Complications and Fertility Potential Following Adhesiolysis

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14.1 Introduction

The presence of intrauterine adhesions and the association with secondary amenorrhea were first described by Dr. Fritsh in 1894. In 1948, Dr. Joseph G. Asherman published a series of papers describing the etiology, symptoms, imaging findings, and fertility outcomes, and the condition has been known as Asherman's syndrome (AS) since. Asherman's syndrome was primarily described as an outcome of trauma to the basal layer of the endometrium, with subsequent formation of fibrotic adhesions leading to either partial or complete obstruction of the cervical canal or uterine cavity resulting in menstrual abnormalities, infertility, or recurrent pregnancy loss [1]. The initial definition of AS included confirmed IUAs with clinical features of amenorrhea, infertility, or recurrent pregnancy loss; however, today the presence of IUAs regardless of additional clinical features is often referred to as AS. For many, the terminologies Asherman's syndrome (AS), intrauterine adhesions (IUA), and intrauterine synechiae (IUS) are interchangeable.

The exact prevalence of AS is difficult to identify as a large proportion of patients have no symptoms. The last worldwide investigation found that the highest prevalence of AS has been found in Israel, Greece, and South America [2]. AS was initially described to occur following trauma to a gravid uterus. Curettage in the postpartum period, following a spontaneous abortion or during an elective

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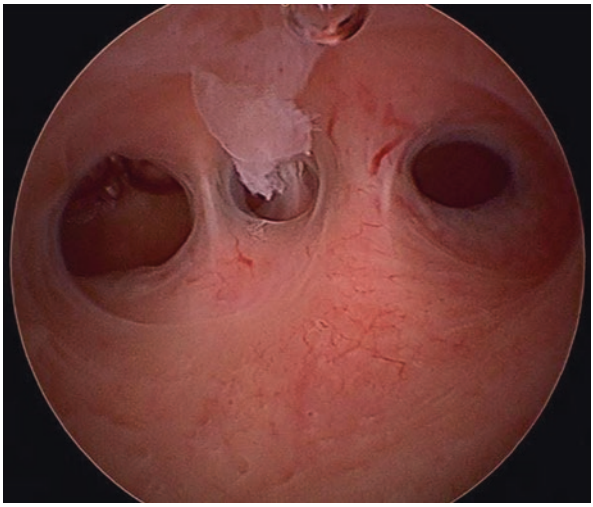
termination of pregnancy, or following a cesarean section have all been implicated to lead to IUAs. While trauma to the gravid uterus remains the most important risk factor for the development of IUAs, trauma to a nongravid uterus, infections, uterine anomalies, and genetic predispositions have also been linked to the development of IUAs resulting in potential AS.

The presence of IUAs can vary dramatically from patient to patient. There are numerous classifications of IUAs that exist, and all require the use of hysteroscopy to determine the extent and characteristics of the adhesions. A very commonly used classification system was proposed by the American Fertility Society which classifies the severity of the disease in three stages as follows [3]:



Mild disease: few filmy adhesions involving less than a third of the uterine cavity with normal menses or hypomenorrhea

Moderate disease: filmy and dense adhesions, the involvement of one-third to two-thirds of cavity and hypomenorrhea

Severe disease: dense adhesions involving more than two-thirds of the cavity with amenorrhea

Treatment of IUAs depends on the associated clinical manifestations. IUAs are not life threatening, and in the asymptomatic patient should be treated with expectant management. Surgical intervention is only indicated when patients present with signs or symptoms of pain infertility, recurrent pregnancy loss, or menstrual abnormalities including hematometra. Multiple surgical interventions have been described for the treatment of IUAs; however, hysteroscopic adhesiolysis remains the gold standard for surgical management [4]. Hysteroscopic adhesiolysis has been

proven to be a very safe procedure and provides direct visualization of adhesions to increase surgical precision [5]. In cases of mild disease with thin filmy adhesions, simply distending the uterus with fluid media is enough to break the adhesions and restore normal anatomy. If more disease is encountered, adhesiolysis can be performed with hysteroscopic scissors, biopsy forceps, and monopolar or bipolar electrocautery.

14.1.1 Complications Following Adhesiolysis

Complications can be divided into intraoperative complications, and postoperative complications. As with all operative hysteroscopy, the two major intraoperative complications encountered are bleeding and perforation. The most common intraoperative complication is hemorrhage, which has been reported in 6–27% of cases [1]. Injury to myometrial blood vessels may obstruct a surgeon's view and enable for a more rapid absorption of the distention media possibly leading to major electrolyte disturbances. Uterine perforation is the second most common intraoperative complication and is seen in 2–5% of cases but has been reported in up to 9% of patients where severe IUAs were encountered. Table 14.1 includes documented complications following hysteroscopy adhesiolysis.

Surgical success at the time of surgery is typically believed to be achieved with restoration of a normal-appearing uterine cavity, which is accomplished in 57–98% of cases [6]. Despite removal of all adhesions, and restoration of a normal uterine cavity, adhesiolysis is associated with a high rate of IUA re-formation. The rate of re-formation of adhesions is high and is seen in 3.1–23.5% of cases, and has been reported in 20–62% of severe cases (Table 14.2). Numerous studies have investigated methods to decrease the re-formation of intrauterine adhesions.

Table 14.1 Complications of hysteroscopic adhesiolysis for Asherman's syndrome

Study	Year of publication	Complications	All cases	Severe cases
Valle and Sciarra	1988	Perforation	5/187 (2.7%)	3/47 (6.4%)
Pistofidis et al.	1996	Hemorrhage	5/86 (5.8%)	3/11 (27.3%)
Pabuccu et al.	1997	Perforation	1/40 (2.5%)	1/10 (10%)
McComb and Wagner	1997	Perforation	–	3/6 (50%)
		Hemorrhage	–	1/6 (16.7%)
Broome and Vancaillie	1999	Perforation	–	2/55 (3.6%)
Feng et al.	1999	Perforation	4/365 (1.1%)	4/39 (10.3%)
Capella-Allouc et al.	1999	Perforation	–	4/31 (12.9%)

Adapted from Yu et al. [1]

Table 14.2 Outcome of hysteroscopic adhesiolysis for Asherman's syndrome: restoration of menstruation in women presenting with amenorrhea or hypomenorrhea

Study	Year of publication	Normal menses following surgery, number (%)	Re-formation of intrauterine adhesions	Re-formation of intrauterine adhesions in severe cases
Fedele et al.	1986	11/21 (52.4%)	–	–
Valle and Sciarra	1988	149/169 (88.2%)	44/187 (23.5%)	23/47 (48.9%)
Pabuccu et al.	1997	29/34 (85.3%)	8/40 (20%)	6/10 (60%)
Feng et al.	1999	294/351 (83.8%)	–	–
Capella-Allouc et al.	1999	–	–	10/16 (62.5%)
Preutthipan and Linasmita	2000	45/50 (85%)	2/65 (3.1%)	2/10 (20%)

Adapted from Yu et al. [1]

Table 14.3 reports different studies investigating IUA re-formation. At this time, no consensus protocol exists to prevent the recurrence of IUAs. Patients with severe disease should be counseled at the time of initial surgery for need for possible repeat surgery, as approximately 1/3 required a repeat procedure due to IUA re-formation [7].

14.1.2 Fertility Potential Following Adhesiolysis

Secondary infertility as the initial presenting symptom has been reported in up to 45% of patients, and the pursuit of fertility is the most common indication for hysteroscopic adhesiolysis [8]. Implantation issues have been hypothesized in patients with IUAs, and hysteroscopic adhesiolysis has been shown to improve endometrial thickness and endometrial receptivity [9]. Numerous studies have been performed documenting fertility outcomes following adhesiolysis, with pregnancy rates ranging from 10.5% to 100% [10]. Guo et al. performed a meta-analysis which included 54 studies, and found an overall pregnancy rate for all subjects of 50.7% following adhesiolysis, Table 14.4. When looking at pregnancy rates before and after surgery, one study found a pregnancy rate of 65.5% after adhesiolysis, compared to only 18% preoperatively [5]. That same study found a live birth rate of 36% after adhesiolysis, compared to only 14.7% preoperatively. Most patients attempting to conceive are able to achieve a pregnancy within 1 year postoperatively, and up to 97.2% can conceive within 24 months [11, 12].

Table 14.3 Reports comparing various modalities to reduce re-formation of adhesion postresection

	Study design	Comparison groups	Relevant information	Outcomes
Solid barriers				
Orhue et al.	Prospective cohort study	IUD vs. Foley catheter	IUD arm: 51 women with Lippes loop IUD placed after surgery for 3 months Foley arm: 59 women with a Foley catheter placed postoperatively for 10 days	Absent menses: 19% in Foley group vs. 38% in IUD group ($p<0.03$) Pregnancy rate: 34% in Foley group vs. 28% in IUD group ($p=0.4656$) Fewer infections and fewer recurrent adhesions in Foley group
Lin et al.	Randomized trial	IUD vs. intrauterine balloon	IUD arm: 80 women for 1 week postsurgery Foley arm: 82 women for 1 week postsurgery	No difference in adhesion re-formation (35% in IUD vs. 30% in Foley group) No report on pregnancy outcomes
Semisolid barriers				
Acunzo et al.	Randomized trial	Hyaluronic acid gel (hyalobarrier gel; Baxter International Inc., Deerfield, IL) vs. no treatment	Hyalobarrier arm: 43 women No treatment arm: 41 women	Second-look hysteroscopy 3 months after surgery for intrauterine adhesions 14% (6/43) in hyaluronic acid arm vs. 32% (13/41) in no-treatment arm ($p < 0.05$)
Guida et al.	Randomized trial	ACP vs. no treatment	ACP arm: 67 women No-treatment arm: 65 women	Second-look hysteroscopy after surgery for intrauterine adhesions 10.4% with adhesions in the ACP arm vs. 26.2% in the no-treatment arm ($p < 0.05$)
Tsapanos et al.	Randomized trial	Modified hyaluronic acid + carboxymethylcellulose (Seprafilm; Genzyme Corp., Cambridge, MA) vs. no-treatment control	Seprafilm arm: 50 women Control arm: 100 women Data were stratified on whether or not a woman had a D&C before surgery for removal of adhesions	8 months after surgery in women who did not have a D&C: 100% (32/32) pregnant in Seprafilm arm vs. 54% (34/56) in the control arm ($p < 0.05$) If no pregnancy after 8 months all got hysterosalpingography: 10% (1/10) had intrauterine adhesions at hysterosalpingography in Seprafilm arm vs. 50% (7/14) in the control arm

(continued)

Table 14.3 (continued)

	Study design	Comparison groups	Relevant information	Outcomes
Hooker et al.	Randomized trial	ACP vs. no treatment	ACP arm: 77 women Control arm: 72 women	Second-look hysteroscopy Intrauterine adhesions in ACP arm were seen in 13% (10/77) vs. 30.6% (22/72) in the control group ($p = 0.013$)
Hormonal treatments				
Farhi et al.	Randomized trial	Hormones vs. no hormones	Hormone arm: 30 women (daily 2 mg estradiol valerate for 21 days + 0.5 mg norgestrel for 10 days) Control arm: 30 women	Hormone arm had greater endometrial thickness than control group (0.84 cm vs. 0.67 cm) ($p = 0.02$)
Mixed comparisons				
Sanfilippo et al.	Randomized trial	IUD + hormones vs. hormones only	IUD + hormone arm: 26 women Hormone-only arm: 9 women	No difference in postoperative intrauterine adhesion re-formation Pregnancy rate slightly higher in IUD + hormone group
Amer et al.	3-arm pilot randomized trial	Fresh amnion vs. dry amnion vs. intrauterine balloon	Fresh amnion arm: 15 women Dry amnion arm: 15 women Intrauterine balloon arm: 15 women	Diagnostic hysteroscopy after 2–4 months Amnion grafts reduced re-formation of adhesions ($p = 0.003$) Fresh amnion superior to dry amnion ($p = 0.01$) Of the 10 patients who were pregnant, 80% (8/10) had amnion graft and 20% (2/10) had balloon placement
Lin et al.	Retrospective cohort	Balloon catheter vs. IUD vs. hyaluronic gel vs. control	Balloon catheter arm: 20 women IUD arm: 28 women Hyaluronic gel arm: 18 women Control arm: 41 women	At second-look hysteroscopy: balloon group had the lowest number of adhesions ($p < 0.001$). IUD group had fewer adhesions than the gel and control groups

Adapted from Khan and Goldberg [8]

Table 14.4 Pregnancy rate and live birth rate following adhesiolysis

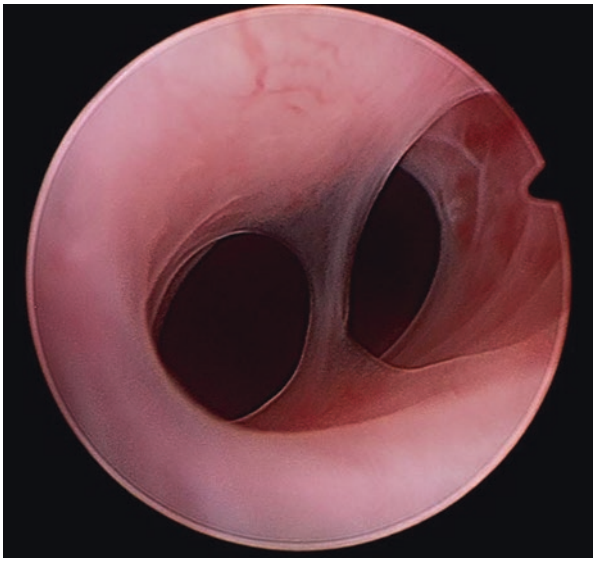
Authors	Design	Pregnancy rate	Live birth	Authors	Design	Pregnancy rate	Live birth
Forssman L, 1965	Retro	15/35 (42.9)	13/24 (54.2)	Fernandez H, 2012	Retro	9/22 (40.9)	6/9 (66.7)
Comninos AC, 1969	Retro	30/68 (44.1)	28/30 (93.3)	Myers EM, 2012	Retro	6/8 (75.0)	–
Oelsner G, 1974	–	16/41 (39.0)	14/20 (70.0)	Malhortra N, 2012	Pro	5/40 (12.5)	2/5 (40.0)
Jewelewicz R, 1976	Retro	18/34 (52.9)	10/18 (55.6)	Tuuli MG, 2012	Retro	–	–
Sugimoto O, 1978	Retro	79/192 (41.2)	47/79 (59.5)	Sendag F, 2013	Retro	4/14 (28.5)	3/4 (75.0)
Bergquist CA, 1981	Pro	19/25 (76.0)	13/19 (68.4)	Urman B, 2013	Retro	13.70%	–
Friedman A, 1986	Retro	36/33 (78.8)	23/24 (95.8)	Fuchs N, 2014	RCT	10/52 (19.2)	–
Valle RF, 1988	Retro	143/187 (76.5)	–	Ghahiry AA, 2014	Pro	6/16 (37.5)	–
Goldenberg M, 1995	Pro	20/35 (57.1)	–	SongD, 2014	Retro	20/76 (26.3)	12/20 (60.0)
Roge P, 1996	Retro	28/50 (56.0)	24/34 (70.6)	Tsui KH, 2014	Retro	4/4 (100)	2/4 (50.0)
Chen FP, 1997	Retro	3/7 (42.9)	2/3 (66.7)	Xiao SS, 2014	Retro	314/475 (66.1)	201/314 (64.0)
McComb PF, 1997	–	5/6 (83.3)	4/5 (80.0)	Bhandari S, 2015	Pro	16/60 (16.3)	10/16 (62.5)
Pabuccu R, 1997	Retro	34/40 (85.0)	23/34 (67.7)	Bougie O, 2015	Retro	6/19 (31.6)	5/6 (83.3)
Protopapas A, 1998	Pro	3/7 (42.4)	1/4 (25.0)	Kim MJ, 2015	–	8/47 (17.0)	4/8 (50.0)
Capella-Allouc S, 1999	Retro	12/28 (42.9)	9/15 (60)	Krajcovicova R, 2015	Pro	42/60 (70.0)	18/42 (42.9)
Feng ZC, 1999	Retro	156/186 (83.9)	–	Takai I, 2015	Retro	25/78 (32.1)	–
Orhue AAE, 2003	Retro	34/110 (30.9)	18/34 (52.9)	Thubert T, 2015	Retro	29/73 (39.7)	20/29 (69.0)
Zikopoulos KA, 2004	Retro	20/46 (43.5)	20/20 (100)	Sanad AS, 2016	Pro	40/61 (65.6)	22/40 (55.0)
Efetie ER, 2006	Retro	8/71 (11.3)	–	Chen L, 2017	Retro	160/332 (48.2)	137/160 (85.6)
Fernandez H, 2006	Retro	28/64 (43.8)	21/28 (75.0)	Chen Y, 2017	Pro	43/97 (44.3)	24/73 (62.8)
Thomson AJM, 2007	Retro	9/17 (52.9)	8/9 (88.9)	Cai H, 2017	Retro	24/72 (33.3)	13/24 (54.2)
Yasmin H, 2007	Retro	2/19 (10.5)	1/2 (50.0)	Gan L, 2017	RCT	16/80 (20.0)	–

(continued)

Table 14.4 (continued)

Authors	Design	Pregnancy rate	Live birth	Authors	Design	Pregnancy rate	Live birth
Yu D, 2008	Retro	39/85 (45.9)	25/39 (64.1)	Roy KK, 2017	RCT	16/60 (26.7)	9/16 (56.3)
Pabuccu R, 2008	RCT	37/71 (52.1)	22/37 (59.5)	Zhao J, 2017	Pro	63/104 (60.6)	41/63 (65.1)
Robison JK, 2008	Retro	10/15 (66.7)	4/10 (40.0)	Baradwan S, 2018	Retro	22/41 (53.7)	–
Amer MI, 2010	RCT	10/43 (23.3)	–	Hui CYY, 2018	Retro	25/44 (56.8)	19/25 (76.0)
Roy KK, 2010	Retro	36/89 (40.4)	31/89 (34.8)	Xu WZ, 2018	Retro	108/151 (71.5)	80/108 (7401)

Adapted from Guo et al. [10]



The degree of preoperative adhesions has been well documented to negatively impact postoperative fertility rates. Severe adhesions are more difficult than mild to restore normal uterine anatomy, and often require multiple procedures to achieve restoration of anatomy. Mild, moderate, and severe adhesions have been associated

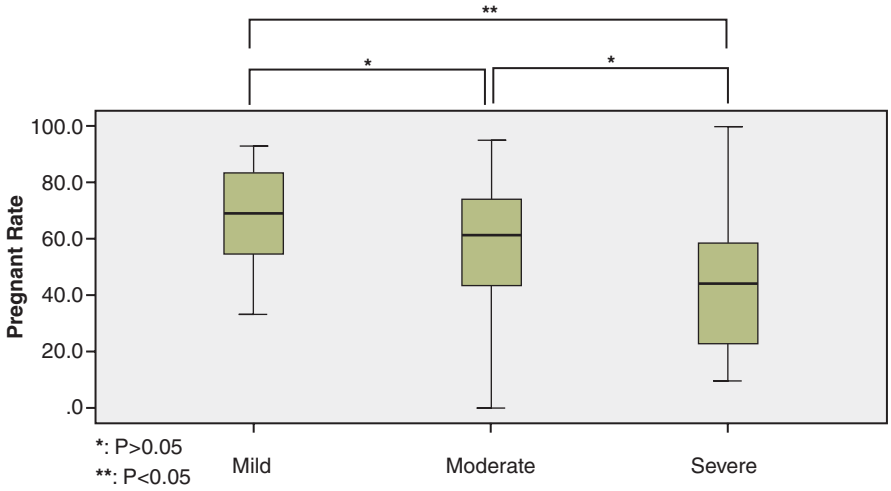


Fig. 14.1 Pregnancy rate after hysteroscopic adhesiolysis. Adapted from Guo et al. [10]

with conception rates of 64.7–69.1%, 53.6–61.3%, and 32.5–44.3%, respectively; see Fig. 14.1 [1, 10]. Two factors are implicated to effect conception when evaluating for the degree of preoperative adhesions: return to normal menstruation, and re-formation of adhesions. Patients with severe adhesions are more likely to have re-formation of IUAs, and are also less likely to have return of normal menstruation compared to patients with moderate or mild IUAs [1].

Hysteroscopic adhesiolysis helps increase both pregnancy and live birth rates, and while this is the goal for a large majority of patients undergoing adhesiolysis, patients need to be counseled on future pregnancy complications. Pregnancies that follow adhesiolysis have been associated with a number of adverse pregnancy complications; see Table 14.5. Compared to the general population, pregnancy after adhesiolysis is associated with increased rates of early pregnancy loss, placental abnormalities, cervical insufficiency, preterm birth, and most significantly complications associated with placenta accreta syndrome. Damage to the endometrium and prior intrauterine surgery increase the risk for development of placenta accreta.

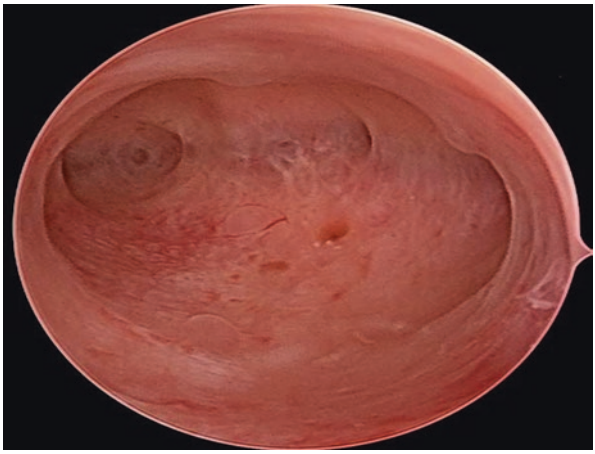
Table 14.5 Prevalence of various adverse pregnancy outcomes for women who conceived after surgical treatment of AS compared with the rates in the general population

Obstetrical complications	IUA population, pooled prevalence (%, 95% CI)	General population (%)
Pregnancy loss		
Early pregnancy loss	17.7 (15.9–19.6)	10–25
Ectopic pregnancy	4.2 (2.8–6.3)	1.1–2
Midtrimester loss	11.5 (7.6–17.8)	1–5
Stillbirth	1.8 (0.9–3.4)	0.5–0.6
Neonatal death	10.3 (4.3–21.8)	1.4–4.1
Obstetrical hemorrhage		
Placenta previa	2.8 (1.8–4.2)	0.3–0.5
Placental abruption	2.3 (1.0–5.0)	0.3–1.2
Postpartum hemorrhage	11.4 (9.1–14.1)	5–15
Others		
Placenta accreta syndrome	10.1 (8.6–11.8)	0.14–0.9
Premature rupture of membrane	5.7 (3.6–8.7)	2–3
Cervical insufficiency	12.5 (3.3–33.5)	1–2
Intrauterine growth restriction	8.4 (6.0–11.6)	8
Preterm birth	14.5 (12.7–16.5)	5–18

Adapted from Guo et al. [10]

14.2 Conclusion

Hysteroscopic adhesiolysis for patients with IUAs has been proven to be a safe and effective surgical intervention. Intraoperative complications are rare, and restoration of a normal uterine cavity is achieved in most cases. Patients with severe IUAs have increased risk of intraoperative complications and are more likely to require more than one procedure to restore normal intrauterine anatomy. Re-formation of IUAs is the most common postoperative complication and is seen in 1/3 of those with severe disease. Adhesiolysis significantly improves conception rates, and most patients are able to conceive within 2 years. Severity of IUA disease is negatively correlated with conception rates, likely due to increased re-formation of IUAs. Patients treated for IUAs should be counseled on increased risks for subsequent pregnancies, specifically the increased risks for placenta accreta syndrome.



Key Points

1. Hysteroscopic adhesiolysis for patients with IUAs has been proven to be a safe and effective surgical intervention.
2. Intraoperative complications are rare, and restoration of a normal uterine cavity is achieved in most cases.
3. Severe IUAs have increased risk of intraoperative complications and are more likely to require more than one procedure to restore normal intrauterine anatomy.
4. Re-formation of IUAs is the most common postoperative complication and is seen in 1/3 of those with severe disease.
5. Adhesiolysis significantly improves conception rates, and most patients are able to conceive within 2 years.
6. Severity of IUA disease is negatively correlated with conception rates, likely due to increased re-formation of IUAs.
7. IUA-treated women should be counseled about increased risks of obstetric complications including placenta accreta syndrome.

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