11 Postoperative Care (Hormonal Therapy, Physical Barriers, Vasodilators, Antibiotics)

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Intrauterine adhesions (IUAs) can occur after mechanical or infectious injury to the endometrium. Normal endometrial repair occurs without scar formation; however, in some women, these normal repair mechanisms are aberrant, resulting in IUA formation. The exact alteration in repair mechanisms is not well understood; however, it likely involves hypoxia, reduced neovascularization, and altered expression of adhesion-associated cytokines.

IUAs can lead to partial or complete closure of the uterine cavity, which may result in symptoms including abnormal menstruation, infertility, and pelvic pain (Fig. 11.1a, b).

The IUAs have been studied and classified since the 1978 (*classification is described in detail in Chap. 4*).

Although numerous observational studies suggest potential benefit with the use of anti-adhesion therapies (intrauterine device or balloon, hormonal treatment, barrier gels, or human amniotic membrane grafting) for decreasing IUAs, currently,

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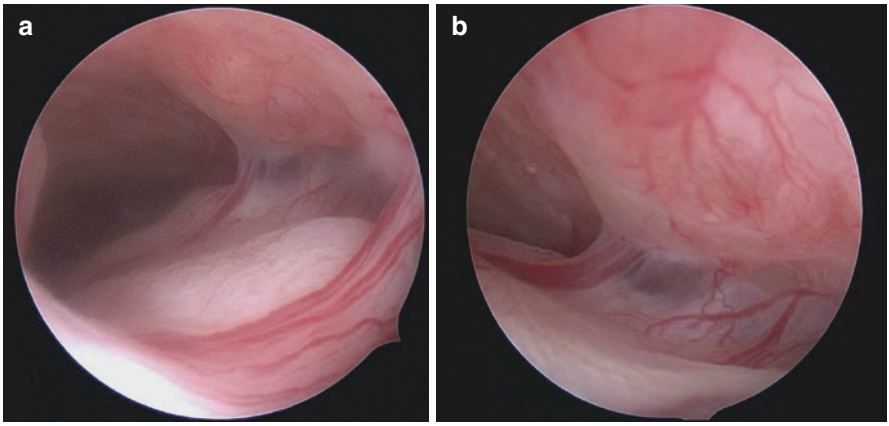

Fig. 11.1 (**a**, **b**) Mild intrauterine adhesions

there are no strong recommendations in favor of the use of anti-adhesion therapies after operative hysteroscopy.

At present the effectiveness of the anti-adhesion treatment following operative hysteroscopy for decreasing IUAs remains uncertain as suggested by the Cochrane Review of 2017 [1] because of the low quality of the evidence [1].

The pathogenesis of IUAs is related to many physiopathologic mechanisms, such as the lesion of the basal layer of the endometrium, caused by curettage, hysteroscopic surgery, uterine artery embolization, B-lynch sutures, abdominal myomectomy, hysteroscopic myomectomy, genital tuberculosis, and surgical treatment of Mullerian anomalies. They could cause the partial or complete obstruction of the cervix and the uterine cavity, with the consequent obstruction of sperm transport into the cervix, impaired embryo migration within the uterine cavity, and failure of embryo implantation [2, 3].

The occurrence of new adhesions after primary hysteroscopic adhesiolysis is so much frequent and the recurrence rate is associated with the grade of adherences (Figs. 11.2 and 11.3).

According the classification system of the former European Society of Hysteroscopy, Hanstede et al. found 21–25% recurrence with grade 1–2 adherences, 29.1% with grade 3, 38.5% with grade 4, and 41.9% with grade 5 [4].

There are several methods for secondary prevention, such as the use of estrogen, intrauterine device, Foley catheter, antibiotics, hyaluronic acid, and stem cell treatment used alone or in combination with each other.

The Cochrane Review (2017) of Bosteels et al. compared a device versus no treatment (two studies; 90 women), hormonal treatment versus no treatment or placebo (two studies; 136 women), device combined with hormonal treatment versus no treatment (one study; 20 women), barrier gel versus no treatment (five studies; 464 women), device with graft versus device without graft (three studies; 190

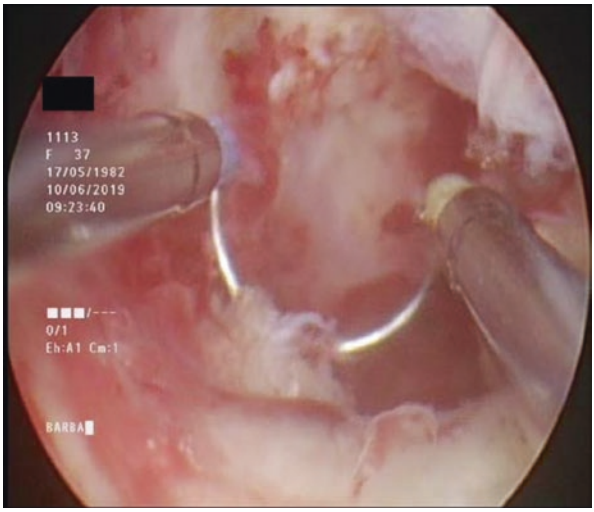

Fig. 11.2 Resectoscopic adhesiolysis

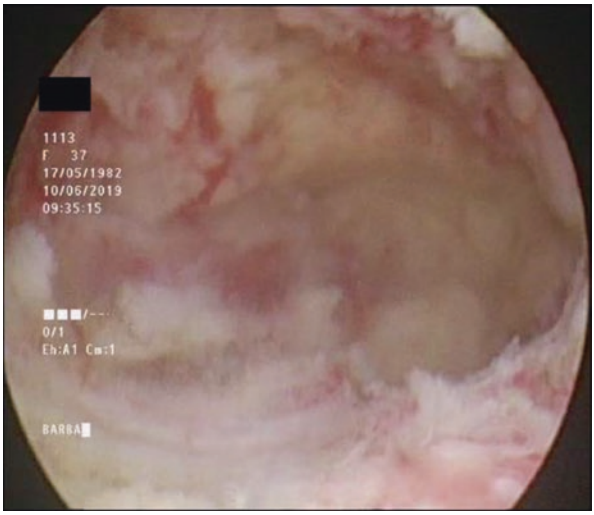

Fig. 11.3 Shows adhesion formation following primary hysteroscopic adhesiolysis

women), one type of device versus another device (one study; 201 women), gel combined with hormonal treatment and antibiotics versus hormonal treatment with antibiotics (one study; 52 women), and device combined with gel versus device (one study; 120 women) [1].

They concluded that the quality of the evidence ranged from very low to low. The effectiveness of anti-adhesion treatment for improving key reproductive outcomes or for decreasing IUAs following operative hysteroscopy in subfertile women remains uncertain.

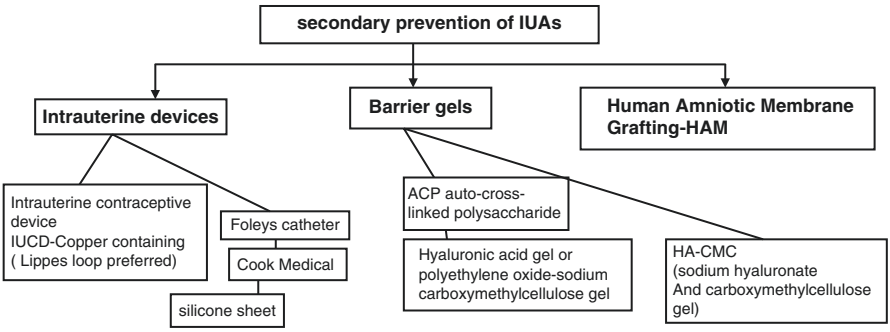

Fig. 11.4 Secondary prevention of IUAs

11.1 Intrauterine Devices (Fig. 11.5a–f)

The characteristics of an intrauterine device (IUD) to prevent intrauterine adhesion formation should be the tolerability of the device, the suppression of IUA formation, and the restoring of healing of the endometrium. There are several observational studies that recommended the insertion of a device after lysis of IUAs such as IUD and Foley catheter balloon after lysis of IUAs or septoplasty. The IUD may provide a physical barrier between the uterine walls, separating the endometrial layers [5]. There are different kinds of IUD with particular characteristics and mechanism of actions: copper-containing IUD provokes an excessive inflammatory reaction, and T-shaped IUD may have a surface too small to maintain separation of the uterine walls; instead the loop IUD is generally considered the IUD of choice for treatment of IUAs; however, it is not available in many geographic areas [6]. The Cook Medical balloon (Indianapolis, IN, USA) has been designed to be a heart-shaped intrauterine balloon for prevention of secondary intrauterine adhesions thanks to its triangular shape, which conforms to the configuration of a normal uterus and maintains separation at the margins of uterine cavity [7].

In a randomized controlled trial, Lin et al. compared the efficacy of intrauterine balloon (removed after 7 days) and IUD demonstrating similar efficacy [8].

The use of other mechanical barriers is also suggested for the prevention of secondary adhesions. Orhue et al. compared an IUD with a pediatric Foley catheter and found that the catheter was a safer and more effective adjunctive method of treatment of IUA compared with the IUD. The persistent posttreatment amenorrhea and hypomenorrhea occurred less frequently in the Foley catheter group (18.6%) than in the IUD group (37.3%) ($P < 0.03$), and the conception rate in the catheter group was 33.9% compared with 22.5% in the IUD group. The need for repeated treatment was also significantly less in the Foley catheter group [9].

Recently, Shi et al. compared the efficacy of intermittent intrauterine balloon dilatation versus standard care in the prevention of adhesion reformation in 200 patients with moderate-to-severe IUAs who underwent hysteroscopic adhesiolysis. In this randomized controlled trial, the balloon group received intrauterine balloon

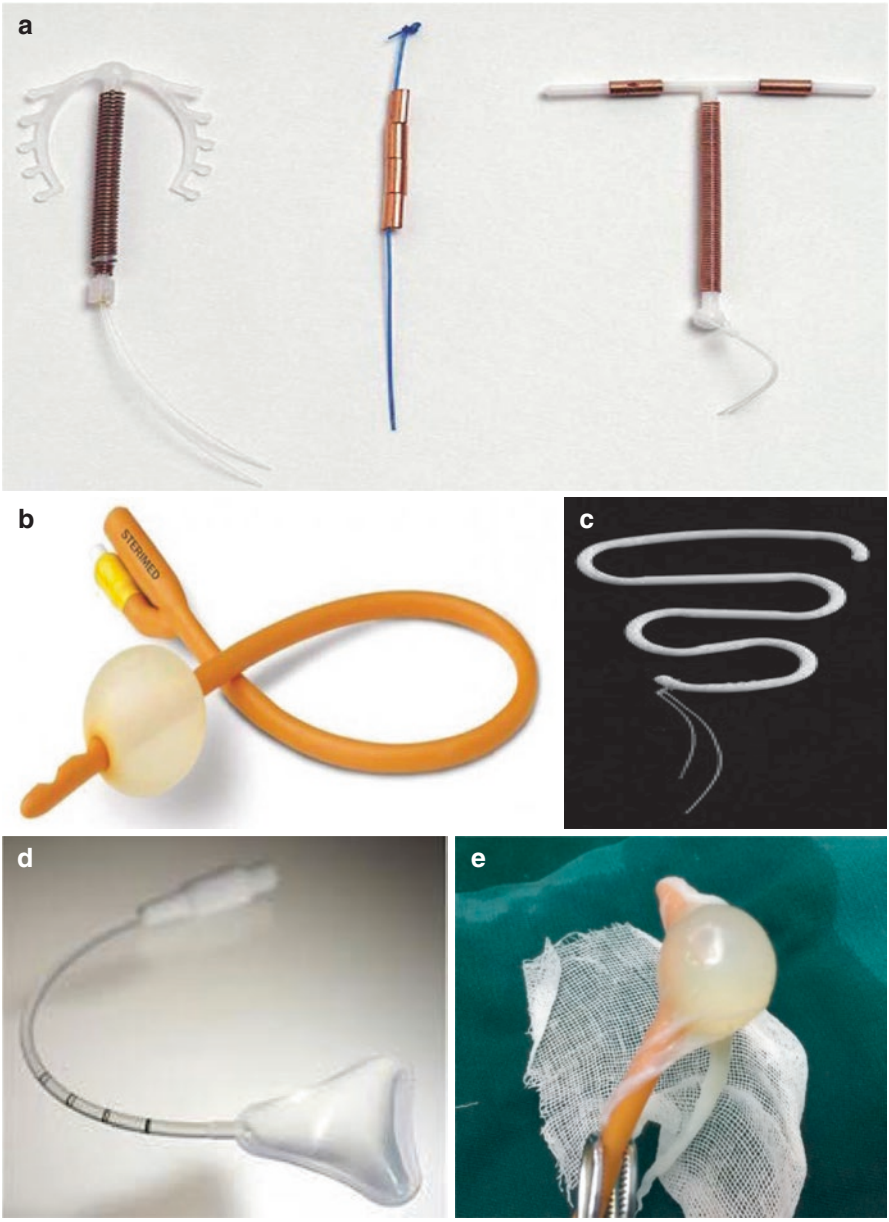

Fig. 11.5 (**a**) Copper T. (**b**) Foley catheter. (**c**) Lippes loop. (**d**) Cook Medical balloon. (**e**) Foley catheter with mounted amnion. (**f**) Silicon sheet cut into shape of uterus

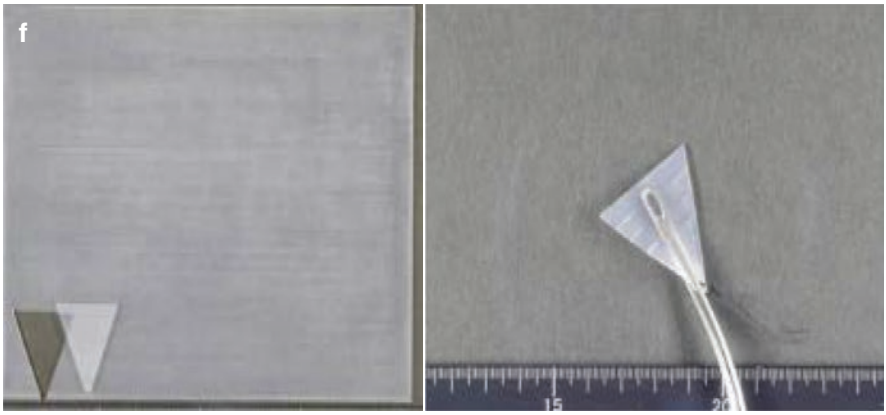

Fig. 11.5 (continued)

dilatation therapy at 2 and 6 weeks after surgery, whereas the control group did not. A total of 191 patients successfully completed the study protocol (94 cases for the balloon group and 97 cases for the control group). According to hysteroscopic evaluation at the 8th week, the overall adhesion reformation rate was significantly lower in patients in the balloon group than patients in the control group (20.2% vs. 40.2%, respectively; $P < 0.05$).

This study shows that postoperative intermittent intrauterine balloon dilatation therapy can significantly reduce postoperative adhesion reformation and significantly increase menstruation flow [10].

Silicone sheet: Atsushi Azumaguchi et al. [11] evaluated the efficacy of silicone sheet as a new type of barrier for preventing adhesion reformation following hysteroscopic adhesiolysis of intrauterine adhesions (IUAs). Hysteroscopic adhesiolysis was performed for 36 patients with IUAs. The adhesion reformation rate was retrospectively compared between 26 patients treated with silicone sheet (group 1) and 10 patients treated with an intrauterine device wrapped in oxidized regenerated cellulose as a barrier (group 2). The size and shape of the uterine cavity were observed by hysterosalpingography, and a silicone sheet ($200 \times 150 \times 1$ mm^3) was cut to fit the size and shape of the uterine cavity. Following adhesiolysis during surgery, the silicone sheet was inserted into the uterine cavity using small placental forceps, and then the fitness of the silicone sheet in the uterine cavity was observed by hysteroscopy. When necessary, the sheet was pulled out, and the size and/or shape corrected as many times as needed. After confirming an appropriate fit, six slits were made in the sheet to prevent the sheet from slipping out of the uterine cavity, nylon thread was threaded through a small hole in the lower part of the sheet to allow easy retraction after insertion, and the device was placed in the uterine cavity (Fig. 11.5f). The adhesion reformation rate was significantly lower in group 1 (4/26, 15.4%) than in group 2 (4/10, 40.0%; $P = 0.03$), although the pregnancy rate (14/20, 70.0% vs. 5/10, 50.0%; $P = 0.28$) and miscarriage rate (2/14, 14.3% vs. 1/5,

20.0%; $P = 0.72$) were not significantly different. They concluded that the use of silicone sheets appears to be effective for preventing adhesion reformation following hysteroscopic adhesiolysis of IUAs.

11.1.1 Barrier Gels

Several adhesion barriers are reported to be useful in reducing the risk of adhesion recurrence after surgical treatment of IUAs [12–14]. Use of biodegradable gel surgical barriers is based on the principle of keeping adjacent wound surfaces mechanically separate [15]. The exact mechanisms by which ACP (auto-cross-linked polysaccharide) and HA-CMC (sodium hyaluronate and carboxymethylcellulose gel) can reduce adhesion reformation are not well known but may be related to "hydro-flotation" or "siliconizing" effects. Hyaluronic acid gel or polyethylene oxide-sodium carboxymethylcellulose gel for the prevention of intrauterine adherences has been investigated demonstrating conflicting results. Acunzo et al. found a significant effect of hyaluronic acid compared to no treatment (14% vs. 32%) [14]. Instead Lin et al. demonstrated that the balloon and IUCD were more effective than hyaluronic acid [8].

Ducarne et al. compared application of ACP gel (30 women) versus no gel (24 women) at the end of an operative hysteroscopic procedure performed to treat myomas, polyps, uterine septa, or IUAs, finding no statistically significant differences between comparison groups in the rate of adhesion formation or in mean adhesion scores and severity of adhesions [16].

11.1.2 Human Amniotic Membrane Grafting

Human amniotic membrane (HAM) is a rich source of biologically active factors, supports epithelialization, and exhibits anti-fibrotic, anti-inflammatory, antiangiogenic, and antimicrobial features, as the ophthalmology studies suggest [17]. The clinical use of HAM in regenerative medicine is currently increasing. In the field of obstetrics and gynecology its use is limited for vaginoplasty and radical vulvectomy and for prevention of postoperative intra-abdominal adhesion. HAM acts as a biologically active mechanical barrier to suppress adhesion formation while promoting endometrial healing [18], through regeneration of epithelium facilitating migration of epithelial cells, reinforcing adhesion of the basal epithelium, promoting epithelial cell differentiation [19], preventing cellular apoptosis [20], producing factors, or creating a microenvironment for effective tissue repair and endometrial regeneration, possibly by stimulating endogenous stem cells [21].

According to a randomized controlled trial of Zheng et al. including 300 patients, which evaluated the ability of HAM to prevent the recurrence of IUAs after hysteroscopic adhesiolysis, the use of HAM increased menstrual blood volume (mean difference 6.15, 95% CI 4.20–8.11; $P < 0.001$) but failed to improve the rate of intrauterine adhesion recurrence or spontaneous abortion [22].

Yan et al. in a network meta-analysis of randomized controlled trials have found a significant advantage with the use of freeze-dried amniotic agents plus a balloon to reduce IUA recurrence and IUA scores after adhesiolysis [23].

A prospective randomized controlled trial conducted among 88 women with severe IUA who underwent hysteroscopic adhesiolysis analyzed the efficacy of freeze-dried amnion graft that covered the balloon portion of the Foley catheter for prevention of IUAs. Also, this study concluded that the use of HAM was effective in improving menstruation, but the rates of IUA reformation and pregnancy were not significantly different [24].

11.1.3 Vasodilators

Vasodilators have been proposed to increase endometrial receptivity and endometrial thickness in order to enhance the chances for successful assisted pregnancy. But evidence was insufficient to show whether vasodilators increase the live birth rate [25].

Many studies described the use of medications to increase vascular flow to endometrium such as aspirin, nitroglycerine, and sildenafil citrate in order to increase vascular perfusion to the endometrium and enable pregnancy. Zinger reported two cases of woman with a history of a postpartum uterine curettage, with inadequate endometrium thickness after surgical resection of IUAs that are treated with sildenafil citrate, and with the results of having achieved pregnancy [26].

However, the number of women treated using these therapies remains small, and because all such treatments are off label, these medications cannot be endorsed outside of rigorous research protocols.

11.1.4 Antibiotics

Transcervical intrauterine procedures entail a risk of contamination by vaginal flora and might result in infection. However, there is no clear recommendation in the literature on whether it is necessary to use prophylactic antibiotics for minor operative procedures such as dilatation and curettage for evacuation of conceptive products, fractional curettage for abnormal uterine bleeding, hysterosalpingography for infertility evaluation, and hysteroscopy for intrauterine cavity diagnosis and treatment.

The Cochrane of 2013 regarding the prophylactic antibiotics for transcervical intrauterine procedures versus placebo concluded that there are no randomized controlled trials that assess the effects of prophylactic antibiotics on infection complications and therefore it is not possible to draw any conclusions [27]. However, when obvious infection is seen, antibiotics are mandatory.

In India genital tuberculosis appears to be an important and common cause of IUA causing primary and secondary infertility with various grades of adhesions [28] and so it is important to investigate the patients who come from those areas.

11.1.5 Hormonal Therapy

Already in 1964 Wood and Pena hypothesized the beneficial effects of estrogen therapy on endometrial regeneration after surgical treatment for IUAs [29]. Postoperative treatment with estrogen in order to promote the regeneration of the endometrium has been recommended in several studies, either as estrogen only [30, 31] or with IUD [8, 32–38] or Foley catheter [31, 32, 38].

In several studies different regimens consisting of estrogen with or without a progestogen have been used [6]. There are no comparative studies that examine dosage, administration, or combinations of hormones [2]. In a recent randomized study, 4 and 10 mg estradiol orally was compared. No superior effect of the high dosage was demonstrated [39]. When comparing 2 and 6 mg in a prospective randomized trial, no benefit was demonstrated in the 6 mg arm.

In the randomized controlled trials of Farhi et al., 60 women undergoing dilatation and curettage during the first trimester of pregnancy were allocated to receive estrogen combined with progestogen or no treatment [40]. The authors have found that women in the intervention group had a significantly thicker endometrium compared with women in the control group (8.4 with intervention vs. 6.7 mm with no treatment; $P = 0.02$) and so they concluded that postoperative hormonal treatment may be useful for IUA prevention following curettage. Nevertheless, this study does not report the data about pregnancy rates and IUA recurrence [40]. The systematic review of Johary et al. concluded that estrogen therapy may be beneficial for women with IUAs, but as adjunctive therapy combined with other anti-adhesion strategies [41]. Also, in three prospective randomized studies, the administration of oral estrogen did not reduce the risk of IUAs [35, 42, 43].

Sravani Chithra et al. [44] (2016) conducted a retrospective analysis of 101 women with IUAs. They proposed and recommended the doses of conjugated estrogen and progesterone according to severity of AS, showing good results (Table 11.1).

11.2 Guidelines for Secondary Prevention of Intrauterine Adhesions: AAGL/ESGE 2017 [45]

1. The use of an IUD, stent, or catheter appears to reduce the rate of postoperative adhesion reformation. There are limited data regarding subsequent fertility outcomes when these barriers are used: **Grade A**.
2. The risk of infection appears to be minimal when a solid barrier is used compared with no treatment: **Grade A**.

Table 11.1 Dosage of conjugated estrogen and progesterone according to severity of AS

Severity	Conjugated estrogen (21 days)	Medroxyprogesterone acetate (7 days)
Mild	0.625 mg twice a day	10 mg twice a day
Moderate	1.25 mg twice a day	10 mg twice a day
Severe	1.25 mg four times a day	10 mg twice a day

3. There is no evidence to support or refute the use of preoperative, intraoperative, or postoperative antibiotic therapy in surgical treatment of IUAs: **Grade C**.
4. If an IUD is used postoperatively, it should be inert and have a large surface area such as a Lippes loop. Intrauterine devices that contain progestin or copper should not be used after surgical division of IUAs: **Grade C.**
5. Semisolid barriers such as hyaluronic acid and auto-cross-linked hyaluronic acid gel reduce adhesion reformation. At this time, their effect on posttreatment pregnancy rates is unknown: **Grade A**.
6. Following hysteroscopic directed adhesiolysis, postoperative hormone treatment using estrogen, with or without progestin, may reduce the recurrence of IUAs: **Grade B**.
7. The role of medications designed as adjuvants to improve vascular flow to the endometrium has not been established. Consequently, they should not be used outside of rigorous research protocols: **Grade C**.
8. Stem cell treatment may ultimately provide an effective adjuvant approach to the treatment of Asherman syndrome; however, evidence is very limited and this treatment should not be offered outside of rigorous research protocols: **Grade C**.

Key Points

1. Many devices, used alone or in combination, have been proposed to prevent IUA formation after intrauterine procedures.
2. At present it is difficult to establish which approach is the best, due to the heterogeneity of the studies, the contrasting results reported, and the different outcomes investigated.
3. To avoid adhesion relapse, it would seem to be recommendable the use of balloon catheters and IUD with adjunctive estrogen therapy.
4. More research is needed to assess the best approach to prevent adhesions in order to increase reproductive chances and if pregnancy occurs to reduce obstetrics risk such as miscarriage, preterm birth, abnormal placentation, and intrauterine growth restriction.

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