Intrauterine Adhesions

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Gautam N. Allahbadia

Introduction

Ever since the first description of intrauterine adhesions (IUA) by Joseph Asherman in 1948, this intrauterine pathology has been recognized as a significant gynecological complication, diagnosed with increased frequency [1, 2]. Commonly referred to as Asherman's syndrome and intrauterine synechiae, these lesions cover a spectrum that ranges from minor and insignificant to severe cohesive adhesions that affect menstrual function and fertility [3]. Pathology shows fibrous connective tissue bands with or without glandular tissue, although this may range from filmy to dense [1]. Adhesions may be classified into grades I to IV depending on the consistency and severity. Seven classification systems are described, with no universal acceptance of any one system and no validation of any of them [4].

Incidence

Intrauterine adhesions are the most frequent complications after hysteroscopic surgery in women of reproductive age, the prevalence of IUA after hysteroscopic surgery being correlated with intrauterine pathology (myoma, polyp, or adhesions) [5].

G.N. Allahbadia, MD, DNB, FNAMS
Rotunda-The Center for Human Reproduction,
36 Turner Road, 201 Second Floor, B Wing,
Bandra (W), Mumbai, Maharashtra 4400 050, India
e-mail: drallah@gmail.com

The true incidence of IUA is unknown, with most cases occurring within close temporal proximity to a pregnancy, usually within 4 months and usually, while the woman is in a hypoestrogenized state [1]. Westendorp et al. [6] reported intrauterine adhesions in 40 % of patients at ambulatory hysteroscopy, performed 3 months after secondary removal of placental remnants more than 24 h after delivery or a repeat curettage for incomplete abortions [6]. Salzani et al. [7] reported IUA on hysteroscopy performed 3 to 12 months after curettage following abortion in 37.6 % of the women, which were mostly mucous and grade I (56.1 %) [7]. Khanna and Agrawal [8] reported intrauterine adhesions in 34.8 % of the women at hysteroscopy of whom, 68.8 % were positive for tubercular bacilli [8]. The number of previous abortions and curettage procedures did not correlate with the presence of IUA [7].

Manifestation

Intrauterine adhesions may be manifested by amenorrhea accompanied with cyclic pelvic pain caused by outflow obstruction or hypomenorrhea, with up to a fourth of the patients having painless menses of normal flow and duration [1, 2], frequently associated with infertility [1].

Causes

Intrauterine adhesions or synechiae evolve after trauma to the endometrium from surgical procedures usually secondary to curettage of a recently

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pregnant uterus in the context of missed abortion or pregnancy-related hemorrhage [1–3], following hysteroscopic myomectomy (10 %) and transmural myomectomies, especially when combined with uterine ischemia [9]. Previous curettage on a gravid uterus has been reported as the possible cause of Asherman's syndrome in the majority (64 %) of patients [10]. In a prospective, randomized, controlled trial in 82 women, Tam et al. [11] reported that conservative management and medical evacuation for spontaneous abortion are both acceptable alternatives to standard surgical evacuation, which resulted in a prevalence of 7.7 % filmy IUA at hysteroscopic diagnosis of IUA, 6 months after initial treatment [11].

Dawood et al. [12] evaluated the predisposing factors and treatment outcomes of different stages of intrauterine adhesions over a 7-year period in 65 patients. They identified stage I intrauterine adhesions in 36.9 %, stage II in 46.2 %, and stage III in 16.9 % of patients, the main reasons for referral being infertility (stage I 75 %, stage II 73.3 %, stage III 27.3 %) and amenorrhea (stage I 25 %, stage II 23.3 %, stage III 72.7 %). The main predisposing factor was dilatation and curettage, with 40 patients reporting IUA related to early pregnancy curettage; 45 % had stage I adhesions, 42.5 % had stage II, and 12.5 % had stage III in contrast with 10 patients who had peripartum curettage, in whom 60 % developed stage III adhesions ($p=0.004$) [12].

Genital tuberculosis has been reported as an important and common cause of Asherman's syndrome in India, causing oligomenorrhea or amenorrhoea with infertility. Sharma et al. [13] studied 28 women with positive evidence of genital tuberculosis on endometrial biopsy (histopathology or culture) or positive polymerase chain reaction (PCR) on endometrial aspirate or positive findings of tuberculosis on laparoscopy or hysteroscopy who underwent hysteroscopy with or without laparoscopy for suspected Asherman's syndrome. They reported various grades of adhesions (grade I in 17.8 %, grade II in 28.5 %, grade III in 28.5 %, and grade IV in 17.5 %) at hysteroscopy in all women, bilateral (28.5 %) or unilateral (21.3 %) blocked ostia, or inability to see the ostia (28.5 %). Only four women (14.3 %) had open ostia. On laparoscopy performed on 18 women, there were varying grades of adhesions in 16 (88.8 %) women, with beading (33.3 %), tubercles (33.3 %), caseation (11.1 %), and tuboovarian masses (11.1 %) [13].

Risk Factors

In women with menstrual disorders, a statistically significant 12-fold increased risk for Asherman's syndrome grades I–IV was found, previous abortion, as well as infection during surgery being associated with a mildly but nonsignificant increased risk [6]. Myomectomy for multiple, apposing fibroids is reported to have a higher incidence of IUA [9]. Uterine arteries embolization also carries a risk of intracavitary adhesions. Poujade et al. [14] reported a significant risk of uterine synechiae after placement of uterine compression sutures [(Hackethal technique) that transverse the uterine cavity for controlling postpartum hemorrhage (PPH)], with the development of uterine synechiae on explorative hysteroscopy or HSG in 26.7 % of women [14].

Effects

In addition to abnormal menses, infertility and recurrent spontaneous abortion are common complaints of IUA, and the accompanying retrograde menstruation may lead to endometriosis [2, 15]. Adhesions are a significant source of impaired organ functioning, decreased fertility, bowel obstruction, difficult reoperation, and possibly, pain with consequent financial sequelae [16].

Diagnosis

History and a high index of suspicion contribute significantly to the diagnosis of IUA. Several confirmatory tests, such as hysteroscopy, ultrasound-guided techniques-3D hysterosonography (3D HS), 2-dimensional (2D) and 3-dimensional (3D) transvaginal ultrasonography (TVS), hydrosonography, minimal invasive saline contrast

hysterosonography (SCHS), saline infusion hysterography (SIS), sonohysterosalpingography], radiographic techniques [hysterosalpingography (HSG)], and rarely magnetic resonance imaging have been used for the diagnosis of IUA. However, hysteroscopy has been documented as the gold standard for the diagnosis and treatment of IUA, and the several comparative studies evaluating these techniques have used hysteroscopy as the reference standard to evaluate the efficiency of a particular technique against the other. Hysteroscopy may be recommended in patients who develop menstrual disorders, either after secondary intervention for placental remnants after delivery or after a repeat curettage [6].

The Role of Ultrasound in the Diagnosis

Several ultrasound techniques, such as transvaginal color Doppler sonography (TCDS), sonohysterosalpingography (SHSG), and three-dimensional sonography (3DS), are capable of providing diagnostic information that, in some cases, is equivalent to the information afforded by established techniques that require exposure to radiation, such as hysterosalpingography (HSG), or that are more invasive, such as hysteroscopy or diagnostic laparoscopy [17], tissue biopsies, and dilation and curettage (D&C). The role of ultrasonography for the diagnosis of IUA has been studied by several authors with mixed opinions, and all these studies used hysteroscopy as the most reliable reference standard.

El-Mazny et al. [18] reported abnormal hysteroscopic findings, including IUA, in 33.1 % of patients with reported normal uterine findings on HSG who were scheduled for assisted reproductive techniques (ART) [in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI)] investigations [1].

Transvaginal sonography (TVS) has been reported to be specific (100 %), but not sensitive (41.7 %) compared with outpatient hysteroscopy, which leads the authors to suggest that outpatient hysteroscopy should be part of the infertility workup before ART even in patients with normal HSG and/or TVS and especially in patients with prior failed ART cycles who reported a significantly higher incidence of abnormal hysteroscopic findings. The procedure was acceptable in almost all patients with no reported complications [18].

Fedele et al. [19] performed transvaginal US before hysteroscopy as part of the routine diagnostic workup in 77 women who had repeated spontaneous abortions. They were able to correctly identify uterine adhesions (minimal in ten instances and moderate in one) with TVS in 90.0 % (10/11) of the women in whom this finding was subsequently confirmed at hysteroscopy. The sensitivity, specificity, PPV, and NPV of transvaginal US were 91, 100, 100, and 98.5 %, respectively. Hysteroscopic findings were considered the reference. They concluded that TVS, which is a noninvasive and relatively inexpensive procedure, seems to be effective in screening for uterine adhesions in a population at risk [19].

Narayan and Goswamy [20] correlated preoperative TVS (performed on days 7, 14, and 21 in spontaneous ovulatory cycles) with hysteroscopic findings (performed in the subsequent cycle) in 200 patients being investigated for infertility. A total of 182 patients were diagnosed correctly to have an abnormality by TVS giving a false-positive rate of 5.5 %. The sensitivity and PPV of TVS in detecting endometrial pathology were 98.9 and 94.3 %, respectively, with a PPV of 98.5 % for the detection of intrauterine adhesions and a strong correlation between findings from transvaginal sonography and hysteroscopy. The authors concluded that TVS may be used to detect intrauterine pathology and identify patients in whom hysteroscopy and hysteroscopic surgery are indicated [20]. With further advance in ultrasound technology, Knopman and Copperman [21] assessed the value of 3-dimensional (3D) ultrasound in the management of patients with suspected Asherman's syndrome in a case series of 54 infertile patients who presented with suspected Asherman's syndrome. Intrauterine adhesions (IUAs) were demonstrated on 3D ultrasound and HSG in all cases and confirmed by hysteroscopy. They reported 100 % sensitivity with 3D ultrasound for correctly

grading the extent of IUAs compared to only 66.7 % for HSG. In 61.1 % of cases in which HSG results were inconsistent with hysteroscopy, lower uterine segment outflow obstruction was present, and HSG misclassified findings as severe Asherman's with complete cavity obstruction. With a postoperative conception rate of 90 %, the authors concluded that 3D ultrasound provides a more accurate depiction of adhesions and extent of cavity damage than HSG in patients with suspected Asherman's syndrome, particularly when differentiating severe IUAs from lower uterine segment outflow obstruction. Therefore, grading systems utilizing HSG to classify severity of disease should be revised to include 3D ultrasound findings [21].

Sonohysterography, a simple ultrasound (US) procedure technique, involves placement of a 5-F catheter into the endometrial canal with subsequent instillation of sterile saline solution under US guidance. Saline infusion offers a good contrast, enabling improved visualization and distinction between diffuse and focal abnormalities. Sonohysterography has been shown to be a safe, simple, and cost-effective outpatient method for evaluating the potentially abnormal endometrium using transvaginal ultrasound (US) in an outpatient setting and to plan the next step in case management [22]. Besides the cost-related issues, it has been indicated as a well-tolerated technique with a short learning curve in the diagnosis of abnormal uterine bleeding (premenopausal and postmenopausal), bleeding while using tamoxifen, suspected congenital uterine abnormality, and Asherman's syndrome [23]. According to Badu-Peprah et al. [24] sonohysterography is an affordable and feasible diagnostic modality in developing nations for evaluating the endometrial cavity that should be used more often where equipment and skill permit [24], thereby obviating the need for laparoscopy and hysteroscopy in the majority of cases [25]. In a very recent study, Kowalczyk et al. [26] reported real-time 3D sonohysterography (SIS 3D) to be a minimally invasive advance to conventional 2D sonohysterography (sensitivity 72 % and specificity 96 %) that enables a three-dimensional image of the uterine cavity and enables examination of endometrial lesions with a sensitivity and specificity of 83 and 99 %, respectively and a diagnostic precision similar to the results achieved by hysteroscopy [26].

In a prospective study on 65 infertile women 19 to 43 years of age, Soares et al. [27] compared the diagnostic accuracy of sonohysterography (SHG) in uterine cavity diseases in infertile patients with that of HSG and TVS, using hysteroscopy as the gold standard. Sonohysterography and HSG had a sensitivity of 75 % in the detection of intrauterine adhesions and respective PPVs of 42.9 and 50 %, while TVS showed a sensitivity and PPV of 0 % for this diagnosis. The authors concluded that, while sonohysterography was in general the most accurate test with a markedly superior diagnostic accuracy for polypoid lesions and endometrial hyperplasia (EH), with total agreement with the gold standard, however, in diagnosis of intrauterine adhesions, SHG had limited accuracy, similar to that obtained by HSG, with a high false-positive diagnosis rate [27]. Makris et al. [28] compared 3D hysterosonography (3D HS) and diagnostic hysteroscopy in 242 women with abnormal uterine bleeding. They reported a similar specificity (99.4 %), but a higher sensitivity for hysteroscopy compared to 3D HS (98.7 % vs. 93.5 %, respectively). The PPV and NPV of 3D HS were 98.6 and 97 %, respectively, compared to 98.7 and 99.4 % for hysteroscopy, respectively. The two techniques were in agreement for eight cases of adhesions and in 165 cases of normal endometrium [28].

de Kroon et al. [23] evaluated the accuracy of minimal invasive saline contrast hysterosonography (SCHS) in the diagnosis of uterine pathology. They reported that this technique can detect intracavity abnormalities (with a prevalence of 54 %) with a sensitivity, specificity, PPV, and NPV of 94, 89, 91, and 92 %, respectively, and in combination with endometrial sampling, whenever indicated, it might be able to replace diagnostic hysteroscopy as the gold standard in the evaluation of the uterine cavity in 84 % of the diagnostic hysteroscopies as SCHS is two to nine times cheaper than diagnostic hysteroscopy. However, SCHS fails more frequently in postmenopausal women than premenopausal women (12.5 % vs. 4.7 %; $p=0.03$), and the

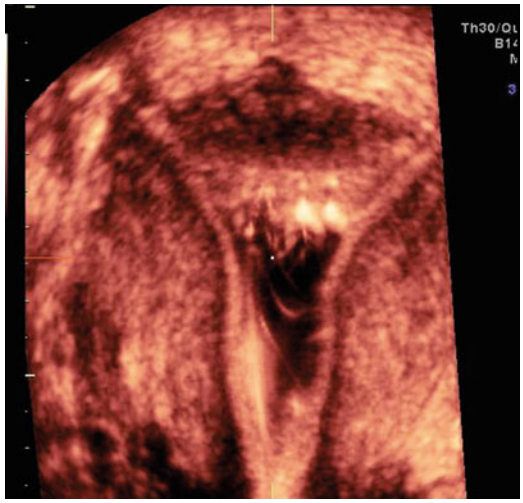

Fig. 12.1 Saline sonogram showing intrauterine adhesions

chance of a non-conclusive SCHS is 7.6 %, being higher if the uterine volume is greater than 600 cm^3 (relative risk, 2.63; 95 %-CI, 1.05–6.60) and if two or more myomas are present: (RR, 2.65; 95 %-CI, 1.16–6.10) [23].

Yucebilgin et al. [29] reported a sensitivity, specificity, positive, and negative predictive values of 85, 75, 75, and 84 %, respectively, for hydrosonography in the detection of structural endometrial cavity lesions were 45 (85 %) of 53 women, who were supposed to have normal findings on hydrosonography, were confirmed by hysteroscopy. They, however, suggested that hydrosonography may be a useful tool in the evaluation of intrauterine cavity structural pathologies in infertile patients with the exception of intrauterine adhesions [29].

Alborzi et al. [30] compared the diagnostic accuracy of hysterosalpingography and sonohysterosalpingography in detecting tubal and uterine abnormalities with surgical findings as the gold standard. They reported a sensitivity, specificity, positive predictive value, and negative predictive value of 78.2, 93.1, 82.7, and 91 %, respectively, for the detection of total tubal and uterine pathologies compared to 76.3, 81.8, 90.9, and 59.2 %, respectively, for HSG. They concluded that sonohysterosalpingography is a safe, easy, and promising procedure and more accurate than hysterosalpingography for detecting intrauterine adhesions and various forms of uterine anomalies [30].

There have been reports of MRI appearances in four cases of Asherman's syndrome in which the diagnosis was confirmed by hysteroscopy. However, the full range of MRI appearances in Asherman's syndrome has not been established and there has been only one case reported in the literature [31]. Figure 12.1 shows intrauterine adhesions using a multiplanar view after sonohysterography.

Management of IUA

Diagnosis and treatment of intrauterine adhesions are integral to the optimization of fertility outcomes [15]. Surgical management of IUA presents a challenge to the hysteroscopic surgeon. Though the appropriate management is controversial [3], and more often than not, guided by the clinician's choice, skill, and operative setting, hysteroscopic adhesiolysis with antibiotic prophylaxis followed by the use of postoperative adjuvants such as systemic estrogens and intrauterine devices or systems designed to impede the development of adhesions is the treatment of choice with favorable results in terms of pregnancy and live birth rates [3, 15, 32, 33]. Clinicians should maintain a level of suspicion of intrauterine adhesions and should investigate by hysteroscopy if necessary [32]. Non-hysteroscopic techniques are also beginning to be developed, but whether they will replace the current "gold" standard of hysteroscopy remains to be seen [34]. The success of treatment regarding term deliveries and rate of abortions depends on the severity of the adhesions, and pregnancy, when achieved, may be complicated by premature labor, placenta previa, and placenta accreta [33].

Hysteroscopic Surgery

Technological progress in optic fibers and instrumentation has made it possible to video endoscope and determine the fibrous nature of the lesions

and its precise localization and control endocavitary surgeries such as hysteroscopic adhesiolysis for uterine synechiae [35]. Though sonohysterography and hysterosalpingography are useful as screening tests of intrauterine adhesions [15], hysteroscopy has been considered the mainstay of diagnosis, classification, and treatment of the intrauterine adhesions, with medical treatments having no role in management [1, 2, 4, 15, 32, 36]. Diagnostic and therapeutic hysteroscopy is a simple, feasible, safe, reproducible, effective, quick, well-tolerated, and low-cost surgical procedure that is highly successful in an outpatient setting, offering a see-and-treat approach in majority of the subjects with intrauterine adhesions [37, 38]. Hysteroscopy has also become accepted as the optimum route of surgery, the aim being to restore the size and shape of the uterine cavity, normal endometrial function, and fertility [15, 16]. Lysis of intrauterine adhesions, for the treatment of infertility and recurrent pregnancy loss, results in improved fecundability and decreased pregnancy loss. Though adhesiolysis for pain relief appears efficacious in certain subsets of women, unfortunately, even when lysed, adhesions have a great propensity to reform [16]. According to Bettocchi et al. [38] there is no consensus on the effectiveness of hysteroscopic surgery in improving the prognosis of subfertile women. However, office hysteroscopy is a powerful tool for the diagnosis, and treatment of intrauterine benign pathologies and in patients with at least two failed cycles of assisted reproductive technology, diagnostic hysteroscopy and, if necessary, operative hysteroscopy is mandatory to improve reproductive outcome [38]. A descriptive study (Canadian Task Force classification II-2) concluded that hysteroscopic adhesiolysis is an effective and safe option even for postmenopausal women with intrauterine lesions adhesions on hysteroscopy or ultrasound. It allows the correct diagnosis to be made, reduces the need for major and unnecessary surgery, and is therapeutic in most patients [39].

Treatment can range from simple cervical dilatation in the case of cervical stenosis, but an intact uterine cavity, to extensive adhesiolysis of dense intrauterine adhesions using scissors, electro- or laser energy, or a combination of blunt and sharp dissection [32, 34]. Various techniques for adhesiolysis and for prevention of scar reformation have been advocated. According to March, [2] the use of miniature scissors for adhesiolysis and the placement of a balloon stent inside the uterus immediately after surgery appear to be the most efficacious [2]. Patients with more severe adhesions, in whom the uterine fundus is completely obscured, and those with a greatly narrowed fibrotic cavity present the greatest therapeutic challenge. Several techniques have been described for these difficult cases, but the outcome is far worse than in patients with mild, endometrial-type adhesions [4, 34]. A significantly obliterated cavity may require multiple hysteroscopic adhesiolysis to achieve a satisfactory anatomical and functional result [15, 36], while laparoscopic or ultrasound guidance may aid in the hysteroscopic lysis of dense scar tissue and difficult entry into the cervix [1].

Treatment Outcome

Treatment outcomes are difficult to assess as there is no universally agreed upon classification system [1]. Anatomic, but most of all functional prognosis, is directly correlated to the severity of adhesions, and the number of surgical procedures required to complete treatment [40].

Restoration of menstruation is highly successful (more than 90 %), and pregnancy rates around 50–60 % with live birth rates around 40–50 % can be achieved [32]. The risk of complications for those that achieve pregnancy is significant with a significant risk for placenta accreta and subsequent blood loss, transfusion, and hysterectomy [12]. In perhaps the largest study, involving 6,680 hysteroscopies with hysteroscopic adhesiolysis in 75 patients, 94.6 % functional restoration and 93.3 % anatomic resolution, with pregnancy rates ranging from 28.7 to 53.6 %, were achieved. At 2-month follow-up, the uterine cavity was completely regular in 70 cases, while in four cases, a second surgical treatment was necessary [41].

Using a standard technique with a loop electrode and glycine 1.5 % as distension medium, Dawood et al. [12] reported an improvement in

the rate of amenorrhea from 32.3 % before adhesiolysis to 9.2 % after the procedure with an overall pregnancy rate of 51.2 % and the live birth rate 32.6 % among women who wished to conceive. Severe intrauterine adhesions were managed with the assistance of abdominal ultrasound to ensure that the uterine cavity was not breached, and the rates of pregnancy and term pregnancy among this selected group of women were similar regardless of the severity of adhesions [12].

Yu et al. [42] evaluated the outcome of hysteroscopic adhesiolysis with electrode needle or loop under direct vision in 85 women with Asherman's syndrome who presented with a history of infertility or recurrent pregnancy loss. After hysteroscopic adhesiolysis, the chances of conception among the 18.2 % of women who remained amenorrheic were significantly lower than those who continued to have menses (50 %). The conception rate in women who had reformation of intrauterine adhesions at second look hysteroscopy (11.8 %) was significantly lower than that of women who had a normal cavity (59.1 %), suggesting that the outcome of hysteroscopic adhesiolysis for Asherman's syndrome is significantly affected by recurrence of intrauterine adhesions [42].

Hysteroscopic adhesiolysis with monopolar or bipolar energy can be performed safely and effectively for severe stage 3 and 4 adhesions with a 97 % restoration of menses, 43.8 % PR, and 32.8 % LBR. The pregnancy rate was significantly higher in patients ≤35 years compared to patients older than 35 years (66.6 % vs. 23.5 %, respectively; $p=0.01$), suggesting that age is the main predictive factor of success: the pregnancies were at risk of abnormal placentation [43]. The impact of age on the outcome of hysteroscopic adhesiolysis is in agreement with a previous study by Capella-Allouc et al. [44] that reported a pregnancy rate of 42.8 %, live birth rate of 32.1 %, the pregnancy rate being much higher in patients ≤35 years compared to patients older than 35 years (62.5 % vs.16.6 %, respectively; $p=0.01$) following hysteroscopic adhesiolysis in 31 patients with severe Asherman's syndrome. However, these pregnancies were at risk for hemorrhage with abnormal placentation [44].

Roy et al. [10] reported an overall conception rate of 40.4 %, live birth rate of 86.1 % and a miscarriage rate of 11.1 % in a mean conception time after surgery of 12.8 months following hysteroscopic adhesiolysis with the monopolar electrode knife in 89 infertile patients with Asherman's syndrome. The cumulative pregnancy rate showed that 97.2 % of patients conceived within 24 months. The conception rate was higher (58 %) in mild Asherman's syndrome compared to 30 % conception rate in moderate and 33.3 % conception rate in severe cases. There was a significantly higher likelihood of conception (44.3 %) in those who continued to have improved menstrual pattern compared to only 10 % likelihood of conception in those who continued to have amenorrhea after adhesiolysis. A second-look office hysteroscopy, performed after 2 months, showed reformation of adhesions in12 patients that needed a repeat adhesiolysis with no conception in these patients. The authors concluded that hysteroscopic adhesiolysis for Asherman's syndrome is a safe and effective method of choice for restoring menstrual function and fertility [10].

Shokeir et al. [45] attempted to analyze the adhesion grade in multiple hysteroscopic-guided biopsies from IUA following the initial hysteroscopic adhesiolysis at a follow-up diagnostic hysteroscopy, performed early (2–4 weeks) after the initial operation or late, about 12 months (8–16 months). They observed that at follow-up hysteroscopy, 25 % of both groups had no significant adhesions. Grade I adhesions (thin, filmy) occurred in 60 % of the early hysteroscopy patients and in only 12 % of the late group ($P<0.05$). Grade II adhesions were present in 10 % of the early group and in up to 41 % in the late group ($P<0.05$), whereas grade III adhesions were present in only 5 % of the early hysteroscopy group, but in 22 % of the late one ($P<0.05$). Correlation between hysteroscopic and histologic findings were good in most of cases in both groups. The follow-up to determine the subsequent reproductive outcome revealed similar conception rates in both groups. The authors suggested that the IUA that might be formed immediately following hysteroscopic reproductive surgery is histologically different from those

appearing a longer time after the original operation. Routine early follow-up hysteroscopy can influence the prognosis resulting from the original surgery [45].

Having excluded hormonal imbalances, premature ovarian failure, and congenital uterine abnormalities Yasmin et al. [46] reported thick fibrous adhesions in 45 % of patients, flimsy adhesions in 40 %, and muscular adhesions in 15 % at hysteroscopy, with 65 % adhesions in the body of uterus, 25 % at the site of internal os, and 1 % had adhesions in the cervical canal as well as the body of the uterus. Following diagnostic hysteroscopy and resection of adhesions in 20 patients (median age 26 years), presenting with scanty menses and secondary infertility (65 %), secondary amenorrhoea (20 %), or with primary infertility alone (15 %), they reported a restoration of menses in 95 % of the patients and conception in 10 % of the patients. Though the patient number was small, the authors suggested that hysteroscopy is an effective procedure for not only diagnosing Asherman's syndrome, but is equally effective for treating it [46].

Hysteroscopic adhesiolysis in women with Asherman's syndrome and poor reproductive performance (previous spontaneous abortions or a premature delivery) contributes significantly to a successful reproductive outcome. Whereas pregnancy outcome prior to the hysteroscopic adhesiolysis was 18.3 % term deliveries, 3.3 % premature deliveries, 62.4 % first-trimester abortions, and 16.0 % late abortions, after hysteroscopic adhesiolysis, the pregnancy outcome was 68.6 % term deliveries, 9.3 % premature deliveries, 17.4 % first-trimester abortions, and 4.7 % late abortions. The operative success rate, measured by delivering a healthy newborn, improved from 18.3 % preoperatively to 64 % postoperatively in women with two previous unsuccessful pregnancies [47], whereas in women with three or more unsuccessful pregnancies, the success rate improved from 18.3 to 75 %. Successful outcome of adhesiolysis was observed in 61.9 % of mild (stage I) and in 70.6 % of moderate to severe cases (stages II and III) of intrauterine adhesions [47].

Blunt adhesiolysis with a flexible hysteroscope, following primary treatment of intrauterine adhesions with sharp adhesiolysis has been suggested as an effective technique for the maintenance of cavity patency with an improvement in menstrual flow in 95 % of the patients, relief of dysmenorrhea in 92 %, 92 % improvement in disease staging over the treatment interval, and a pregnancy rate of 46 %. Initially, 50 % had severe adhesions, 46 % had moderate, and 4 % had minimal disease according to the March criteria [48].

Colacurci et al. [49] analyzed the reproductive outcome in 53 women undergoing hysteroscopic lysis of intrauterine adhesions, according to their localization and severity. Hysteroscopic surgery restored an acceptable menstrual cycle in almost all the patients affected by intrauterine isolated adhesions in 52 % of women with complex incomplete adhesions, and in none of the patients with an entirely obliterated cavity. In isolated, isthmic, central, or marginal synechiae, a pregnancy rate of 73.3 % was observed with a pregnancy rate to term, respectively, of 63.3 % and of 86.3 %, while in case of complex but not complete adhesions, the pregnancy rate was 25 % with only two term pregnancies. There were no pregnancies in three cases of complex synechiae. The authors concluded that the basic parameter to define the functional and reproductive prognosis of the hysteroscopic lysis of intrauterine adhesions is not the menstrual profile or the histological characteristic of the lesions, but rather their extension [49].

Hysteroscopy and hysteroscopic surgery have been the gold standard of diagnosis and treatment, respectively, for patients with Asherman's syndrome who presented with amenorrhea or hypomenorrhea, infertility, or recurrent pregnancy loss. However, according to most authors, despite the advances in hysteroscopic surgery, the treatment of moderate to severe Asherman's syndrome still presents a challenge [40, 50]. Furthermore, pregnancy after treatment remains high risk with complications including spontaneous abortion, preterm delivery, intrauterine growth restriction, placenta accreta or previa, or even uterine rupture, that necessitate close antenatal surveillance and monitoring for women who conceive after treatment [50]. According to Piketty et al. [40] despite the infrequent but well-

known complications during surgery and the less frequent but often severe obstetrical complications, the benefit gained by the recovery of fertility (either spontaneous or not) remains superior to the risks of the surgical management [40].

Role of Ultrasonography in the Treatment

Serial intrauterine device-guided hysteroscopic adhesiolysis of intrauterine synechiae, especially for early intervention, may prevent complications during the treatment of severe intrauterine adhesions and may present a secure and effective alternative for constructive clinical outcomes with spontaneous pregnancy rates of 47.2 and 30 % and live birth rates of 28 and 20 % in patients who did and did not undergo early intervention of office hysteroscopy, 1 week after insertion of the IUD at hysteroscopic adhesiolysis, respectively [51]. Following echo-controlled hysteroscopic surgical cure of complex and/or recurrent uterine synechiae in 11 patients, Salat-Baroux et al. [35] concluded that intraoperative echography allowed hysteroscopic adhesiolysis of intrauterine adhesions at a controlled and equivalent distance from the uterine walls, enabling better treatment of the uterine cornua since the operator is informed when to limit progression to avoid massive fluid infusion into the abdominal cavity and perforation of the uterus. The intraoperative echographic control was validated in the operating theater radiographically. With this technique normal cavities with bilateral tube permeability were obtained in 72.72 % of the patients and normal cycles in 90.9 % of the patients [35]. Following hysteroscopic lysis under ultrasound control for significant intrauterine synechiae, Bellingham [52] reported normal menstruation in 61 % of the patients and live births in 80 % of the patients, of whom 50 % had had severe adhesions. They reported that ultrasound control is ideally essential if the adhesions are extensive [52]. However, in both these studies, the number of patients was very small to effectively document the role of ultrasound in the treatment of IUA.

Coccia et al. [53] described a new therapeutic procedure called pressure lavage under ultrasound guidance (PLUG) for selected cases of IUA. This technique is based on sonohysterography to monitor the effects of intrauterine injections of saline solution on the continuous accumulation of saline in the uterine cavity for the mechanical disruption of IUA. In an open clinical investigation with no control group, they reported satisfactory lysis of adhesions and restoration of menses in 71.4 % of the patients with mild IUA with a pregnancy rate of 66.63 % following the use of the PLUG technique. A second-look hysteroscopy after 1 month showed the persistence of filmy adhesions in two patients with moderate IUA that were removed successfully during hysteroscopy. The authors suggested that PLUG is a safe and ideal in-office procedure that allows complete lysis in mild IUA cases avoiding the need for therapeutic, and possibly, follow-up hysteroscopy, and may represent a useful initial step in moderate IUA cases reducing the need for operative hysteroscopy [53]. In a recent study, Taniguchi and Suginami [54] also suggested that sonohysterographic (SHG) lysis for recurrent adhesions following hysteroscopic lysis may be a treatment option for recurrent adhesions in infertile patients, with improved menstrual cycles and restored tubal patency [54].

Tiras et al. [55] demonstrated the value of laparoscopic intracorporeal ultrasound (LIU)-guided hysteroscopic adhesiolysis in a patient with amenorrhea and infertility with total intrauterine synechiae. Adequate intrauterine adhesiolysis was performed by a resectoscope with a wire loop, suggesting that complex intrauterine procedures can be easily performed by the guidance of endoscopic ultrasonography to avoid the possibility of inadvertent uterine perforation [55].

Schlaff and Hurst [56] evaluated the predictive value of preoperative endometrial sonography in the diagnosis and surgical treatment of women with amenorrhea due to severe Asherman's syndrome, characterized by complete obstruction of the cavity at hysterosalpingogram. They suggested that an endometrial pattern, demonstrating a well-developed endometrial stripe on transvaginal sonography is highly predictive of a positive surgical and clinical outcome in women with

severe Asherman's syndrome with resumption of normal menses and normalization of the cavity after hysteroscopy in contrast to women with minimal endometrium who had no cavity identified and derived no benefit from surgery [56]. However, this study was limited to just seven patients and hence, substantial evidence in this direction is lacking.

Radiographic Methods

In a small but significant study, Karande et al. [57] demonstrated that in-office lysis of intrauterine adhesions, under fluoroscopic control, using a specially designed catheter (gynecoradiologic control) can be carried out safely in the majority of patients, using minimally invasive techniques. They could successfully lyse adhesions in 76 % (13/17) of the patients (9 mild, 3 moderate, and 1 severe), while in remaining 4 patients (2 moderate and 2 severe), lysis was only partially successful. Nine procedures were performed with the catheter's balloon tip and four with hysteroscopic scissors. Procedure complications resulting in the abandoning of the procedure included patient discomfort before attempting the use of scissors ($n=1$), extravasation of dye into the myometrium making visualization difficult ($n=1$), and thick, fibrotic adhesions that were resistant to scissors ($n=2$). They opined that the potential cost savings with this technique in comparison with endoscopic procedures, which require utilization of expensive operating room time, are especially relevant in a cost-conscious managed care environment and only failures of in-office procedures would reach the operating room. [57] The fluoroscopic approach to adhesions was further evaluated a decade later by Chason et al. [58] who used hysteroplasty with fluoroscopic cannulation and balloon uterine dilation to treat intrauterine adhesions and cervical stenosis and lower uterine defects in select cases. They concluded that while the treatment of intrauterine adhesions resulted in an improved pregnancy outcome, albeit in a case study, the effect of lower uterine segment-filling defects from cesarean deliveries on pregnancy outcome in assisted reproductive technology cycles warrants further investigation [58]. In a 5-year retrospective, uncontrolled cohort study, Thomson et al. [59] conducted fluoroscopically-guided hysteroscopic synechiolysis for Asherman's syndrome in 30 patients (13 % AFS grade I, 43 % AFS grade II, and 43 % AFS grade III), 60 % of whom were amenorrheic. They reported a 96 % restoration of regular menses with a 53 % pregnancy rate among patients who attempted to conceive and concluded that hysteroscopic synechiolysis, performed by injecting radiographic contrast medium and visualized under image-intensifier control, followed by cyclic high-dose estrogen therapy to stimulate endometrial proliferation, appears to be an effective treatment for Asherman's syndrome. Repeat procedures were performed monthly until the endometrial cavity was re-established [59].

Prevention of IUA

One of the most important features of treatment for intrauterine synechiae is the prevention of recurrence [4]. Follow-up studies to assure resolution of the scarring are mandatory before the patient attempts to conceive as is careful monitoring of pregnancies for cervical incompetence, placenta accreta, and intrauterine growth retardation [2]. The best available evidence demonstrates that the newly developed adhesion barriers, such as hyaluronic acid, show promise for preventing new adhesions [4, 15]. Postoperative mechanical distention of the endometrial cavity with the use of intrauterine contraceptive devices and postoperative hormonal treatment with estrogen +/− progestogen to facilitate endometrial regrowth are important in the prevention of recurrence [15, 32].

With regard to primary adhesion formation, a recent study by Rein et al. [60] demonstrated that selective hysteroscopic resection (HR) of residual trophoblastic tissue after first- or second-trimester miscarriage or term delivery significantly reduces the incidence of intrauterine adhesions and increases pregnancy rates compared to ultrasound-guided evacuation with

a curette (D&E). They reported mild adhesion in 4.2 % of the patients after selective HR compared to an incidence of 30.8 % after D&E, of which 17.9 % were mild, 7.7 % single dense adhesions, and 2.6 % with extensive endometrial fibrosis. Conception rates were significantly higher in the HR patients compared to curetted patients (68.8 % vs. 59.9 %, respectively; $p < 0.05$) and 78.1 % vs. 66.6 %, respectively; $p < 0.05$ in patients younger than 35 years of age with a significantly ($p < .05$) shorter time to conception (11.5 months vs. 14.5 months) [60]. Operative hysteroscopy for selective curettage of residual trophoblastic tissue instead of nonselective conventional curettage may prevent intrauterine adhesions [36].

Mechanical Barriers

The efficiency of barrier agents' postoperative hysteroscopic adhesiolysis to prevent the recurrence of adhesions has been addressed in a few clinical trials. Barrier agents have been grouped under mechanical agents (intrauterine device-IUCD, Foley catheter), fluid agents [Seprafilm, Hyalobarrier, auto-cross-linked hyaluronic acid (ACP) gel], postoperative systemic treatment (cyclic estrogen-progesterone therapy), and the latest tissue barriers (fresh or dries amnion grafts).

Several comparative studies, evaluating the efficacy of various barrier agents, have been conducted. Orhue et al. [61] compared two adjunctive treatments following intrauterine adhesiolysis—the intrauterine contraceptive device (IUCD) and the Foley catheter. In a 4-year initial period, patients with intrauterine adhesions were treated with the insertion of an IUCD after adhesiolysis. In the next 4 years, a pediatric Foley catheter balloon was used after adhesiolysis instead of the IUCD. They reported a significantly higher restoration of normal menstruation (81.4 % vs. 62.7 %, $p < 0.05$), less frequent persistent posttreatment amenorrhea and hypomenorrhea (18.6 % vs. 37.3 %; $P < 0.03$), a higher conception rate (33.9 % vs. 22.5 %), and a significantly lesser need for repeated treatment in the Foley catheter group compared to the IUCD group, respectively. They concluded that the Foley catheter is a safer and more effective adjunctive method of treatment of IUA compared with the IUCD [61].

Fluid Barriers

The application of auto-cross-linked hyaluronic acid (ACP) gel has been reported to significantly reduce the incidence and severity of de novo formation of intrauterine adhesions after hysteroscopic surgery, with a significant decrease in adhesion severity on staging of adhesions [62].

Tissue Barriers

The role of amnion grafts as barrier agents to prevent recurrence of adhesions has currently gained a lot of attention. In a pilot study involving 25 patients with moderate or severe intrauterine adhesions, Amer et al. [63] reported that hysteroscopic adhesiolysis followed by intrauterine application of a fresh amnion graft over an inflated balloon of a Foley catheter for 2 weeks seems to be a promising procedure for decreasing recurrence of adhesions and encouraging endometrial regeneration. They reported failure to achieve normal menstrual flow in 16.7 % of the patients with moderate versus 23.1 % of the patients with severe adhesions and observed adhesion reformation at follow-up hysteroscopy in 48 % of the patients, all with severe adhesions. However, randomized comparative studies are needed to validate its benefits, including reproductive outcome [63].

In a more recent pilot prospective randomized comparative study (Canadian Task Force classification I), Ameret et al. [64] estimated the efficacy of inserting fresh and dried amnion graft after hysteroscopic lysis of severe intrauterine adhesions in decreasing its recurrence and encouraging endometrial regeneration in 45 patients. Hysteroscopic lysis of intrauterine adhesions was followed by insertion of an intrauterine balloon only (group 1) or either fresh amnion graft (group 2) or dried amnion graft (group 3) for

2 weeks. Diagnostic hysteroscopy, performed at 2 to 4 months postoperatively, revealed significant improvement in adhesion grade with the amnion graft versus intrauterine balloon alone ($p=0.003$) and significant improvement with fresh compared to dried amnion graft ($p=0.01$). Restoration of normal menstruation (46.7 % in group 3, 35.7 % in group 2, 28.6 % in group 1) and the conception rate (80 % after amnion graft and 20 % without amnion) was higher in patients with the graft compared to the balloon. The overall conception rate was 23.3 % with a miscarriage rate of 60 %. The authors concluded that hysteroscopic lysis of severe intrauterine adhesions with grafting of either fresh or dried amnion is a promising adjunctive procedure for decreasing recurrence of adhesions and encouraging endometrial regeneration [64].

Prevention strategies, including bipolar resection, barrier gel, or postoperative estradiol, might be useful, but stronger evidence is needed and there is a need for other randomized controlled trials to fully justify the use of adhesion barriers for clinical use [5, 9]. In view of the current knowledge, Gambadauro et al. [9] recommend a prevention strategy based on a combination of surgical trauma minimization and identification of high-risk cases, with early hysteroscopic diagnosis and lysis possibly representing the best means of secondary prevention and treatment of postoperative intrauterine adhesions [9]. Considering the decreased pregnancy outcome in patient with recurrence of adhesions, further research in Asherman's syndrome should be directed toward reduction of adhesion reformation with a view to improving outcome [42].

Recent Advances

In an effort to treat injured endometrium nonresponsive to conventional treatment for Asherman's syndrome (IUCD) with cyclical hormonal therapy for 6 months, Nagori et al. [65] demonstrated that placement of endometrial angiogenic stem cells in the endometrial cavity under ultrasound guidance after curettage followed by cyclical hormonal therapy can regenerate injured endometrium. These cells could be isolated from adult autologous stem cells isolated from a patient's own bone marrow using immunomagnetic isolation [65]. Gargett and Healy [66] also reported regeneration of thin endometrium refractory to estrogen stimulation following intrauterine administration of bone marrow stem/progenitor cells sufficiently to support a pregnancy in a case study. However, whether its local endometrial damage is induced by concurrent curettage that stimulated endogenous endometrial stem/progenitor cells into action, or both, is open to question [66].

Conclusion

Intrauterine adhesions are a significant gynecological complication that require prompt and accurate diagnosis and treatment. Despite its invasiveness, cost issues and the technical skill required, hysteroscopy is recognized as the gold standard for the diagnosis, classification, and treatment of adhesions with an encouraging restoration of fertility in terms of menstruation, pregnancy rates, and live birth rates in patients with mild, moderate, and severe IUA, including postmenopausal women. Moreover, it offers a see-and-treat approach in majority of the patients where therapy is required, thus obviating the need for a second intervention. Though ultrasonography is gradually gaining acceptance in the diagnosis of IUA, particularly in economically compromised settings, with the purpose of avoiding costly invasive techniques, it has limited accuracy and sensitivity in the diagnosis of IUA compared to hysteroscopy. The addition of 3D ultrasound is reported to have improved accuracy in the diagnosis, but consistent large-scale studies are lacking. However, with regard to treatment, ultrasound may have a significant role in controlling hysteroscopic surgery, especially in patients with complex severe adhesions, to avoid inadvertent uterine perforation. More large-scale randomized trials will be required before ultrasonography can be established as a more functionally effective alternative to hysteroscopy in the diagnosis and treatment of IUA.

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