remesothelialization, stay in place without sutures, remain active in the presence of blood, and be completely biodegradable [11]. Several types of biologic barriers have been tested; Gynecare Interceed (Ethicon, Inc., Somerville, NJ), Preclude (W.L. Gore & Associates, Hertogenbosch, the Netherlands), and Sepra-film (Genzyme, Naarden, the Netherlands) are solid barriers [12], and Adept (Baxter Healthcare, Deerfield, IL) is a liquid [13]. None of these is suitable for intrauterine application because of their physical characteristics. Oxiplex/AP gel (FzioMed, Inc., San Luis Obispo, CA) is a new intraperitoneal gelatinous compound that is a viscoelastic gel composed of polyethylene oxide and carboxymethylcellulose stabilized by calcium chloride. It has been hypothesized that carboxymethylcellulose decreases injured tissue apposition required for adhesion formation [14]. Furthermore, precursors of fibrin bridges that lead to adhesions do not interact well with polyethylene oxide because of steric repulsion forces [15]. When stabilized together into a composite gel, the properties of protein repulsion and tissue adherence are additive in preventing postsurgical adhesions [16]. Several studies have shown Oxiplex/AP gel is safe and effective in reducing adnexal adhesions after laparoscopic surgery [17,18], even endometriosis [19,20].

To our knowledge, this product has never been used in the uterine cavity. In the present pilot study, we evaluated the safety and effectiveness of Oxiplex/AP gel in reducing adhesion formation after hysteroscopic treatment of RPOC.

Materials and Methods

The protocol of this prospective, double-blind, randomized, controlled study was approved by national and institutional review boards. Patients who underwent hysteroscopic surgery because of suspected RPOC at our institution between September 2009 and June 2012 were invited to participate in the study, and enrollees gave signed informed consent. Inclusion criteria were age 18 to 50 years and suspicion of RPOC on transvaginal ultrasound, diagnostic office hysteroscopy, or both. Exclusion criteria were signs/symptoms of infection or active bleeding at admission. The study entrants, in blocks of 12, were randomly allocated via a computer-generated randomization schedule, using institutional computer software, to treatment with (study group) or without (control group) Oxiplex gel. Twenty-six women were allocated to each group. More than one-third of study participants had undergone previous cesarean section, manual lysis of adherent placenta, or manual revision of the uterine cavity because of postpartum hemorrhage (Table 1).

Surgical Procedure and Gel Application

All hysteroscopic procedures were performed with the patient under general anesthesia. A pelvic bimanual examination was performed with the patient under anesthesia, and findings were recorded in the medical records. The uterus was considered enlarged when the uterine fundus was palpated above the pelvic brim. Saline solution (NaCl 0.9%) was used as the distention medium. Suspected RPOC was removed via blunt dissection, using a 4-mm loop resectoscope (Stryker Corp., Kalamazoo, MI) as a curette and under direct hysteroscopic view. All specimens were sent for pathologic analysis. After completion of the hysteroscopic dissection, Oxiplex gel was inserted into the uterine cavity in the study patients, up to complete filling of the cavity or up to 10 mL gel, whichever occurred first. All patients were discharged from the hospital several hours after the procedure.

Table 1

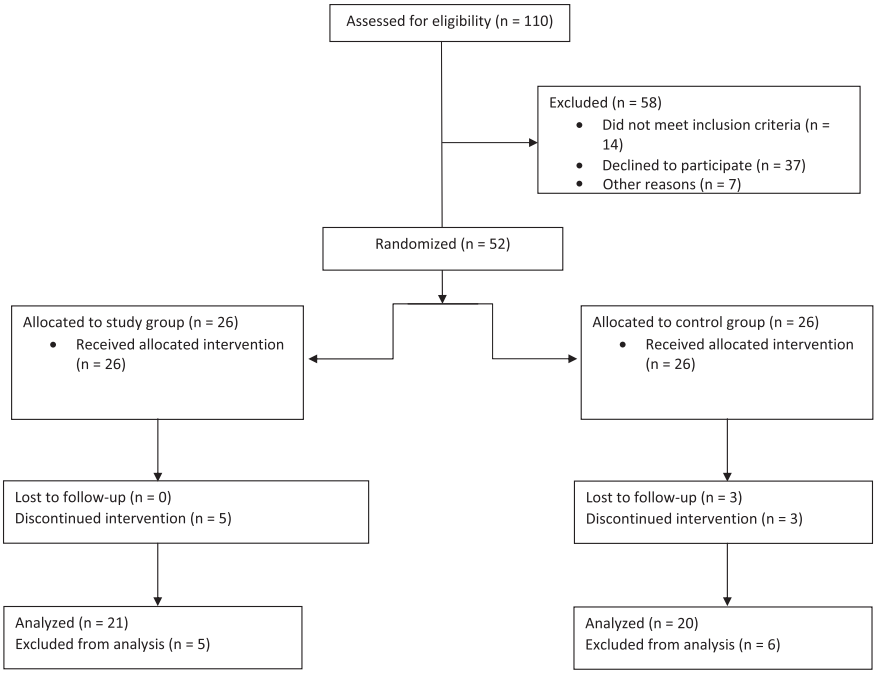
Patient characteristics

Variable	Study Group (n = 26)	Control Group (n = 26)	p value
Age, yr, mean (SD)	29.5 (5.1)	31.4 (6.5)	.20
Obstetric history, No. (range)			
Gravidity	2 (1–6)	2 (1–4)	NA
Parity	1 (0–3)	2 (0–3)	.08
Abortions	0 (0–4)	0 (0–1)	NA
Direct intervention in uterine cavity[a]	10	9	.80

NA = not available.
[a] Previous cesarean section, manual lysis of adherent placenta, or revision of uterine cavity because of postpartum hemorrhage.

Fig. 1

CONSORT (CONsolidated Standards of Reporting Trials) Statement 2010 flow diagram of the progress through the phases of a parallel randomized trial: enrollment, intervention, allocation, follow-up, and data analysis.



Postoperative Treatment and Follow-up

Both treatment and control groups received sequential hormone treatment (estradiol valerate, 2 mg/d, for 11 days, followed by estradiol valerate, 2 mg/d, and norgestrel, 0.5 mg/d, for 10 days) and antibiotic therapy (amoxicillin–clavulanic acid, 875 mg, twice daily for 7 days). All patients underwent diagnostic office hysteroscopy at 6 to 8 weeks after the operative procedure, performed by a surgeon who was blinded to the treatment group. Different surgeons performed the operative hysteroscopy and the follow-up diagnostic hysteroscopy. Both the patients and the surgeons who performed the follow-up studies were unaware of patient group assignment. Findings at follow-up hysteroscopy were graded according to the American Fertility Society (AFS) classification [21]. Patients with a diagnosis of adhesions (AFS grade ≥ 1) were offered an additional procedure for adhesiolysis.

A follow-up telephone survey was conducted to screen for late adverse events, verify menstrual regularity, and document subsequent pregnancies. This follow-up was conducted for all participants during 1 week.

Statistical Analysis

Statistical analysis was performed using a commercial software program (SPSS version 15.0 for Windows; SPSS, Inc., Chicago, IL). Variables with normal distribution were compared using the 2-tailed *t* test for unpaired data. Discrete variables were compared using the Fisher exact test. Statistical significance was accepted at $p < .05$. Because this was a pilot study using a non-inferiority design, post hoc power analysis was performed. This calculation showed that the power for detection of a statistically significant difference in rates of intrauterine adhesions between the 2 groups was 24%.

Results

Fifty two patients with suspected RPOC were included in the study and were randomly allocated to a treatment group ($n = 26$) or a control group ($n = 26$) (Fig. 1). Twenty-two women (42%) were seen after direct intervention in the uterine cavity (cesarean section, manual separation of placenta, or revision of the uterine cavity after vaginal delivery). Four women (7%) had previously been treated for RPOC. The 2 groups were similar insofar as demographic and obstetric data (Table 1) and clinical characteristics (Table 2).

The mean time between the index obstetric event and inclusion in the study was 7 weeks in both groups. The groups did not differ significantly in terms of needing further pharmacologic intervention (i.e., oxytocin or vasopressin) after operative hysteroscopy to enhance uterine involution and decrease bleeding (3 women in the study group vs 5 in the control group; $p = .70$). There were no other surgical or postoperative complications in either group.

RPOC were verified via pathologic analysis in 37 women (72%), with no statistically significant difference between

Table 2

Clinical characteristics at admission[a]

Variable	Study group (n = 26)	Control group (n = 26)	p value
Asymptomatic	14 (53.8)	9 (34.6)	.20
Enlarged uterus	13 (50)	14 (53.8)	1.00

[a] Values are given as No. (%).

the control and treatment groups (p = .80). At follow-up hysteroscopy, 3 patients in the control group (14%) had AFS stage 2 or 3 (moderate to severe) intrauterine adhesions, compared with 1 woman in the study group (4%), who had AFS stage 3 intrauterine adhesions (p = .30). Final follow-up was performed via telephonic survey of all participants during 1 week. Median follow-up in the control group was 24 months (range, 5–31 months), and in the study group was 22 months (range, 3–41 months). During follow up, 7 women in the study group (27%) and 3 in the control group (14%) achieved pregnancy; however, this difference did not reach statistical significance (p = .5).

Discussion

Surgical treatment of RPOC can result in intrauterine adhesions, which produce substantial obstetric morbidity [21]. Because treatment of these adhesions is unsatisfactory, prevention is crucial. To date, preventive measures include use of hysteroscopy as opposed to sharp curettage to treat RPOC [1], combined with pharmacologic and mechanical measures [9,10]. However, these techniques have not been able to obviate adhesion formation. Therefore, research now focuses on use of biologic barriers as a safe and potentially effective means to prevent occurrence of intrauterine adhesions after surgical treatment of RPOC.

Previous studies have shown that the use of ACP gel, which is a hyaluronic acid derivative, is safe in the uterine cavity; however, its efficacy is controversial [22–24]. One study of ACP gel demonstrated that it was able to separate uterine walls for at least 72 hours, as measured via ultrasound [23], which suggests that the gel possesses the right mechanical properties.

In this cohort study, application of Oxiplex/AP gel was examined. This viscoelastic gel is composed of polyethylene oxide and carboxymethylcellulose stabilized by calcium chloride. Oxiplex/AP gel has a propensity for tissue adherence and persistence sufficient to prevent adhesion formation [11] and is safe and effective in reducing adnexal adhesions after laparoscopic surgery to treat endometriosis [17–20].

We routinely administer preventive antibiotic and hormone therapy to all patients undergoing hysteroscopic resection of RPOC. This approach has been advocated by several authors, although its efficacy in reducing adhesion formation has yet to be established [9].

The only intraoperative complication encountered in our cohort was increased bleeding, which resolved after vasopressin administration. The application of Oxiplex/AP gel did not increase the incidence or severity of this complication. We did not encounter any postoperative complications during our study. A limitation of the present study is that because the procedures were performed in an outpatient setting and patients were monitored only during diagnostic hysteroscopy after 6 to 8 weeks, in theory we could have missed minor postoperative complications. However, the study indicates the safety of Oxiplex/AP gel in this setting. Another possible limitation is that the survey conducted to search for late adverse outcomes, menstrual regularity, and subsequent pregnancies was conducted during 1 week; however the time from procedure to follow-up was similar between the study group (median, 24 months; range, 5–31 months) and the control group (median, 22 months; range, 3–41 months).

In the present pilot study, we were not able to demonstrate a meaningful reduction in adhesion formation after hysteroscopy with use of Oxiplex/AP gel. That 14% of women in the control group had moderate to severe intrauterine adhesions, compared with only 4% in the study group, may imply a tendency toward improved results after treatment with Oxiplex/AP gel. There was also an interesting tendency toward an improved fertility rate in women in the study group. It is important to point out the low power of the study for detection of statistically significant differences in the rates of intrauterine adhesions. A larger study specifically designed and powered to evaluate efficacy of the product may enable detection of those differences.

Pathologic analysis did not confirm RPOC in 29% of patients in each group; however, these cases were not excluded from the analysis because Asherman syndrome can also develop after surgical procedures on the post-gravid uterus without the presence of trophoblast cells. Moreover, the rate of absent pathologic confirmation was similar between groups. Nevertheless, this should be regarded as a limitation of the study.

Overall, our findings in this pilot study indicate that intrauterine use of Oxiplex/AP gel is safe, that there is a tendency toward reduction of frequency of adhesions after operative hysteroscopy to treat suspected RPOC and toward enhanced ability to conceive after this treatment.

We are aware that no firm conclusions can be drawn about the efficacy of this gel preparation from the results derived from such a small pilot cohort. Nevertheless, the present study is the first to demonstrate the safety of this treatment, both in terms of intraoperative complications and postoperative course. The strength of the study lies in its structured method; being a double-blind, randomized, controlled trial helps to avert introduction of selection and ascertainment bias. This design, however, does not completely eliminate the possibility of bias in ascertainment of the rate of intrauterine adhesions in those cases in which adhesions developed later, after completion of the study. To

confirm the capabilities of Intercoat in reducing the formation of uterine adhesions and possibly enhancing the fertility rate in women who have undergone operative hysteroscopy to treat RPOC, additional research with larger sample sizes is needed.

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