Reproductive outcomes in patients after hysteroscopic adhesiolysis: simplifying the procedure

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ABSTRACT

Background: Intrauterine adhesions result in impairment of fertility, causing both primary infertility and recurrent pregnancy losses. Management is heterogeneous and the latest innovations have led to an increase in treatment costs without a real improvement in pregnancy rates. We analyzed reproductive outcomes in patients with intrauterine adhesions after simplified hysteroscopic adhesiolysis management and compared them with published cases.

Methods: Retrospective, descriptive study performed from 2012 to 2016 at a private university hospital in Barcelona. Spain. One hundred and thirty-nine patients were diagnosed with intrauterine adhesions by in-office vaginohysteroscopy. Antibiotics were prescribed at the time of diagnosis. Outpatient hysteroscopy surgery was performed under sedation using a 26 Fr-bipolar resectoscope (Olympus, Germany) and needle electrode with back to front movements with the aim of improving both longitudinal and transverse measures. No mechanical device or anti-adherent barrier was used to prevent postoperative adhesions. An early second-look hysteroscopy was performed.

Results: 61.9% (86/139) of patients were diagnosed with mild adhesions, 32.4% (45/139) with moderate adhesions, and 5.8% (8/139) with severe adhesions. No major complications occurred. Ninety-five patients (68.3%, 95/139) became pregnant after surgery. Of these, 73.7% (76/95) had a delivery. There were no ongoing pregnancies at the end of the study.

Conclusions: Hysteroscopy was found to be an effective technique for diagnosis and treatment of intrauterine adhesions, allowing a pregnancy rate higher than 68%. Our results are in line with published data, but we showed that the procedure could be simplified and rendered more cost-effective, by avoiding the use of postoperative devices or barriers. Antibiotics and early second-look hysteroscopy allow lower rates and quick treatment of recurrences.

KEYWORDS

Hysteroscopy, intrauterine adhesions, adhesiolysis, pregnancy rate.

Introduction

Intrauterine adhesions (IUAs) are formed in the endometrial cavity, often as a result of a trauma to the basalis layer of the endometrium. With or without the involvement of intrauterine bacteria [1], these bands of fibrotic tissue may cause partial or complete obliteration of the uterine cavity. Furthermore, it seems that a hypoestrogenic state may contribute to dense adhesions [2]. As far as is known, most cases are due to the second to fourth week of postpartum or post-abortion trauma [3]. Since the late 1970s, it has been well known that certain symptoms may lead to suspicion of the condition, and that hysteroscopy is the least traumatic and most efficient diagnostic tool [4]. The repair mechanisms of tissues in the endometrium are poorly understood [4]. The duration of the healing process of the endometrium depends on the causal pathology. When related to previous hysteroscopic surgery, the time required for complete recovery of the endometrium has been reported to range from one month after a polypectomy to three months after submucosal myomectomy [2]. The true prevalence of IUAs is difficult to establish because they are often asymptomatic and require an invasive procedure for diagnosis. However, at the risk of underestimation, their incidence could reach 1.5% in infertile women and 40% in women after evacuation of retained placental tissue or repeated curettage due to abortion [5]. Although numerous attempts have been made to classify IUAs in terms of type, extent, severity and vascularity, no one classification has been universally accepted [6-8].

As regards fertility, the aim of surgery is to restore the normal size and shape of the uterine cavity and normal endometrial function, thereby increasing the patient's chances of becoming pregnant. Hysteroscopic surgery is the treatment of choice for IUAs, as shown in recent reviews and multicentric studies in the literature [8-12]. Key aims in hysteroscopic adhesiolysis are to achieve higher pregnancy rates and avoid recurrences through cost-effective procedures. In recent years, devices, barriers, grafts, and medical solutions have been proposed in order to improve results. Our retrospective study was undertaken to evaluate whether a simplified technique and procedure can achieve good fertility rates in patients with adhesions diagnosed by vaginal hysteroscopy and treated with hysteroscopic adhesiolysis.

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Materials and methods

One hundred and thirty-nine women were included in our retrospective and descriptive study. They were recruited between January 2012 and December 2016 at the Department of Obstetrics, Gynecology and Reproductive Medicine at Dexeus University Hospital (a private teaching hospital in Barcelona). Patients were diagnosed with intrauterine adhesions by in-office diagnostic vaginohysteroscopy performed using a 3.9 mm caliber, 240 mm length, 30º hysteroscope (KarlStorz Iberica, Spain). All patients had previously been clinically evaluated and underwent a transvaginal ultrasonography. Patients were included regardless of the seniority of the hysteroscopist, thus minimizing inter-observer differences. At the time of the study, ten hysteroscopists belonged to the Hysteroscopy Unit.

Patients complaining of amenorrhea and showing isthmic synechia that were lysed at the time of in-office hysteroscopy were not included in our study as they all immediately recovered menstrual bleeding (between two and four weeks after the procedure). In some patients, simultaneous benign intrauterine pathology was found during the vaginohysteroscopy: 7.9% (11/139) endometrial polyps, 7.2% (10/139) retained products of conception, 3.6% (5/139) uterine septum, and 2.9% (4/139) submucosal myoma. In all cases hysteroscopically diagnosed with adhesions, both partners were prescribed antibiotic therapy (doxycycline 100 mg every 12 hours for 10 days) at the time of the in-office hysteroscopy, in accordance with our gynecology protocols. In the event of allergy, doxycycline was substituted by azytromicine 1g one dose.

Hysteroscopic surgery took place in the operating room under sedation. It was performed using a 26-Fr Olympus® bipolar resectoscope (Olympus, Germany) and the Collins loop or scalpel, with sodium chloride 0.9% infusion. The irrigation pump was set at 75 mmHg pressure. Simultaneous benign intrauterine pathology was also treated. No serious intraoperative complications were recorded. At the end of the procedure, no mechanical device or any kind of anti-adherent barrier or solution was placed in the uterine cavity.

Two months after surgery, 80.6% (112/139) of patients underwent a "second-look" in-office hysteroscopy. In four of those patients (3.6%), the result was deemed unsatisfactory and a second surgical procedure was needed in order to achieve a normal intrauterine shape. Clinical follow up to record reproductive outcomes was performed either face to face in the office or by telephone call.

The following information was recorded: operative complications, number of adhesiolysis procedures, dates of pregnancy (with or without assisted reproductive treatment), date of delivery, abnormal pregnancy results and pregnancy complications.

Results

The mean age of patients who underwent hysteroscopic adhesiolysis was 35.2 ± 3.20 years (range: 25-39). Previous miscarriages were reported by 57.6% (80/139); more than half of these patients (42/80, 52.5%) had had more than one miscarriage. On the basis of hysteroscopic uterine cavity involvement, adhesions were classified as mild (Figure 1), moderate, or severe (Figure 2) corresponding to involvement of one third, between one third and two thirds, or more than two thirds of the cavity, respectively. Mild adhesions were diagnosed in 61.9% (86/139), moderate adhesions in 32.4% (45/139), and severe adhesions in 5.8% (8/139) (Table 1).

The mean conception time after surgery was 10.9 months. Ninety-five patients (68.3%, 95/139) became pregnant after

Figure 1 Fibrotic tissue involving left wall of the uterine cavity (personal folder).

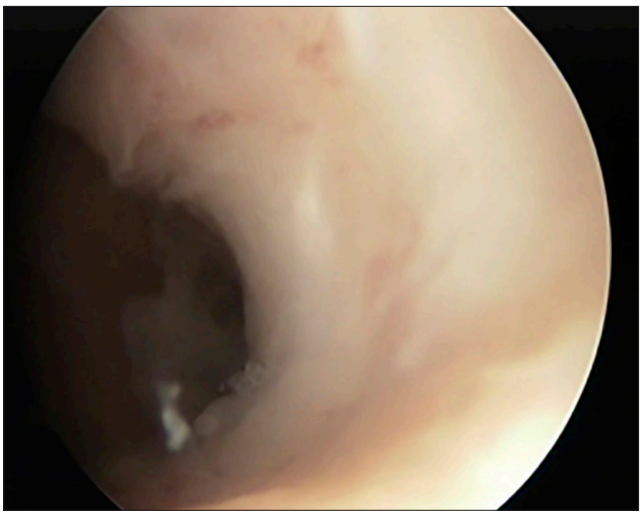

Figure 2 Uterine cavity reduced in more than 50% of its capacity due to fibrotic tissue resulting in a tubular appearance (personal folder).

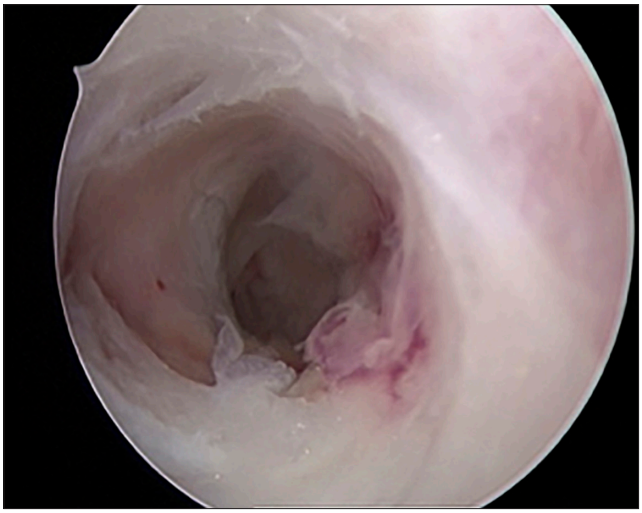

Table 1 Groups of patients according to extension of adhesions. Pregnancy rates and outcomes after hysteroscopic adhesiolysis.

			N	%
Adhesions	Mild		86	62
	Moderate		45	32
	Severe		8	6
Total			139	
Pregnancies	Miscarriages		19	209
	Deliveries	Cesarean section	38	40
		Vaginal delivery	38	40
Total			95	

adhesiolysis at a mean age of 36.9±2.8 years (28-41); 40% (38/95) of these patients needed assisted reproduction techniques after surgery.

Twenty per cent (19/95) of the patients who became pregnant suffered a miscarriage and did not go on to become pregnant, whereas 80.0% (76/95) had a delivery (Table 1). Among the 76 patients who had a delivery, 50.0% (38/76) had a cesarean section and 50.0% (38/76) a vaginal delivery (Table 1). Full-term deliveries accounted for 68.4% (52/76) of the total. Among the patients who had a vaginal or cesarean section delivery, 10.5% suffered a miscarriage in the period between the adhesiolysis procedure and the delivery. Dividing the data according to the adhesion classification, the pregnancy rate in women with severe adhesions was 37.5% (3/8), lower than in those with mild or moderate adhesions, in whom the pregnancy rate was 70% (92/131).

Regarding obstetric complications, only one patient underwent a postpartum hysterectomy after adhesiolysis of moderate adhesions, 14 patients suffered a postpartum hemorrhage (in eight cases due to uterine atony), five patients had placenta accreta, and one patient suffered a placental abruption; two other patients underwent a postpartum hysterectomy, one because of excessive postpartum bleeding and the other because of a uterine wound infection. Overall, 22% of all the deliveries presented obstetric complications of some kind; of these 65% belonged to the moderate intrauterine adhesions group. The patient with placental accretism were in the severe adhesions group.

At the time of second-look in-office hysteroscopy, 85.7% (96/112) of uterine cavities were of normal shape; in 10.7% (12/112) it was necessary to recut minimal adhesions with microscissors using the Bettocchi™ set (KarlStorz Iberica, Spain), and in 3.6% (4/112) the adhesiolysis surgical procedure needed to be repeated in the operating room under sedation (Table 2). Among these latter cases, one patient became pregnant and had a normal delivery, another one suffered a miscarriage, and the other two patients did not become pregnant.

Table 2 Results of in-office hysteroscopy at a mean time of two months after surgery.

		N	%
Second-look hystersocopy	Normal shaped	96	86
	In-office adhesiolysis	12	11
	OR adhesiolysis	4	4
Total		112	

OR: operating room

Discussion

Hysteroscopic adhesiolysis has been shown to be the best approach in the management of intrauterine adhesions. Even though many classifications based on the extent, strength and vascularity of adhesions have been proposed, no one classification has been universally accepted [8,12].

In our study, we decided to simplify the classification, reducing the categories to mild, moderate and severe based on the extent of the involvement of the uterine cavity (one third, between one and two thirds, and more than two thirds, respectively), as other authors have previously done in a large meta-analysis of 18 prospective studies that included 2,682 patients [10].

Most of these patients suffer from infertility, recurrent miscarriages, hypomenorrhea or even amenorrhea, dysmenorrhea, or abdominal or pelvic pain [1,6-12]. When intrauterine adhesions are symptomatic they are usually called Asherman's syndrome, although at present both terms are used indifferently [1].

The risk of formation of adhesions seems to be reduced if intrauterine procedures do not involve the myometrium or opposed surfaces, but only the endometrium [12], if cold or mechanical instruments are used rather than electrocautery, when resection is as limited as possible, and if it is carried out under vision rather than as a blind or ultrasound-guided curettage [10,13,14]. The latter seems to be an important aspect, to be taken into account in cases of retained products of conception [14]. Intrauterine devices (IUDs) have sometimes been related to intrauterine adhesions, although there is no solid evidence and, moreover, they are often used as a postoperative prevention measure [12,15,16].

The role of infection in adhesion formation and the rate of simultaneous chronic endometritis (CE) are aspects that are still under debate [17]. Data are scarce and it is not known whether bacteria inside the cavity are the cause or the consequence of adhesions. However, they were diagnosed through endometrial biopsy in nearly one out of three cases in a study of 85 cases, and when they were present, the recurrence rate was lower (44.8% vs 20.8%, respectively; p = .022) [17]. Through CD138 staining, the prevalence of concomitant CE may be even higher, increasing the rate of moderate and severe adhesions to 46% [18]. Other authors have suggested abnormal function of bone marrow-derived stem cells at the time of regeneration of both endometrial cell types, functional stromal and epithelial. Without the help of an intrauterine trauma, a dysfunction of the specific subpopulation required for tissue repair could result in an inactive endometrium unresponsive to hormone stimulation and subsequent formation of fibrotic tissue [19]. It seems that, in these cases too, infection would play a key role [20].

As regards reported fertility and delivery outcomes after hysteroscopic adhesiolysis, pregnancy rates of around 63% (968/1542) have been reported, and in women who conceived, delivery rates were 75% (696/930) [1,9,11,15]. In our study, we achieved a pregnancy rate of 68.3% (95/139), a delivery rate of 73.7% (70/95), and an at-term delivery rate of 70% (49/70), fully in line with the literature. Due to some cases of previous symptomatic curettages (fever, mild pelvic pain) and post-hysteroscopy adnexal inflammation or infection, we protocolled antibiotic prophylactic prescription in all cases diagnosed with intrauterine adhesions (100 mg of doxycycline every 12 hours for 10 days given to both partners to cover the most frequent bacteria related to pelvic inflammatory disease following European and CDC guidelines) [21,22]. Given that no solid agreement has been reached in the literature to date, our experience of possible collateral tubal damage after hysteroscopy made us take the decision to administrate antibiotic therapy.

Although description of obstetric complications was not an aim of our study, they were significantly high. Most of them occurred in cases with moderate and severe intrauterine ad-

hesions. From our point of view, this information should be offered to patients so as to allow them to decide whether to undergo surgery after being informed about its risks.

Prevention of intrauterine adhesions is a major challenge. On the basis of the abovementioned risks, it might be concluded that avoiding intrauterine procedures and infections would be advisable as a primary prevention measure [8,16,22]. In the latter case, appropriate antibiotics are of key importance, and therefore, in that sense, involving obstetricians is crucial. Adhesion barriers are not justified in order to avoid adhesions after any routine gynecology procedure that could damage the endometrium, as the AAGL and ESGE report stated after reviewing the existing literature [8,18].

With regard to secondary prevention, there is no optimal, universally accepted management approach after surgery [4,6,8,18,23,24]. It seems logical that anti-adherent systems or products should have certain characteristics: as previously pointed out, they should be effective, cheap, easy to use, locally acting, re-absorbable, biocompatible and should allow the normal repair process to take place [24].

In recent times, many papers have compared newly developed anti-adherent semi-solid barriers or solutions, known intrauterine mechanical devices, new intrauterine balloons, and even recent amniotic grafts or silicone plates or sheets, and most highlight the lack of sufficiently large patient samples and of well-designed studies, and the contradictory results reported [4,5,18,21,22,25]. Even when comparing groups with one or more than one anti-adherent management, the results do not seem to be statistically different [25]. One review of randomized controlled clinical trials from 1989 to 2014, conducted in the MEDLINE, Embase, ClinicalTrials.gov, and Cochrane Library databases and comparing postoperative measures to avoid intrauterine adhesion after hysteroscopy, concluded there was a lack of consistent evidence to recommend any treatment to effectively prevent relapse of intrauterine adhesions after hysteroscopic surgery, including intrauterine balloons, IUDs, any kind of anti-adherent barriers and estrogen therapy [23].

Platelet-rich-plasma (PRP) has been shown to improve thin and/or refractory endometrium in assisted reproductive techniques and, overall, in cases of repeated implantation failure [26-28]. The effect seems to be obtained rapidly, within 48 hours [28]. When compared with hyaluronic acid, the efficacy of PRP is higher in the animal model on the 30th post-operative day [27,28]. Another emerging promising strategy may be stem cell therapy, but further investigation is required.

As a whole, even if intrauterine prevention techniques were able to achieve a reduction in new adhesions, the impact on pregnancy rates needs further work. Not only does this approach increase the costs of surgery costs, it does not guarantee further improvement with regard to the obstetrics goal. This is the reason why, based on the published evidence and our experience, and in searching for the best cost-effective management, our procedure does not include intrauterine placement of any IUD, balloon, membrane, gel or PRP immediately after hysteroscopy adhesiolysis.

The other key point is estrogen therapy after hysteroscopy surgery. There are no solid recommendations in this regard, because the literature compares different dosage patterns, formulations, combinations and durations [8,29]. When reviewing the available literature, only seven out of 30 eligible studies reported the results of isolated estrogen therapy with no association with other prevention measures [30]. Thirty days of estradiol or conjugated equine estrogens, plus ten days of medroxyprogesterone acetate or noretisterone acetate from the 21st to the 30th day of the cycle, are the most commonly used formulations to stimulate a withdrawal bleed.[16]. Other authors would also give hormonal treatment preoperatively, wielding the argument that pregnancy results would be as good in moderate-severe cases as in mild ones [31]. At present, micronized progesterone should be the progestin of choice. In the end, it seems that the maximum benefit of estrogen therapy could be reached when it is prescribed with other ancillary prevention measures and when the endometrial lining appears thin on ultrasound or hysteroscopy examination [8,16,30,32]. In our experience, 53 out of 139 (38.1%) patients had moderate to severe adhesions, but not all of them had an endometrium below 7 mm in thickness. As estrogen therapy was prescribed according endometrial thickness no conclusions based on the estrogen therapy results can be drawn due to the low number of patients. Advantages of a second-look hysteroscopy have been reported in the literature. Early evaluation of recurrences allows easier remodeling of the uterine cavity as new adhesions may not be as firm as the older ones [8,16,24,33,34], and this may improve pregnancy and live birth rates [34].

The most concerning cases are those with moderate and severe adhesions, in which more than one third of the cavity is involved, the endometrium lacks good quality, there is scarce menstrual bleeding, and fertility improvement is the goal. Efforts have been made to homogenize diagnostic criteria in order to improve evidence-based management.

Finally, intrauterine adhesions are a matter of concern for gynecologists due to their adverse impact on fertility outcomes. Hysteroscopy has been shown to be an effective technique in the diagnosis and treatment of intrauterine adhesions, but in moderate to severe cases, good pregnancy and live birth rates are difficult to achieve. In the quest to achieve better results, many additional therapies have been applied postoperatively, such as IUDs, intrauterine balloons, silicone sheets, amniotic grafts, gels, PRP, and even stem cells from the umbilical cord, which make the whole management more expensive.

In our study we diagnosed and treated all cases through in-office hysteroscopy and all patients were also treated with antibiotics. No intrauterine device or solution was used to prevent secondary adhesions after surgery and most of the patients had an early second-look hysteroscopy, which allowed diagnosis of recurrences. Our obstetrics results were in line with those published in the literature, although our approach was based on simpler, more cost-effective management.

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