# Intrauterine Adhesions: Etiopathogenesis

61

José Luis Metello and José Florencio Jimenez

## 61.1 Introduction

Intrauterine adhesion (IUA) refers to partial or complete adhesions between the uterine walls which might result in several clinical manifestations such as hypomenorrhea, amenorrhea, dysmenorrhea, abdominal pain, infertility, habitual abortion, premature delivery, and abnormal placenta implantation.

The pathology also known as Asherman syndrome (AS) was first described in 1894 by Heinrich Fritsch. In 1927, Bass reported on 20 cases of cervical obstruction after induced abortions in Russia [1] and Stamer [2] in 1946 reported on a couple of cases of IUA after abortion or postpartum. However, the full characterization of the disease was carried out by Joseph Asherman [3]. He considered two different entities, a traumatic one and the stenosis of the cervical os. He also linked endometrial trauma and adhesion to menstrual disturbance, cyclical pelvic pain and even subfertility. Moreover, he recognized that the cause had to do with endometrial damage and not to pure obstruction of the menstrual flow. He described it as one type of complication of uterine curettage, where adhesions between the uterine walls were the result of an inflammatory process, mostly aseptic. Since then [4, 5] other underlying causes have been described.

J.L. Metello, M.D. (✉)
Hospital Garica de Orta, Almada, Portugal

Ginemed-Maloclinics, Lisbon, Portugal
e-mail: jmetello@gmail.com

J.F. Jimenez, M.D.
Clinica "Leopoldo Aguerrevere", Caracas, Venezuela

Unidad de Fertilidad Unifertes, Caracas, Venezuela
e-mail: fertilidad@gmail.com

## 61.2 Definition

IUA or synechia are composed of scar-fibrotic tissue that may result in the adherence of opposing surfaces of the endometrial lining. The adhesions can vary widely, if in one extreme they can be just simple thin bands of filmy tissue easily broken, in a small part of the uterus (Fig. 61.1); on the other hand, in cases of severe disease, all the endometrium can be obliterated by thick fibrous tissue (Figs. 61.2 and 61.3).

There is some discussion about the differences between the concept of IUA and AS. Often they have been used synonymously. However, syndrome is defined as a group of symptoms and medical signs that characterize a disease. Taking this into consideration, the term Asherman Syndrome should be avoided when no symptoms are present. However, other authors [6] have suggested that this term—AS, should be used exclusively in cases of IUA related to endometrium trauma of the gravid uterus.

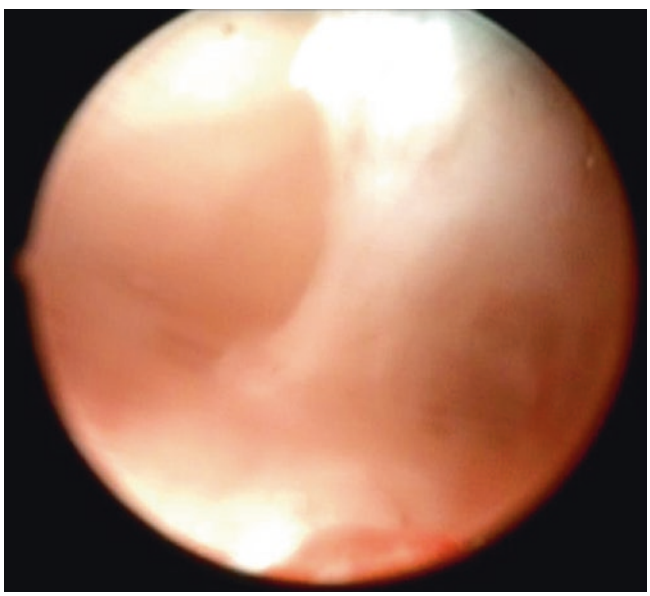

**Fig. 61.1** Filmy adhesion on hysteroscopy


A. Tinelli et al. (eds.), *Hysteroscopy*, https://doi.org/10.1007/978-3-319-57559-9_61

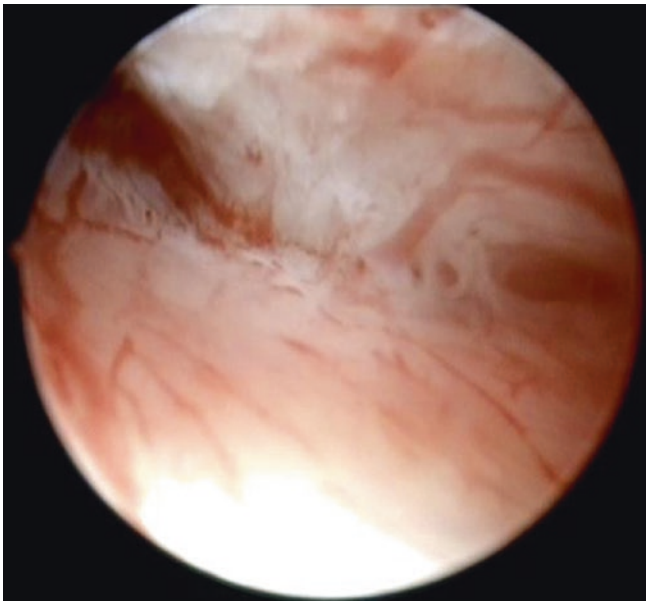

**Fig. 61.2** Thick adhesion on hysteroscopy

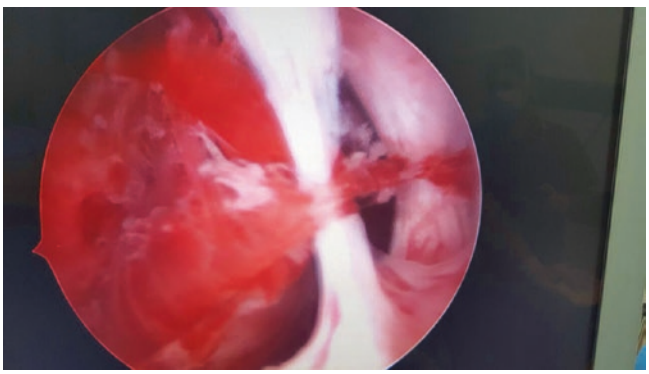

**Fig. 61.3** Thick adhesion on hysteroscopy

## 61.3 Prevalence

It is very difficult to estimate the true prevalence of IUA, especially because in many cases they might be asymptomatic and undiagnosed. A 1982 review showed a wide variability on the geographical prevalence of adhesions, being especially high in Israel [4]. The authors tried to explain this, with the different incidence of legal and illegal abortion and the incidence of postpartum endometritis. The technique for puerperal and postabortion evacuation was also an issue. Other reasons had to do with the degree of awareness of the physicians, the criteria used for diagnosis, and the incidence of genital tuberculosis.

Taking this into consideration, the true incidence has been estimated to be around 0.3% in the general population, 1.5% of the patients undergoing hysterosalpingography [7], between 5 and 39% of women with recurrent pregnancy lost [8–10], up to 21% after postpartum curettage [11], and up to 40% of patients who have a history of surgical treatment for retained products of conception [12], while in infertile women, the incidence of IUA might be over 2%.

## 61.4 Etiology

### 61.4.1 Pregnancy Related

Most cases of synechiae are the result of intrauterine trauma of the gravid uterine cavity [13, 14] (Table 61.1). This trauma could be caused by curettage either after spontaneous or induced miscarriage or in the postpartum period. According to the publication of Schenker and Margalioth [4] who reviewed 1856 cases of Asherman syndrome, pregnancy was the predisposing factor in 90% of cases. In their description (Table 61.1), 67% of cases occurred after postabortion curettage, 22% after postpartum curettage, 2% after cesarean section, and around 1% after evacuation of a hydatidiform mole (Fig. 61.4).

Westendorp et al. [12] reported on the prevalence of intrauterine adhesions after secondary removal of placental remnants after delivery and after a repeated curettage for incomplete abortion. A hysteroscopy was performed 3 months after the intervention in 50 women and they found adhesions in 40% of these, of which 75% had grade II–IV adhesions. The authors considered several risk factors and they concluded for a non significative risk increase in the presence of infection or lactation or history of previous abortion. Women with menstrual disorders after the procedure were more likely to have intrauterine adhesions as 13/25 with any menstrual disorder were found to have IUA.

In 2014, Hooker [15] published a methanalysis in over 900 women evaluated with hysteroscopy within 12 months following a spontaneous abortion and reported a prevalence of IUA in 19.1% (Figs. 61.5 and 61.6). He also concluded that the risk of adhesions seems to increase when two or more curettage procedures are performed, with a relative risk of 2.1. In a review by Fejgin [16], the author reports that repeated curettage for pregnancy loss increases the risk of adhesions from 8 to 35% between the first and the third procedure. Gilman [17] published a review on 884 patients submitted to active management of early pregnancy loss. According to their symptoms, six were found to have AS, all of them had undergone sharp curettage, and three had repeated curettage performed; there were no cases of AS after manual vacuum aspiration (0/191) or medical management with misoprostol (0/210). In a 2016 publication, the same author [18] concluded in favor of an association between IUA and mechanical suction dilatation and curettage (D&C), increased uterine size, particularly in the presence of multiple gestation, but not when manual vacuum aspiration was performed.

**Table 61.1** Asherman syndrome according to the review of Schenker and Margalioth (1982 based on 1856 cases) [4]

| Risk factors | % |
|---|---|
| Miscarriage curettage | 66.70 |
| Postpartum curettage | 21.50 |
| Infection (genital tuberculosis) | 4 |
| Cesarean section | 2 |
| Trophoblastic disease evacuation | 0.60 |
| Diagnostic curettage | 1.60 |
| Abdominal myomectomy | 1.30 |
| *Insertion of IUD* | 0.2 |

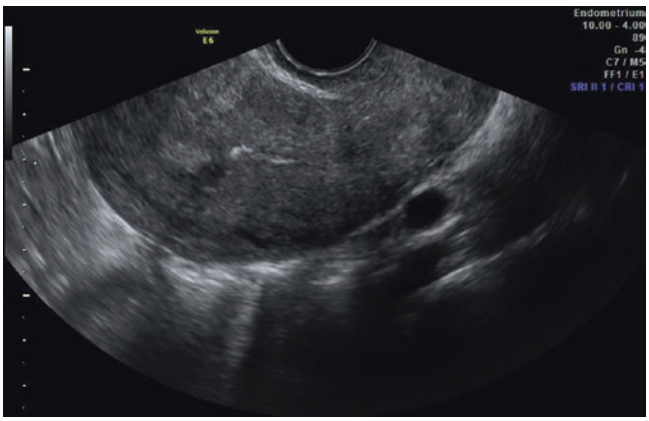

**Fig. 61.4** Ultrasound of adhesions after first trimester curettage

Other authors describe rates of adhesions between 17 and 30% after incomplete or missed abortions [19–21], while Lurie et al. found a prevalence of 39% after midtrimester abortion in women who underwent curettage [22] in contrast with the findings of Golan et al., who found a prevalence of intrauterine adhesions of 2% after manual removal of placenta in 48 patients [23]. It seems that the highest risk for a postpartum curettage to end up in adhesions in between 2 and 4 weeks postpartum, compared to when performed within 48 h postpartum, perhaps due to the different levels of circulating estradiol [24].

Women submitted to uterine compression sutures for postpartum hemorrhage also have an increased risk of IUA as it has been described in around 20–25% of them [25–27]. The reason is uncertain; however, the B-Lynch type creates a brace-like effect that apposes the anterior with the posterior wall, which in theory [28] can occlude uterine blood flow, leading to adhesions.

There is also a description of several case reports describing severe adhesions after uterine devascularization for the treatment of severe postpartum hemorrhage [29]. A 2014 review [30] reported on two cases of synechiae or necrotic uterus after bilateral uterine artery ligation followed by bilateral suspensory ligament of ovary ligation in two out of 12 patients. No complications were reported in ten patients submitted to bilateral uterine artery ligation.

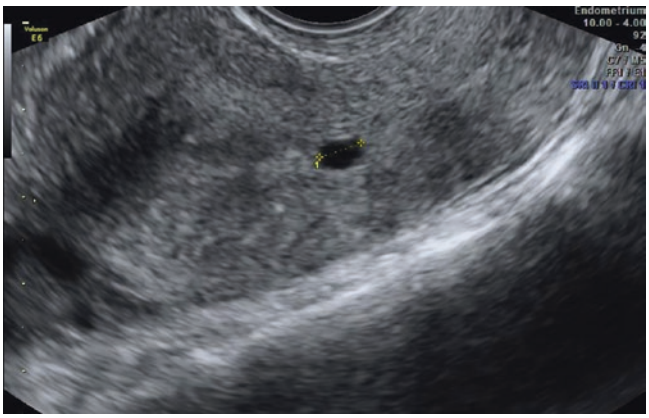

**Fig. 61.5** Ultrasound of adhesions after molar pregnancy evacuation: adhesions with an isthmic endometrial cyst

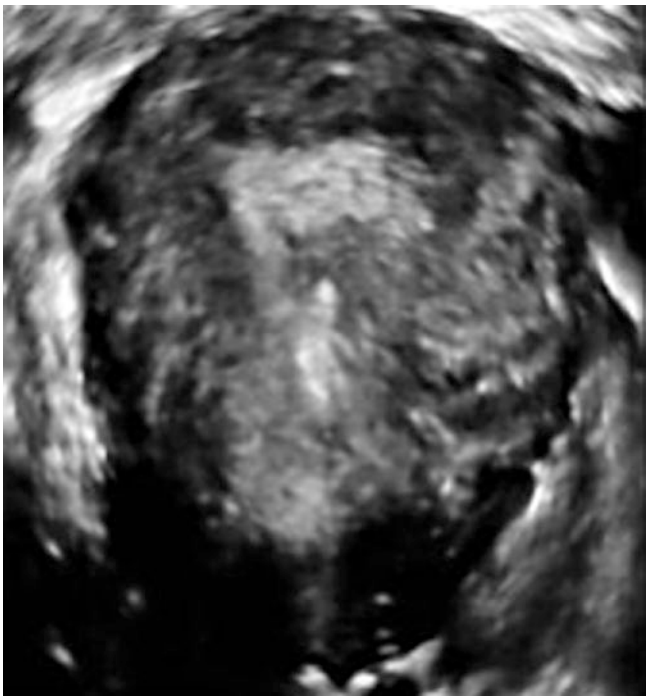

**Fig. 61.6** 3D-ultrasound of adhesions after curettage

### 61.4.2 Nonpregnant

Pregnancy is not the only factor related to uterine adhesions. According to the publication of Schenker and Margalioth [4] previously stated, out of the 1856 cases reported 30 (1.6%) had a previous history of a diagnostic curettage, while 24 an abdominal myomectomy, ten a cervical biopsy or polypectomy, and three the insertion of an intrauterine contraceptive device.

For long, the formation of adhesions has been described as a complication of hysteroscopic surgery, especially in cases of myomectomy. Taskin [31] described the rate of adhesion formation after a second-look hysteroscopy according to

different procedures and concluded that adhesions were uncommon after treatment for polyps and uterine septa, while mild IUA formation were present in 31% with solitary fibroids and 45% with multiple ones. Most of them could be easily treated during the procedure. Other studies report different rates [32–34], Mazzon reported on 688 women with one or more type I–II fibroids submitted to Cold loop resectoscopic myomectomy to conclude that synechiae were found in 29 patients (4.2%) [35].

Bilateral uterine artery embolization (UAE) has also been associated with adhesion formation, with reports varying between 10 and 14% [36]. It also seems that AS after this treatment has a poorer prognosis with more severe adhesions than in other situations. Song hypothesized that adhesions after UAE performed for obstetric complications might carry a worse prognosis than when it is used for gynecological situations.

As expected, IUA are common complications of endometrial ablation. There are several techniques that can be used, but overall when properly performed, they all lead to the removal or destruction of the basal layer of the endometrium, followed by cicatricial fibrosis. Studies have shown that around 35% of women submitted to this procedures will have adhesions on hysteroscopy [37, 38].

Despite the fact that endometrial tuberculosis may contribute to the development of IUA [39, 40], this is more common in undeveloped areas, like the North of India. In the review of Schenker and Margalioth [4], only 4% of the cases were found to be related to tuberculosis. *Schistosoma* sp. have also been implicated [41], but as tuberculosis it is expected to be rare in developed countries.

Other situations have been related to IUA, like congenital anomaly of the Uterus. In a study by Stillman and Asarkof [42], seven out 43 (16%) infertile patients with Mullerian duct malformations had IUAs. They could not establish if the anomaly was the cause of the adhesions or if the anomaly could predispose to the adhesions, for example, by increasing the risk of recurrent pregnancy loss.

Pelvic irradiation can also be a rare cause of IUAs [4]. The so-called genetic predisposition might have its role. Possibly there might be an individual response to injury that leads to the formation of IUAs in some while it does not in others.

### 61.4.3 Pathogeny

Several explanations have proposed. One of this stated that the functional layer of the endometrium of the gravid uterus might somehow be more vulnerable to aggression and prone to be destroyed [5]. Another explanation is that endometrium depends on estrogens for regeneration and so a low estrogen status immediately after the procedure as it happens during lactation might predispose to adhesion formation.

The role of infection is not established. On the one hand, it is clear that tuberculosis or schistosomiasis might be responsible for IUAs; however, as told before these situations are quite uncommon in developed countries. On the other hand, the role of postpartum and postabortion endometritis is more controversial. Polishuk et al. using hysterography [43] reported on 171 women who had undergone cesarean sections. Of these, 28 had endometritis and only one developed adhesions. Charles [44] reported that less than 1% of his patients had a history of infection by the time of their initial surgery. However, as described by Yu et al. [5] some investigators believe in the synergy between the inflammatory processes and trauma to the damaging of the endometrium.

The natural history is unknown. There are women with a consistent clinical diagnosis of AS who resumed menses. Schenker and Margalioth [4] reported on the fertility outcome of 292 patients who received no treatment. Only a few had the diagnosis confirmed by hysteroscopy and so some of them might have resumed menses as a result of a cervical stenosis that was overcome by the pressure of a hematometra. Although 46% conceived, only half of them had a viable infant and 13% had placenta accreta.

### 61.4.4 Histopathology

Histologically, in IUA the normal endometrium is replaced by fibrous tissue. The intrauterine adhesions may involve endometrium, myometrium, or connective tissue.

Normal endometrium consists of simple columnar glands with or without cilia and vascular stroma composed of connective tissue and richly vascularized, with spiral arteries. In women of reproductive age, two layers can be distinguished. The functional layer (stratum spongiosum) is closer to the lumen and changes during the cycle according to the hormonal milieu established by estrogens and progesterone. The glands are regularly spaced. The basal layer (stratum basale) is adjacent to the myometrium and contrary to the functional layer does not shed during menstruation. This layer is less responsive to steroid hormones as typically the glands are irregularly shaped and the stroma is dense. The spiral arteries are different too, as they have thicker muscular walls [45].

With adhesions there is a loss of the distinction between the basal and the functional layer of the endometrium [46]. The functional layer is replaced by an inactive epithelial monolayer. This epithelia is much less or nonresponsive at all to hormone stimulation. Sparse and inactive glands can be identified. In most cases, the tissue is avascular although sometimes thin-walled telangiectatic vessels can be observed [47]. Yaffe [48] comparing biopsy specimens of the uterine

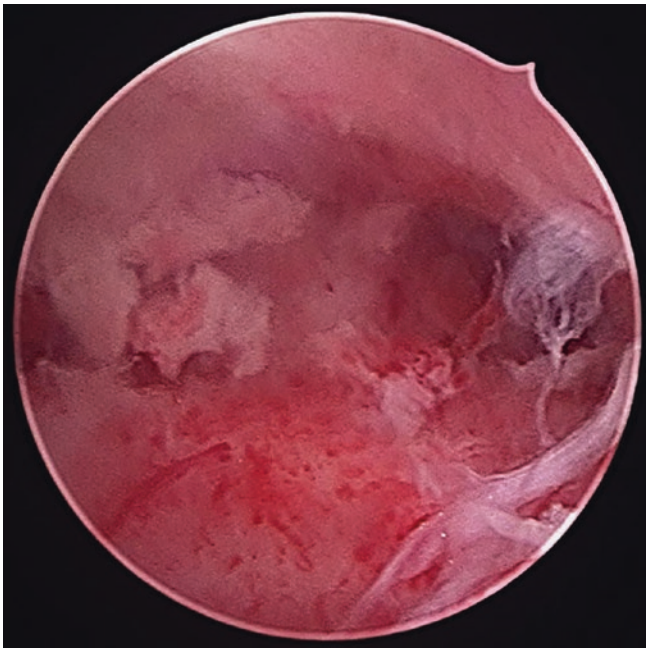

**Fig. 61.7** Left uterine cornus after adhesiolysis showing atrophic endometrium and bleeding from the muscularis

wall from patients with intrauterine adhesions with controls concluded that the first ones contained 50–80% of fibrous tissue compared with 13–20%. Moreover, according to McCulloch [49] it seems that histological changes after transcervical resection of the endometrium are similar to those with Asherman syndrome. The changes are extended to the surrounding endometrium even in a nonaffected part of the uterus as this tissue also appears atrophic with an increased amount of connective tissue. This might help to explain why sometimes the hipomenorrhea symptoms seem disproportionally higher than the adhesions observed (Fig. 61.7).

On electric microscopy [50], the glandular epithelial cells present with swelling, with a loss in the ribosomes and expansion of the endoplasmic reticulum. There are also changes in the mitochondria that have their cristae shortened and reduced and vacuolization. The interstitium is looser, with closed capillaries and tight junctions between endothelial cells. On the molecular level, there is a suggestion that adhesion-related cytokines, such as transforming growth factor β, platelet-derived growth factor, and b-fibroblast growth factor might be associated with IAU [51].

The use of pelvic angiography [11] has demonstrated a reduction in the myometrial vascular flow in patients with severe hypomenorrhea and amenorrhea.

Sometimes, calcification or even ossification of the stroma might be present.

VEGF [50] expression might have an important role. Chen, comparing patients pre- and post treatment, concluded that patients with IUA had microscopically vascular closure and hypoxic changes, with clear improvement after treatment. After treatment, they also concluded in favor of more expression of VEGF and increased microvascular density score.

Malhotra [52] compared endometrial thickness and blood flow impedance of the uterine spiral artery post-menstrual on day 2/3 pre- and post-hysteroscopic adhesiolysis and concluded in favor of a significant improvement in the endometrial thickness and a higher blood flow impedance of spiral artery after the procedure.

It seems that adhesions might progress, which means that they begin as thin endometrial bands to progress to thicker ones. When there are muscular adhesions and the endometrial basalis is lost, the prognosis is poor as there is no starting point to the proliferation of new endometrium after adhesiolysis [53].

## References


1. Bass B. Ueber die Verwachsungen in der cervix uterinach curettagen. Zentralbl Gynakol. 1927;51:223.
2. Stamer S. Partial and total atresia of the uterus after excochleation. Acta Obstet Gynecol Scand. 1946;26:263–97.
3. Asherman JG. Traumatic intra-uterine adhesions. J Obstet Gynaecol Br Emp. 1950;57(6):892–6.
4. Schenker JG, Margalioth EJ. Intrauterine adhesions: an updated appraisal. Fertil Steril. 1982;37:593–610.
5. Yu D, Wong YM, Cheong Y, Xia E, Li TC. Asherman syndrome: one century later. Fertil Steril. 2008;89:759–79.
6. Hanstede MM, van der Meij E, Goedemans L, Emanuel MH. Results of centralized Asherman surgery, 2003–2013. Fertil Steril. 2015;104(6):1561–8.
7. Dmowski WP, Greenblatt RB. Asherman's syndrome and risk of placenta accreta. Obstet Gynecol. 1969;34:288–99.
8. Rabau E, David A. Intrauterine adhesions: etiology, prevention, and treatment. Obstet Gynecol. 1963;22:626–9.
9. Toaff R. Some remarks on posttraumatic uterine adhesions. Rev Fr Gynecol Obstet. 1966;61:550–2.
10. Ventolini G, Zhang M, Gruber J. Hysteroscopy in the evaluation of patients with recurrent pregnancy loss: a cohort study in a primary care population. Surg Endosc. 2004;18:1782–4.
11. Deans R, Abbott J. Review of intrauterine adhesions. J Minim Invasive Gynecol. 2010;17:555.
12. Westendorp IC, Ankum WM, Mol BW, Vonk J. Prevalence of Asherman's syndrome after secondary removal of placental remnants or a repeat curettage for incomplete abortion. Hum Reprod. 1998;13:3347–50.
13. March CM. Intrauterine adhesions. Obstet Gynecol Clin N Am. 1995;22:491.
14. Schenker JG. Etiology of and therapeutic approach to synechia uteri. Eur J Obstet Gynecol Reprod Biol. 1996;65:109.
15. Hooker AB, Lemmers M, Thurkow AL, et al. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. Hum Reprod Update. 2014;20:262.
16. Fejgin MD, Shvit TY, Gershtansky Y, Biron-Shental T. Retained placental tissue as an emerging cause for malpractice claims. Isr Med Assoc J. 2014;16(8):502–5.
17. Gilman Barber AR, Rhone SA, Fluker MR. Curettage and Asherman's syndrome-lessons to (re-)learn? J Obstet Gynaecol Can. 2014;36(11):997–1001.

18. Gilman AR, Dewar KM, Rhone SA, Fluker MR. Intrauterine adhesions following miscarriage: look and learn. J Obstet Gynaecol Can. 2016;38(5):453–7.
19. Friedler S, Margalioth EJ, Kafka I, Yaffe H. Incidence of post-abortion intra-uterine adhesions evaluated by hysteroscopy—a prospective study. Hum Reprod. 1993;8(3):442–4.
20. Golan A, Schneider D, Avrech O, Raziel A, Bukovsky I, Caspi E. Hysteroscopic findings after missed abortion. Fertil Steril. 1992;58(3):508–10.
21. Römer T. Post-abortion-hysteroscopy—a method for early diagnosis of congenital and acquired intrauterine causes of abortions. Eur J Obstet Gynecol Reprod Biol. 1994;57(3):171–3.
22. Lurie S, Appelman Z, Katz Z. Curettage after midtrimester termination of pregnancy. Is it necessary? J Reprod Med. 1991;36(11):786–8.
23. Golan A, Raziel A, Pansky M, Bukovsky I. Manual removal of the placenta—its role in intrauterine adhesion formation. Int J Fertil Menopausal Stud. 1996;41(5):450–1.
24. Eriksen J, Kaestel C. The incidence of uterine atresia after postpartum curettage. A follow-up examination of 141 patients. Dan Med Bull. 1960;7:50–1.
25. Poujade O, Grossetti A, Mougel L, et al. Risk of synechiae following uterine compression sutures in the management of major postpartum haemorrhage. BJOG. 2011;118:433.
26. Rathat G, Do Trinh P, Mercier G, et al. Synechia after uterine compression sutures. Fertil Steril. 2011;95:405.
27. Ibrahim MI, Raafat TA, Ellaithy MI, Aly RT. Risk of postpartum uterine synechiae following uterine compression suturing during postpartum haemorrhage. Aust N Z J Obstet Gynaecol. 2013;53:37.
28. Marasinghe JP, Saravanabhava N. Risk of synechiae following uterine compression sutures. BJOG. 2011;118(8):1020–1. Author reply 1021–2
29. Roman H, Sentilhes L, Cingotti M, Verspyck E, Marpeau L. Uterine devascularization and subsequent major intrauterine synechiae and ovarian failure. Fertil Steril. 2005;83:755–7.
30. Doumouchtsis SK, Nikolopoulos K, Talaulikar V, Krishna A, Arulkumaran S. Menstrual and fertility outcomes following the surgical management of postpartum haemorrhage: a systematic review. BJOG. 2014;121(4):382–8.
31. Taskin O, Sadik S, Onoglu A, et al. Role of endometrial suppression on the frequency of intrauterine adhesions after resectoscopic surgery. J Am Assoc Gynecol Laparosc. 2000;7:351.
32. Touboul C, Fernandez H, Deffieux X, et al. Uterine synechiae after bipolar hysteroscopic resection of submucosal myomas in patients with infertility. Fertil Steril. 2009;92:1690.
33. Yang JH, Chen MJ, Wu MY, et al. Office hysteroscopic early lysis of intrauterine adhesion after transcervical resection of multiple apposing submucous myomas. Fertil Steril. 2008;89:1254.
34. Ramírez-Sánchez LR, Alanis-Fuentes J, Morales-Domínguez L. Intrauterine synechiae after use of monopolar resectoscope. Ginecol Obstet Mex. 2015;83(6):340–9.
35. Mazzon I, Favilli A, Cocco P, et al. Does cold loop hysteroscopic myomectomy reduce intrauterine adhesions? A retrospective study. Fertil Steril. 2014;101:294.
36. Song D, Liu Y, XiaoY LTC, Zhou F, Xia E. A matched cohort study comparing the outcome of intrauterine adhesiolysis for Asherman's syndrome after uterine artery embolization or surgical trauma. J Minim Invasive Gynecol. 2014;21(6):1022–8. doi:10.1016/j.jmig.2014.04.015.
37. Leung PL, Tam WH, Yuen PM. Hysteroscopic appearance of the endometrial cavity following thermal balloon endometrial ablation. Fertil Steril. 2003;79:1226–8.
38. Taskin O, Onoglu A, Inal M, Turan E, Sadik S, Vardar E, Postaci H, Wheeler JM. Long-term histopathologic and morphologic changes after thermal endometrial ablation. J Am Assoc Gynecol Laparosc. 2002;9:186–90.
39. Sharma JB, Roy KK, Pushparaj M, Gupta N, Jain SK, Malhotra N, Mittal S. Genital tuberculosis: an important cause of Asherman's syndrome in India. Arch Gynecol Obstet. 2008;277(1):37–41.
40. Bahadur A, Malhotra N, Mittal S, Singh N, Gurunath S. Second-look hysteroscopy after antitubercular treatment in infertile women with genital tuberculosis undergoing in vitro fertilization. Int J Gynaecol Obstet. 2010;108(2):128–31.
41. Krolikowski A, Janowski K, Larsen JV. Asherman syndrome caused by schistosomiasis. Obstet Gynecol. 1995;85:898–9.
42. Stillman RJ, Asarkof N. Association between Mullerian duct malformations and Asherman syndrome in infertile women. Obstet Gynecol. 1985;65(5):673–7.
43. Polishuk WZ, Anteby SO, Weinstein D. Puerperal endometritis and intrauterine adhesions. Int Surg. 1975;60:418–20.
44. March CM. Asherman's syndrome. Semin Reprod Med. 2011;29(2):83–94.
45. Mazur M, Kurman RJ. Diagnosis of endometrial biopsies and curettings: a practical approach. 2nd ed. New York, NY: Springer; 2004.
46. Buckley CH. Normal endometrium and non-proliferative conditions of the endometrium. In: Fox H, Wells M, editors. Obstetrical and gynaecological pathology. 5th ed. London: Churchill Livingstone; 2002. p. 391–442.
47. Foix A, Bruno R, Davison T, Baltasar L. The pathology of postcurettage adhesions. Am J Obstet Gynecol. 1966;96:1027–33.
48. Yaffe H, Ron M, Polishuk W. Amenorrhoea, hypomenorrhoea and uterine fibrosis. Am J Obstet Gynecol. 1978;130:599–601.
49. McCulloch T, Wagner B, Duffy S, Barik S, Smith J. The pathology of hysterectomy specimens following trans-cervical resection of the endometrium. Histopathology. 1995;27:541–7.
50. Chen Y, Chang Y, Yao S. Role of angiogenesis in endometrial repair of patients with severe intrauterine adhesion. Int J Clin Exp Pathol. 2013;11:1343–50.
51. Tao Z, Duan H. Expression of adhesion-related cytokines in the uterine fluid after transcervical resection of adhesion. Zhonghua Fu Chan Ke Za Zhi. 2012;47(10):734–7.
52. Malhotra N, Bahadur A, Kalaivani M, Mittal S. Changes in endometrial receptivity in women with Asherman's syndrome undergoing hysteroscopic adhesiolysis. Arch Gynecol Obstet. 2012;286(2):525–30.
53. Al-Inany H. Intrauterine adhesions. An update. Acta Obstet Gynecol Scand. 2001;80:986–93.