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Hysteroscopic and ultrasound evaluation of a novel degradable polymer film for the prevention of intrauterine adhesion formation after hysteroscopic surgery

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ABSTRACT

Objective: To collect information on the application and behavior of a novel degradable polymeric film (DPF) developed to prevent intra-uterine adhesions (IUAs) after hysteroscopic surgery.
Study design: A prospective observational study conducted in a university hospital in Naples, Italy. Women undergoing hysteroscopic myomectomy, metroplasty or adhesiolysis, were eligible for the study. Women had their uterine cavity assessed by transvaginal ultrasound scan before their hysteroscopic surgery, which was followed by the DPF insertion. Ultrasonographic and hysteroscopic assessments were undertaken immediately after insertion then at 2 h, 2–5 days, and 6 weeks postoperative. The main outcome of interest was to assess the behavior of the DPF, from insertion to degradation, by ultrasound and hysteroscopy. Other outcomes included ease of DPF insertion, any patient reported adverse events and the presence of IUAs at 6 weeks.
Measurements and main results: A total of 15 patients were enrolled into the study. The DPF insertion was reported to be very easy in almost all the cases and was visualized immediately and 2 h after insertion in all patients. At the 2–5 day follow-up 5 and 2 of the 15 participants still had the entire or partially hydrolyzed film respectively. By 6 weeks there was no evidence of the DPF in all women. No adverse events were reported at the time of insertion or follow-up. None of the study participants had IUAs at the 6-week assessment.
Conclusions: According to this pilot study, the solid degradable polymer film, Womed Leaf, is a promising, easy to apply and well tolerated novel option for the prevention of intrauterine adhesion formation after hysteroscopic surgery.

Introduction:

Intrauterine adhesions (IUAs) are dense or filmy bands of scar tissue between the inner walls of the uterine cavity. They can be partial or complete resulting in a reduction in the uterine cavity volume and its deformation or, in severe cases, its complete obliteration [1]. IUAs can occur following intrauterine diagnostic and therapeutic procedures that lead to endometrial trauma resulting in scarring, adhesions or fusion of the opposing uterine walls. Women who have IUAs are sometimes asymptomatic, however, infertility, recurrent pregnancy loss, menstrual abnormalities and pelvic pain are common presenting complaints in symptomatic patients [2]. Moreover, once formed, the recurrence rate of such IUAs after adhesiolysis has been reported to be as high as 62.5% [3]. Therefore, preventing their occurrence in the first place is of utmost importance. Nonetheless, prevention of IUA formation is still considered a significant challenge for gynecologists performing intrauterine procedures [4,5].

There is wide variation in the reported incidence and recurrence rates of IUAs following hysteroscopic surgical procedures [3,6–9]. This is probably related to the type of procedure, surgical technique and the different strategies used to mitigate the risk of adhesion formation. Several adjuvant therapies and devices have been used to reduce the risk

Abbreviations: DPF, Degradable polymer film; IUA, Intrauterine adhesion; IUCD, Intrauterine contrceptive device.

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of IUA formation, including, hormonal therapy, intrauterine contraceptive devices (IUCD), intrauterine balloons, hyaluronic acid gel and human amniotic membrane grafts [10]. However, the reports on the effectiveness of these policies are conflicting with no clear superior strategy [4,11–19].

Womed Leaf is a triblock degradable polymer film (DPF) made of poly (D,L-lactide) (PLA) and poly (ethylene oxide) (PEO), designed specifically for intrauterine use as an adhesion prevention barrier device particularly after hysteroscopic procedures. The DPF is designed to stay within the uterine cavity for 5 – 7 days where it initially expands by fluid absorption to a thickness of approximately 1 mm and becoming soft and flexible. Eventually, it hydrolytically degrades resulting in its spontaneous discharge through the cervix (Fig. 1). The non-adhesion properties of DPF were previously tested in animal experiments and more recently in a small cohort of women post hysteroscopic myomectomy [9,20]. The aim of this study was to collect information on the ease of application and behavior of this novel DPF after different types of hysteroscopic surgery in our setting.

Material and methods

Study design and participants

This was a prospective observational study conducted at a single tertiary referral center in Naples, Italy. The study was conducted between March and July 2021 following Institutional Review Board (IRB) approval (Comitato Etico Universita' Federico II - Ref. No 401/20).

Women between the ages of 18 and 45, scheduled to undergo hysteroscopic myomectomy, metroplasty or adhesiolysis with a uterine cavity length between 6 cm and 9 cm on ultrasound scan were consecutively recruited into the study. Women known or suspected to have endometrial hyperplasia or cancer, prior history of cervical or endometrial cancer, active or prior history of pelvic inflammatory disease or known to have hypersensitivity to any of the DPF components were excluded from the study. All study participants provided an informed written consent to participate prior to recruitment.

Procedure

One of two expert hysteroscopists (ADSS or BZ) performed the operative procedures under general anesthesia during the follicular phase using a 5 mm continuous-flow hysteroscope (Bettocchi, Karl Storz, Tuttlingen, Germany). Depending on the procedure performed, a 5 Fr bipolar electrode (Versapoint, Olympus Corp.) and miniaturized instruments, a 16 Fr bipolar miniresectoscope (Karl Storz, Tuttlingen, Germany) or a 27 Fr bipolar resectoscope (Karl Storz, Tuttlingen, Germany) with a 4 mm loop (Olympus, USA) were used. Normal Saline was used for uterine cavity distention with the intrauterine pressure automatically controlled using Endomat® (Karl Storz, Tuttlingen, Germany). No pharmacological preparation of the endometrium was used. At the end of the procedure the DPF (Womed leaf) was inserted through the cervix and released into the uterine cavity using a 5 mm flexible inserter and technique similar to that used for IUCD insertion. Oral azithromycin was prescribed for 3 days after hysteroscopic surgery.

For metroplasty of a dysmorphic uterus, 3–4 mm deep longitudinal lateral incisions were made in the fibromuscular constriction rings up to the isthmic area using a bipolar electrode or a 15 Fr bipolar resectoscope with a pointed electrode. In cases of a spectate uterus, a 15 Fr resectoscope was used for the removal of uterine septum, applied in the median plane starting at the apex and proceeding towards the fundus, until both tubal ostia were visualized. A 5 Fr cold scissors introduced through a telescope bridge with working-channel was used to complete the septal incision. Metroplasty was considered complete when the total fundal uterine wall was estimated to be 1 cm in thickness based on a graduated intrauterine palpator measurement at the end of the procedure and the pre-surgical ultrasound measurements.

In all metroplasty cases, there was an increase in uterine cavity volume and an improvement in its morphology. Complete removal of the uterine septum in one surgical procedure was achieved in all patients but one, who required removal of small residual tissue spurs using 5Fr blunt scissors at the 6-week follow up appointment.

Follow-up and outcomes

All women were assessed by hysteroscopy and ultrasound immediately after Womed leaf insertion, after 2 h, 2–5 days and 6 weeks. Ultrasound scans (2D and 3D) were performed by one of two expert operators (BZ or GS) using a Voluson Swift® (GE Healthcare, Chicago, Illinois, United States) with a transvaginal probe. Apart from immediately following insertion, all follow-up hysteroscopic assessments were undertaken as outpatient procedures without anesthetic.

The main outcome of interest for this study was to assess the

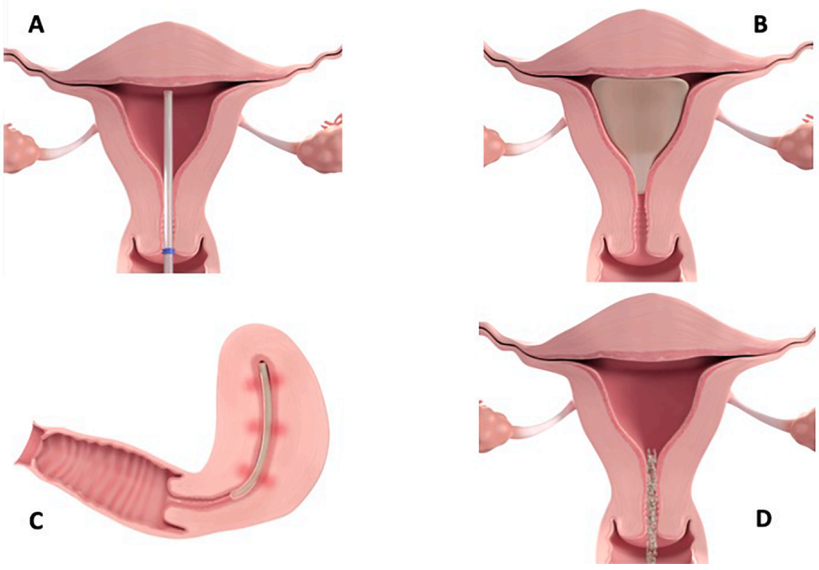

Fig. 1. Illustration demonstrating the Womed Leaf insertion (A), deployment (B), residence within the uterine cavity acting as a mechanical barrier (C) and degradation leading to discharge through the cervix (D).

behavior of the DPF, from insertion to degradation, by ultrasound and hysteroscopy. Additionally, we collected information on the ease of DPF insertion, any patient reported adverse events and the presence of IUAs at 6 weeks. The ease of the DPF insertion, from the operator's perspective, was assessed using a 4-point Likert scale ranging from 0 (not easy) to 3 (very easy). Data are presented as means or percentage where appropriate.

Results

A total of 15 women with a mean age of 37 ± 8 (range 27 – 47) years and a mean BMI of 24.6 ± 4.5 were enrolled into the study. All participants had the intended procedures and completed all the a priori set follow-up time-points. Fig. 2 illustrates the appearance of the DPF on 2D / 3D ultrasound and hysteroscopy at the different time points. The hysteroscopic operative procedures performed on our study cohort included 7 myomectomies, 7 metroplasties and 1 hysteroscopic adhesiolysis.

Based on both ultrasound and hysteroscopic assessments, the undeployed uterine film was present in all patients (15/15) immediately after surgery. By 2 h after surgery, the deployed DPF was visible in all patients (15/15). On the third follow-up (days 2–5 postoperative), the DPF was still present in 7 of the 15 participants (46.6%) either in its entirety or partially hydrolyzed in 5 and 2 women respectively. In the remaining 8 participants, the device was not visible, however, only one participant reported noticing the film being spontaneously expelled 4 h after its insertion. None of the patients reported any adverse events and the operators scored the ease of device insertion as 3 (very easy) in 14 and 2 in one of the 15 procedures. At the 6-week postoperative follow-up, none of the study participants had evidence of Womed Leaf within the cavity and there was no evidence of any IUAs.

The baseline characteristics of our study cohort and type of uterine pathology are presented in Table 1.

Table 1
Participants' characteristic.

Age	Parity	Uterine pathology
37	**0**	Anterior myoma G1 3 cm + posterior myoma G2 2.5 cm
35	**0**	Complete septate uterus U2b
33	**0**	Dysmorphic uterus
35	**0**	Dysmorphic uterus
36	**0**	Right Myoma G1 3 cm + posterior myoma G2 1.5 cm
41	**2**	Anterior Myoma G1 1.5 cm
40	**2**	Anterior Myoma G1 2 cm
47	**2**	Anterior Myoma GO 2.5 cm
36	**1**	Septate uterus U2a
32	**0**	Dysmorphic uterus
41	**0**	Dysmorphic uterus
35	**2**	Severe intrauterine adhesions
27	**0**	Anterior Myoma G2 2.5 cm
37	**0**	Complete septate uterus U2b
44	**0**	Anterior Myoma G1 2 cm

Discussion

In this preliminary study none of our study cohort developed any postoperative IUAs as objectively assessed on hysteroscopy 6 weeks after hysteroscopic myomectomy, metroplasty or adhesiolysis. Moreover, none of our study cohort reported any unexpected side effects that could be attributed to the DPF. The insertion of Womed Leaf was also considered to be easy as evaluated by the two hysteroscopists in all the procedures. As expected, the DPF deployed quickly within 2 h from insertion and was not visible in the uterine cavity at the 6-week follow-up visit.

The important elements underpinning the mechanism of action of Womed Leaf are believed to be its early deployment, the 5–7 days residence time and degradation prior to its spontaneous discharge [9,20]. Hence, the main aim of this study was to monitor these aspects, using, both, ultrasonographic imaging and direct hysteroscopic visualization. We appreciate that the film could not be visualized in 8 of the 15 participants at the third follow-up appointment in our study. However, it is plausible that the hysteroscopies performed immediately after the DPF insertion and 2 h later, the use of saline as a distension medium and the associated cervical dilatation might have contributed to this either by mechanical displacement or by expediting the breakdown of the film

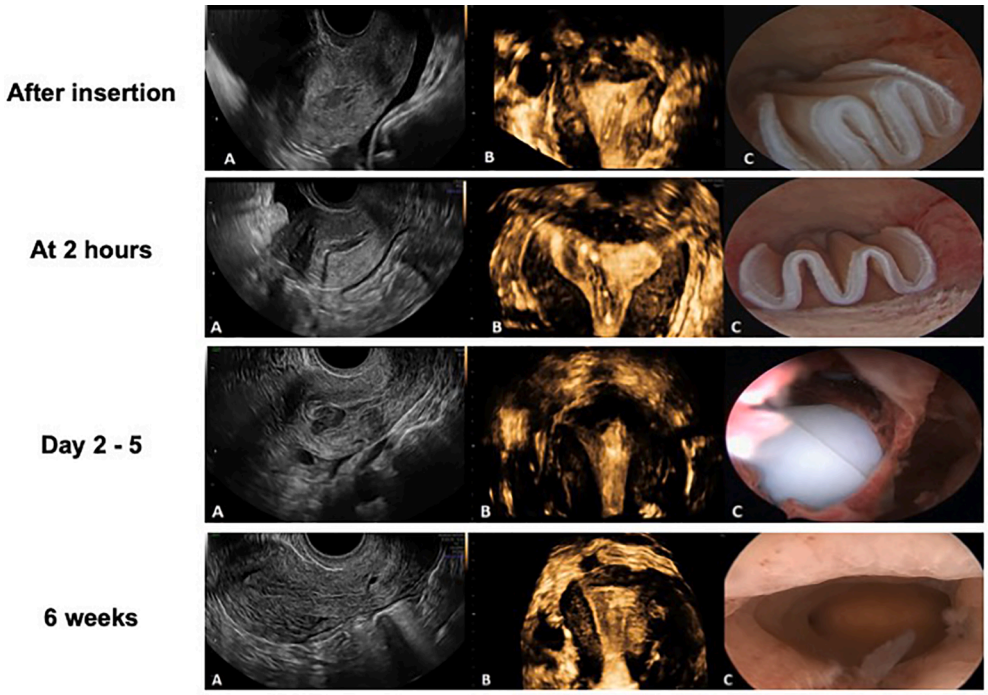

Fig. 2. 2D ultrasound (A), 3D ultrasound (B) and hysteroscopic (C) images showing the appearance of Womed Leaf at the first three follow-up time-points and the appearance of the uterine cavity at 6 weeks after the film was totally discharged.

and early discharge. Indeed, one of the study participants reported noticing the film being spontaneously expelled 4 h after its insertion. These hysteroscopies were performed as part of our study protocol and should not be required in a clinical setting. Additionally, 5 of the 8 women (63%), in whom the DPF was not visible at the third follow-up, had their assessments performed on days 4 and 5 postoperative, which is close to the nominal discharge window.

Weyers et al reported the first in-human study using Womed Leaf prophylactically following hysteroscopic myomectomy to prevent IUA formation [9]. In their cohort of 23 patients, the DPF was not visualized in 4% and 21% of their study cohort immediately and 2–6 h after insertion respectively. In contrast, the DPF in our study was visualized in all our patients immediately and at 2 h after insertion. Nonetheless, compared to Weyers and associates, who used either 2D or 3D ultrasound scan for this assessment, we used 2D / 3D ultrasound and hysteroscopy. This might explain the higher rate of film detection observed in our study at comparable time-points. Yet, our data on no patient reported adverse events and the ease of device insertion reported by surgeons concur with those reported by Weyers et al [9].

We appreciate that our study has several limitations, mainly related to the study design and sample size, and hence the preliminary nature of our report. We are encouraged by the absence of IUAs at the end of the study follow-up period in all the women included in our study. However, we fully appreciate that this could be a reflection of the small number of participants assessed. Moreover, this observation could have been confounded by the earlier hysteroscopies where the insertion of the scope and / or the distension medium might have mechanically disrupted early adhesion formation. We believe that, although our findings should be interpreted with caution in view of the aforementioned limitations; these should not overshadow the importance of our study. It is the first in-human report on the use of the DPF in a consecutive case series of 7 hysteroscopic metroplasties. It also adds 7 hysteroscopic myomectomy patients to the previously reported Weyers et al cohort of 23 women who had Womed Leaf inserted after myomectomy with a reported IUA rate of 13% 4–8 weeks after surgery. Given that none of our myomectomy patients had evidence of IUAs on diagnostic hysteroscopy performed at 6 weeks post operative, pooling our data with Weyers et al gives an overall post hysteroscopic myomectomy IUA rate of 10% (3/30) with the use of the DPF. This rate is much lower than that reported by other studies using alternative anti-adhesion strategies [8,21].

A very concerning long-term complication of hysteroscopic surgery is post-operative IUA formation, which are associated with infertility and other gynecological symptoms such as pelvic pain, dysmenorrhea and amenorrhea. Considering the severity of this condition, effective strategies for its prevention are needed. Barrier methods are widely used strategies for the prevention of IUA formation and their recurrence and they are of comparable prices to Womed Leaf [3,10,13–18,22]. However, there is lack of consensus as to which is the most effective strategy for the prevention of IUA formation [2,4,19]. Furthermore, most of these are far from optimal because of their short lifetime sometimes requiring repeat applications (hyaluronic acid gel), lack of uniform surface area coverage (IUCD) or the inconvenience to the patient because of the need to have them removed (IUCD and intrauterine balloons). The Womed Leaf's relatively longer residence time, large surface area due to its fast deployment and expansion and its hydrolytic degradation resulting in its spontaneous discharge seem to overcome these shortfalls.

The initial results on the DPF use reported in this and previous studies are, indeed, promising [9]. PREG2, currently recruiting, is a randomized controlled trial designed to evaluate the efficacy of the DPF in preventing IUA recurrence after hysteroscopic adhesiolysis (NCT04963179). Information from this should provide definitive answer with regards to the effectiveness of this device.

Conclusions

Based on the findings of our pilot study, the degradable polymer film (Womed Leaf) is easy to apply and was not associated with any reported side effects. The initial results on the use of this device to prevent intrauterine adhesions after hysteroscopic surgery are very encouraging till further evidence is available from a currently recruiting randomized controlled trial.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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