

Late-onset endometrial ablation failure



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A B S T R A C T

Endometrial ablation, first reported in the 19th century, has gained wide acceptance in the gynecologic community as an important tool for the management of abnormal uterine bleeding when medical management has been unsuccessful or contraindicated. The introduction of global endometrial ablation (GEA) devices beginning in 1997 has provided unsurpassed safety addressing many of the concerns associated with their resectoscopic predecessors. As of this writing the GEA market has surpassed a half-million devices in the United States per annum and has an expected compound annual growth rate (CAGR) projected to be 5.5% from 2016 to 2024.

While the short term safety and efficacy of these devices has been reported in numerous clinical trials we only recently are becoming aware of the high incidence of late-onset endometrial ablation failures (LOEAFs) associated with these procedures. Currently, about a quarter of women who undergo a GEA procedure will eventually require a hysterectomy while an unknown number have less than satisfactory results. In order to reduce these suboptimal outcomes physicians must better understand the etiology and risk factors that predispose a patient toward the development of LOEAF as well as current knowledge of patient and procedure selection for EA as well as treatment options for these delayed complications.

1. Introduction

Endometrial ablation (EA) is a gynecologic tool first introduced in the late 19th century as a minimally invasive attempt to control profuse vaginal bleeding without resorting to hysterectomy. Prior to the recent and widespread adoption of EA the only surgical means available for women with failed medical management was hysterectomy. As recently as 20 years ago, in 1997, the Rand Corporation published *Hysterectomy: Clinical Recommendations and Indications for Use* [1]. The recommendations were developed as part of a project conducted by the Southern California Health Policy Research Consortium (SCHPRC) in order to establish uniform clinical guidelines for performing hysterectomy. In their report the authors—which included experts from the American College of Obstetrics and Gynecology, the American College of Internal Medicine and the American College of Family Practice—had not even recognized endometrial ablation as a treatment strategy for managing abnormal uterine bleeding.

EA has become adopted throughout most of the developed world filling an important gap between medical therapy and hysterectomy. The appeal of 21st century endometrial ablation lies in the fact that it can be performed in an office or outpatient setting, often with minimal analgesia and a modest recovery. Additionally, EA is quite safe, requires nominal training and enjoys a substantial rate of success which has contributed to some extent to a significant reduction in hysterectomy

rates in the United States between the years 1998 and 2010 [2].

While modern EA techniques have eliminated many of the intraoperative and immediate postoperative complications associated with earlier methods, several studies [3–6] highlight the fact that late-onset endometrial ablation failures (LOEAFs) can manifest themselves in the months and years following EA requiring nearly a quarter of subjects to undergo hysterectomy. This review summarizes the history and demographics of resectoscopic and non-resectoscopic endometrial ablation, our present understanding of the incidence and presentation of LOEAF and the available data on post-ablation endometrial carcinoma (PAEC). Finally, we will examine the known risk factors for LOEAF, as well as treatment options and measures to reduce the incidence of this common complication.

2. History of Endometrial Ablation

Throughout the early medical history of EA physicians have introduced a variety of energy sources into the uterine cavity in order to selectively destroy the endometrium. These first generation techniques were conducted blindly—without direct observation of the uterine cavity—and included thermal destruction by steam, radiofrequency electrosurgery, radium and cryosurgery.

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Kungelsondenelktrode (ball-end electrode) used by Bardenheuer

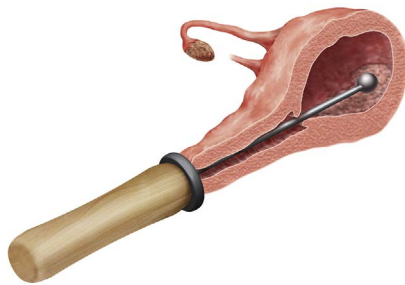


Fig. 1. Bardenheuer's Kungelsondenelktrode.

2.1. First Generation Techniques

The earliest report of endometrial ablation dates to 1898 when Dührssen [7] attempted to provide relief for a 37 year old woman “exhausted by profuse and persistent menorrhagia by introducing steam into the uterine cavity for 2 minutes.” Dührssen noted that “as a result, the uterus underwent complete atrophy.”

Around the turn of the 19th century, medical uses for electricity emerged. In 1891 Jacques-Arsène d'Arsonval [8] noted the relationship between high-frequency alternating current density and the tissues to which it was applied. In the decade that followed d'Arsonval's discovery a Parisian physician, Joseph Rivere [8], performed the very first surgical procedure using electricity and applied the principal of electro-surgical arcing to the treatment for lesions of the skin, oral cavity, and bladder for the coagulation of vascular tumors and skin cancers, a technique he called *fulguration*. In 1937 Bardenheuer [9] published *Elektrokoagulation (ELK) der Uterusschleimhaut*—electrocoagulation of the endometrium—by introducing a unipolar *Kungelsondenelktrode* featuring a 5- to 8-mm diameter steel ball mounted on a 12 to 16 cm shaft (Fig. 1). In 1948 Bauman [10] promoted Bardenheuer's technique and reported a series of 387 women who were treated in an office setting under “light narcosis”. Bardenheuer reported a very low complication rate and also identified the first cases of late-onset endometrial ablation failure (LOEAF) and stressed the importance of avoiding electrocoagulation of the internal os in order to reduce the likelihood of hematometra formation and cyclic pelvic pain.

In the early 20th century—following Marie Curie's discovery—the use of radium attracted the interest of physicians because of its ability to affect human tissue. Subsequently, it was utilized for a variety of medical conditions including gynecologic malignancies. In 1917 Schmitz [11] noted that “radium may be applied to benign and malignant diseases of the female pelvic organs. The benign disorders are myomata uteri, the hemorrhagic metropathies and chronic endometritides and cervicitides...” Schmitz noted that “Radium acts as Nature's curette and [is] hemostatic when applied to the endometrium.” Dr. William Henry Beauford Aikins, a Canadian born physician and educator, became widely known as a specialist in the study of cancer and the application of radiotherapy. In his treatise, *The Value of Radium in Curing Disease, in Prolonging Life, and in Alleviating Distressing Symptoms*, [12] Aikins reported on the use of radium in treating 133 subjects, between 1910 and 1923 for a variety of illnesses including 3 cases of uterine cancer and 3 additional cases of menorrhagia. In 1922 Aikins reported on the use of intrauterine radium to treat a wide range of pelvic conditions, including uterine fibroids, menorrhagia and metrorrhagia. In 1937 Schultze [13] reported a series of 204 women with menorrhagia who were treated with intrauterine radium in doses varying from 1200 to 1500 mCi/h. The treatment was fraught with many undesirable side-effects including atrophic vulvitis and the subsequent development of endometrial cancer. However, Schultze recognized the direct relationship between patient satisfaction and

Nd:YAG laser

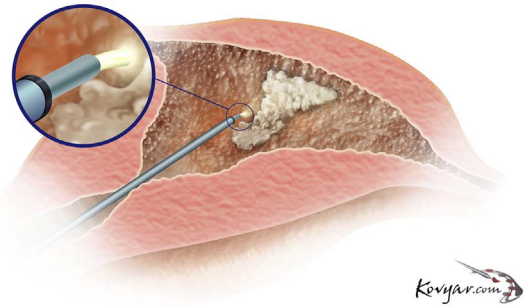


Fig. 2. Hysteroscopic endometrial laser ablation.

age—establishing one of the most important predictors of success.

The next foray into endometrial ablation came in 1967 when Cahan and Brockunier [14] reported the technique of cryoendometrial ablation on 6 patients suffering from severe menorrhagia. The procedure was carried out utilizing a 6 mm diameter liquid nitrogen cooled probe at temperatures varying from -80 to -120 °C. While satisfactory results were achieved in 5 subjects no further studies were performed. Droegemueller et al. [15] described a similar technique in 16 women in which Freon® (DuPont, Deepwater, NJ) probes were utilized. Droegemueller discovered that in all patients endometrium persisted at the uterine cornua citing this as one of the deficiencies of this technique.

2.2. Second Generation Techniques

A new era in the approach to EA was heralded by Goldrath et al. [16] who co-located a rod-lens system (Fig. 2) with a Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser and in 1981 reported the first cases of EA under direct hysteroscopic control. The Nd:YAG laser was particularly well-suited to phocoagulation of the endometrium as a result of its high power and transmission through optical fibers. Unlike other medical lasers such as the carbon dioxide (CO₂) and the potassium titanyl phosphate (KTP) lasers the Nd:YAG provided excellent tissue penetration—up to 4 mm beneath the endometrial surface. Despite Goldrath's success the use of the Nd:YAG for EA never gained widespread acceptance for at least 3 reasons: First, most gynecologists were not trained in basic hysteroscopy. Second, the cost of the Nd:YAG laser in the mid-1980s was in excess of 100 thousand U. S. dollars, prohibitively expensive for an emerging and untested technology. Third, many important ancillary devices, such as the continuous flow hysteroscope and today's fluid management systems had not yet been invented making these procedures both challenging and associated with significant risk.

Several years later, however, DeCherney et al. [17] utilized a conventional urologic resectoscope to perform endometrial ablation. Since DeCherney's energy source—an inexpensive monopolar electro-surgical unit—was already available in most operating rooms the issue of excessive cost had been practically eliminated. However, the lack of a continuous flow resectoscope limited the utility and acceptance of DeCherney's technique.

Although Iglesias [18] reported the use of the first continuous flow resectoscope in 1975, the gynecologic resectoscope as we know it today did not gain United States FDA approval until 1989, following the ground-breaking report by Brooks et al. [19]. Vancaillie [20] in 1989 and Townsend et al. [21], in 1990, reported the first cases of endometrial ablation using a ball-end electrode (Fig. 3). The inexpensive acquisition costs and excellent visualization allowed this technique to gain some limited popularity within the gynecologic community. While resectoscopic EA had its adherents, early reports of fatalities resulting from uterine perforation, visceral injury and distention fluid-overload were of great concern. In 1993 Arieff et al. [22] and Baggish et al. [23]

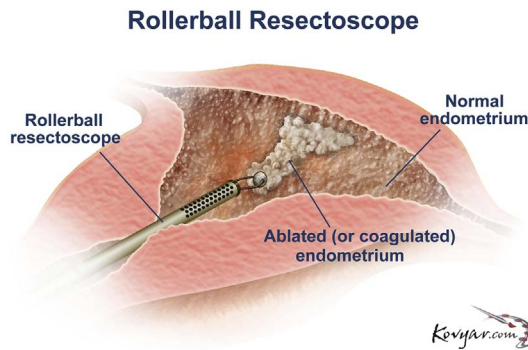


Fig. 3. Hysteroscopic endometrial ablation with the “ball-end” electrode.

separately reported a series of deaths attributable to hyponatremic encephalopathy and the search for safer EA methods ensued. Despite the fact that many of the fluid and electrolyte issues associated with hysteroscopic and resectoscopic techniques have been solved by the introduction of reliable fluid management systems as well as bipolar electrosurgery, the shift toward non-resectoscopic techniques is what propelled the growth of endometrial ablation in the developed world.

2.3. Third Generation Techniques

An important paradigm shift in EA occurred in 1997 with the introduction of the first non-resectoscopic endometrial ablation (NREA) or “Global ablation” devices. These are often collectively called “second-generation” devices—a term that belies their history. Between 1997 and 2003 a total of 5 NREA devices received FDA approval: the thermal balloon (ThermaChoice Uterine Balloon System; Johnson and Johnson, New Brunswick, NJ), the cryoablation system (Her Option; Cooper Surgical, Trumbull, CT), a heated free fluid system (Hydro ThermAblator or HTA System; Boston Scientific, Natick, MA) a bipolar radiofrequency ablation device (NovaSure EA; Hologic, Inc., Bedford, MA, and a microwave ablation system (MEA System; previously produced by Microsulis Medical Limited, Denmead, UK). In 2015 a sixth system utilizing radiofrequency energy and a plasma formation array (PFA) also became available (Minerva Endometrial Ablation System; Redwood City, CA). These systems, reminiscent of the original techniques of the early 20th century, boast 2 important advantages—they are easily learned and exceptionally safe. Global EA techniques obviated the risks of fluid overload and hyponatremia while curtailing the incidence of visceral injuries associated with their resectoscopic predecessors [24,25]. Yet another advantage of GEA devices and techniques is that they can be performed with minimal sedation and local anesthesia in selected patients, making them appropriate for an office-based or outpatient setting [26,27]. The combination of safety, simplicity and patient acceptability has promoted the widespread growth of endometrial ablation in the U. S. and other developed countries. The GEA devices that have received FDA approval in the United States between 1997 and 2015 are summarized in Figs. 4-9.

3. Demographics of Endometrial Ablation

In 2008, GEA procedures constituted the most common surgical treatment for heavy menstrual bleeding in the United States [28,29]. Between 2008 and 2012 the number of domestic GEA procedures grew from 312,000 to 390,000 with a market valued at \$730 million [29]. By 2016 the U. S. GEA market improved to 521,140 units annually [30]. As of 2016 NovaSure (Hologic, Inc. Bedford, MA) maintained 57.1% of the GEA market with Minerva (Minerva Endometrial Ablation System; Redwood City, CA) accounting for 16.1% of sales—these 2 radiofrequency ablation (RFA) devices account for nearly three-quarters of all GEA procedures in the U. S. Fig. 10 summarizes the GEA device market share by supplier for the year 2016 [29]. Hydrothermal

ThermaChoice Balloon

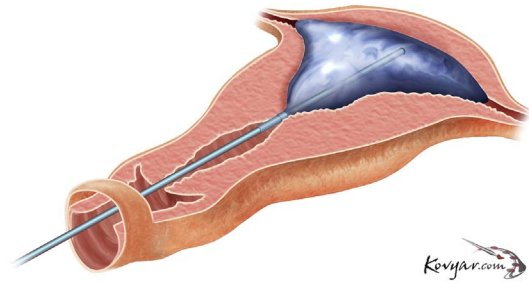


Fig. 4. Thermal Balloon System (ThermaChoice).

Her Option

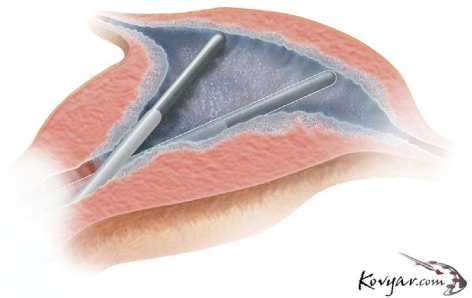


Fig. 5. Cryoendometrial ablation (Her Option).

Hydrothermal ablation

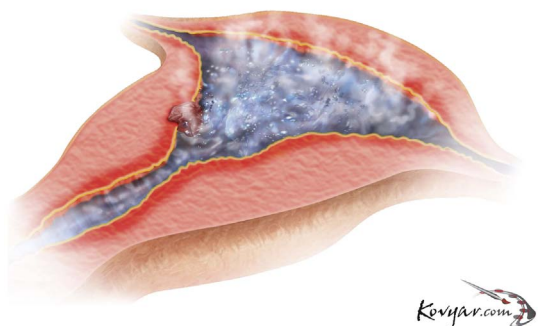


Fig. 6. Heated Free-Fluid System (Hydro ThermAblator).

NovaSure

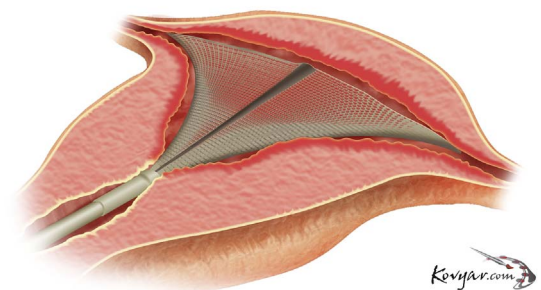


Fig. 7. Bipolar Radiofrequency ablation device (NovaSure).

ablation (Hydro ThermAblator or HTA System, Boston Scientific, Natick, MA) and cryoendometrial ablation (Her Option, Cooper Surgical, Trumbull, CT) account for 21.9% and 4.9% respectively [30]. Table 1 summarizes the past 3 years of GEA device sales in the United States.

Microwave Endometrial Ablation (MEA)

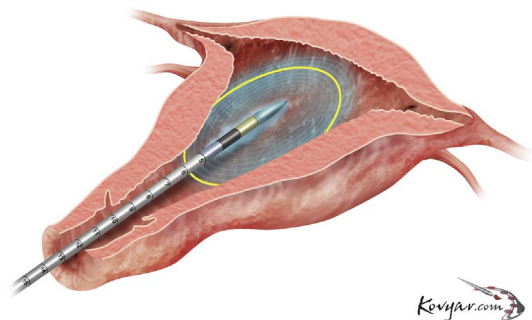


Fig. 8. Microwave ablation system (MEA System).

Minerva Endometrial Ablation

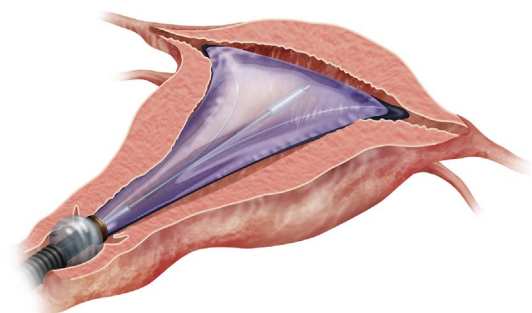


Fig. 9. Radiofrequency ablation (Minerva).

Market Share By Manufacturer/Devices - 2016

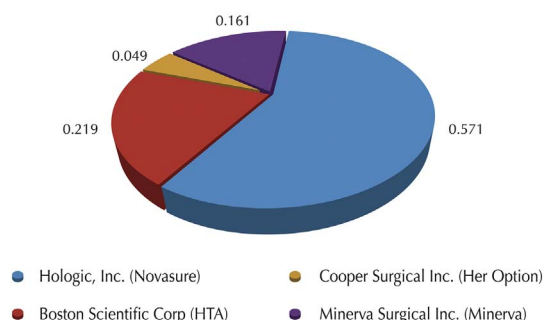


Fig. 10. Global endometrial ablation devices in the U. S. – Market share by device.

Table 1
Annual trends in Global Endometrial Ablations in the United States 2014–2016.

Year	2014	2015	2016
Number of Endometrial Ablations Performed in the U. S. (No. of Units)	482,649	502,513	521,140

The expected compound annual growth rate (CAGR) of the U. S. GEA market is projected to be 5.5% from 2016 to 2024 and is anticipated to reach US \$1.3 billion by the end of the forecast period [31]. Worldwide, the greatest potential market for global endometrial ablation devices is forecast to occur in Asia, Europe, and followed by North America and the Caribbean. The demand for radiofrequency endometrial ablation (RFA) devices is higher than others and is expected to remain so for the next few years [31]. Together with resectoscopic endometrial ablation (REA) the combined number of EAs may soon surpass the number of hysterectomies performed in the U. S. per annum [2,32].

4. Late-Onset Endometrial Ablation Failure (LOEAF): Definition, Incidence and Presentation

LOEAF describes the complications attributable to endometrial ablation that occur beyond the perioperative period of 1 month. LOEAFs present in one of 3 ways: persistent or recurrent vaginal bleeding, the development of cyclic pelvic pain (CPP), and the inability to adequately assess the endometrium in women who later require evaluation. In the healing that follows both resectoscopic and NREA, intense intrauterine fibrosis and scarring occurs. Since endometrial glands are present in the vast majority of subjects following EA [33,34] the interplay of functioning endometrial glands and uterine scarring often leads to delayed complications.

Longinotti et al. [4] studied 3681 women who underwent both REA and NREA procedures by 344 physicians at 30 different Kaiser Permanente facilities. The subjects had a mean age of 44.3 ± 6.2 years; 20.2% had leiomyomas. The majority of LOEAF-related hysterectomies occurred in the first 3 years following EA with the probability of hysterectomy rising to 26% by the 8th year. In Longinotti's series the most common reason for subsequent hysterectomy was vaginal bleeding (51.6%) followed by cyclic pelvic pain (20.3%). Interestingly, the study revealed no relationship between the type of EA and the subsequent requirement for hysterectomy.

Shavell et al. [35] studied 1169 women who underwent either REA (8.1%) or NREA (91.9%) and found that 157 (13.4%) underwent subsequent hysterectomy during a follow-up period ranging from 1 to 64 months. Sixty percent of hysterectomies occurred within the first 24 months following EA and 80% within the first 36 months. Bleeding unaccompanied by pain accounted for 26% of hysterectomies while a combination of bleeding and pain accounted for another 38.3%. An additional 7.1% of subjects underwent hysterectomy for symptomatic leiomyomas while “other indications” accounted for 7.1%.

Vilos et al. [36] reported 163 hysterectomies performed following REA and noted that 64.4% were for cyclic pelvic pain (CPP), 23.3% were performed for a combination of intractable bleeding and pain while 12.3% were for intractable bleeding alone. Similarly the author (MW) [37] found that CPP was the chief complaint in 61.5% of women presenting for reoperative hysteroscopic surgery (RHS) following an EA failure. In the author's experience, which includes well over 300 cases of managing endometrial ablation failures, the pain associated with endometrial regrowth can be quite variable in its presentation. Often the patient ascribes unilateral lower quadrant pain to ovulation. In other instances the pain may be reminiscent of menstrual cramps lasting no > 1–2 days per cycle. With time, however, the pain often evolves and is often described as “labor-like” and disabling and may last up to 2 weeks in duration. In the absence of vaginal bleeding both the patient and physician—particularly one in primary care—often fail to make the diagnosis of obstructed bleeding.

An often overlooked LOEAF was reported by Ahonkallio et al. [38] who noted that attempted endometrial biopsy failed in 23% of women with a history of endometrial ablation. Ahonkallio et al. also stated that even in those subjects where biopsy material was obtained the specimen was likely unreliable because of sequestration of endometrium in the uterine cornua by fibroconnective tissue. In a more recent study of 50 women who presented for RHS following a late-onset GEA failure the author [39] found that 14% of referrals were for failed endometrial biopsy attempts.

5. Etiology of Late-Onset Endometrial Ablation Failure

Late-onset complications following EA are the result of the interplay of 2 competing phenomena—a source of uterine bleeding and intrauterine scarring and contracture. The interplay of these 2 processes determines the clinical presentation of LOEAF. Recurrent uterine bleeding may occur months or years following EA and may result from inadequate endometrial destruction, endometrial regrowth,

unsuspected adenomyosis, persistent or enlarging leiomyomas, endometrial polyps [4,34,39,40], and ablative necrosis [41,42] or development of uterine malignancy. Intrauterine scarring and subsequent contracture are a necessary by-product of healing following thermal destruction of the endometrium. Often scarring that obstructs the outflow of uterine blood—at the internal os and even the tubal ostia produces cyclic pelvic pain (CPP).

5.1. Source of Menstrual Bleeding

5.1.1. Inadequate Endometrial Destruction

Complete endometrial destruction is an uncommon result of any endometrial ablation technique. The reasons include: (1) persistent endometrium in the interstitial portion of the fallopian tube, (2) the limitations in providing adequate access and treatment for visible endometrium at the relatively thin-walled uterine cornua, and (3) the occurrence of GEA device failure.

In 1954 Lisa et al. [43] studied the histoanatomy of 300 uteri and 554 fallopian tubes and discovered the presence of endometrium in the mucosa of the interstitial segment of the fallopian tube in 75 (25%) of cases. One may conclude that current technology does not allow complete endometrial destruction in this delicate anatomic location, which is typically 1 cm or less in length [43]. Similarly the cornua are a frequent site of endometrial gland persistence following EA. Turnbull et al. [44] studied 59 women whose elapsed time since their endometrial resection ranged from 5 to 65 months—with a mean of 34 months—using a 1.5 Tesla magnetic resonance imaging system with a pelvic phased array coil for signal reception. Twenty-two of the women were amenorrheic. Turnbull et al. were able to detect residual endometrium in 94.9% of subjects—most commonly seen at the uterine fundus close to the tubal ostia. The mean volume of endometrium tissue was calculated to be 10.1 cm³ (SD 8.1). In a previous paper the author (MW) noted that 44% of women who presented for reoperative hysteroscopic surgery following a GEA-related late onset failure had virtually untreated uterine cornua [39]. In that same series an additional 10% of women were noted to have an almost normal-appearing uterine cavity with minimal or no bioeffect suggesting the possibility of a device failure. Lethaby et al. [40] also highlighted the possibility of equipment failure for GEA devices noting that it was significantly greater than for hysteroscopic and resectoscopic techniques (RR 4.3, 95% CI 1.5 to 12.4).

5.1.2. Endometrial Regrowth

In a prospective longitudinal study, Taskin et al. [33] performed second-look hysteroscopy on 26 subjects who experienced satisfactory results following hysteroscopic EA at a fixed follow-up interval of 33.4 ± 2.1 months. The study specifically excluded women with dysmenorrhea. The subjects included women with amenorrhea (48.4%), hypomenorrhea (30.6%) and eumenorrhea (21.0%). Taskin et al. found that endometrial glands were present in 21 of 26 (80.1%) of subjects and concluded that endometrial regrowth is an anticipated development in many patients and is not necessarily associated with LOEAF. Onoglu et al. [34] conducted a prospective randomized trial that included 23 women who underwent hysteroscopic rollerball EA and 25 women who underwent hysteroscopic endometrial resection followed by second look hysteroscopy conducted at least 30 months after their procedure. Onoglu et al. concluded that “endometrial regrowth is an expected development in many patients and is not necessarily associated with clinical bleeding that would be termed a failure.”

5.1.3. Unsuspected Adenomyosis

Adenomyosis has often been cited as an important factor in late-onset endometrial ablation failure. Shavell et al. [35] identified adenomyosis in 44.4% of 1169 women undergoing hysterectomy after LOEAF. Riley et al. [45] detected adenomyosis in the hysterectomy specimens of 43% of LOEAFs. Unfortunately these studies provide no information regarding the presence or absence of adenomyosis in

women who have satisfactory outcomes after EA.

The exact role in determining clinical success and failure of EA in the presence or absence of EA is further complicated by the variability in diagnosis for adenomyosis. The evidence for this diagnostic variability is highlighted in a study by Seidman and Kjerulff [46] who reviewed 1252 pathology reports on hysterectomy specimens from the Maryland Women's Health Study. Seidman et al. found that despite established histopathologic guidelines the frequency of adenomyosis varied from 10% to 88% among the 25 pathologists who reviewed specimens. Evaluating the uterus for the presence or absence of adenomyosis is a far greater challenge since diagnostic criteria for adenomyosis following endometrial ablation have yet to be established.

McCausland et al. [47] was able to correlate the presence of adenomyosis with the subsequent outcome of rollerball endometrial ablation. In their study of 50 subjects who underwent an endomyometrial biopsy immediately prior to rollerball EA they found superficial adenomyosis (≤ 2.0 mm of invasion) to be present in 37 of 50 subjects (74%) while the remaining 13 (26%) had severe adenomyosis (≥ 2.1 mm of penetration). An analysis of the “change score for pain” revealed that 27 of the 37 women with superficial adenomyosis penetration had a reduction in pain after endometrial ablation compared with 3 of the 13 (23%) of women with ≥ 2.1 mm of penetration. Although there was a statistically significant relationship between the 2 endometrial depth groups in terms of pain reduction there was not a statistically significant difference in outcome with respect to a reduction in uterine bleeding.

In the author's study of 304 women [48] who underwent endomyometrial resection—which provides an excellent histologic specimen in which the junctional zone is easily identified—adenomyosis was present in 69 (22.7%) of patients. Adenomyosis was considered severe when endometrial glands were present at the resection margin (4–5 mm) and was detected in 7 (2.3%) of all subjects. Of the 69 women whose initial specimens revealed adenomyosis, 9 (13.0%) required a second operative procedure (either reoperative surgery or hysterectomy) during the observation period. Of the remaining 235 women whose histologic specimen did not indicate adenomyosis 18 (7.7%) required subsequent surgery. The presence of adenomyosis in this series did not increase the risk of subsequent surgery (p = 0.17). Unfortunately, this study did not differentiate the depth of adenomyosis with surgical outcomes.

5.1.4. Persistent or Enlarging Leiomyoma and Endometrial Polyps

Leiomyoma and endometrial polyps are common findings in women with EA failures. In a series of 50 women presenting with GEA failures the author [38] identified submucous leiomyomas in 22% of subjects. Gemer et al. [49] conducted a longitudinal study of 128 women who underwent REA and noted that the presence of submucosal leiomyomas was associated with an increased hazard ratio (HR) (HR = 5.22; 95% CI, 1.63–16.73) for subsequent surgery. Hachmann-Neilsen et al. [50] demonstrated that the effect of hydrothermal ablation was significantly diminished in patients with myomas larger than 3 cms. Untreated endometrial polyps provide another source of bleeding after EA and plays a minor role in the incidence of LOEAF [39].

5.1.5. Ablative Necrosis

Ablative necrosis was described by Tresserra et al. [41] as the histologic effects associated with GEA-related thermal damage and includes nuclear streaming and hyperchromasia, cytoplasmic eosinophilia, as well as coagulative necrosis with ghost cells remnants. The authors reported these morphologic changes in 12 hysterectomy specimens obtained from women who had undergone a previous endometrial electrosurgical ablation and noted that ablative necrosis was “seen in the short period post-ablation hysterectomies.” Tresserra et al. also reported that the presence of ablative necrosis is limited to within 1 year of endometrial ablation. Simon et al. [42] studied 145 hysterectomy specimens following a failed endometrial ablation and noted

that women demonstrating ablative necrosis underwent subsequent hysterectomy sooner than those without such debris (median 5 months vs. 23 months respectively).

5.2. Intrauterine Scarring and Contracture

Intrauterine scarring and contracture are near universal findings following all forms of endometrial ablation or resection; in fact it is the intended outcome of endometrial ablation. Magos et al. [51] performed second-look hysteroscopies at 3 months (n = 53) and 12 months (n = 15) after endometrial resection and showed that the majority of subjects had a small fibrotic and contracted uterine cavity. Taskin et al. [33] performed second-look hysteroscopies on 26 women following a thermal EA 33.4 ± 2.1 months earlier and discovered complete atrophy, partial adhesions, or obliteration of the cavity associated with fibrosis. When fibrosis and contracture coexist with a bleeding source, such as functioning endometrial tissue, a leiomyoma or an endometrial polyp, the result is obstructed bleeding and cyclic pelvic pain (CPP) often ensues.

Hopkins et al. [52] were the first to demonstrate that intrauterine “synechiae tend to develop with increasing time after endometrial ablation” and may explain why many complications require time to manifest. Hopkins et al. studied 25 patients with menorrhagia who requested hysteroscopic sterilization at the time of their radiofrequency EA. Of the 21 patients who underwent a hysterosalpingogram (HSG) at 3 months, 9 subjects (43%) had normal appearing cavities, 5 (24%) had mild synechiae and 7 (33%) revealed “subtle filling defects thought to be synechiae.” In the 2 subjects who underwent a HSG at 6 months an increase in intrauterine synechiae was noted. Severe synechiae were present during an HSG performed 9 months following RFA.

5.2.1. Cyclic Pelvic Pain

The coexistence of intrauterine synechiae and a source of bleeding often leads cyclic pelvic pain. If a bleeding source is accompanied by complete obstruction at the internal os patients often present with cyclic pelvic pain (CPP) which may be suprapubic, unilateral or bilateral. In the author's experience the pain is often described as “sharp,” “stabbing” or “labor like.” A transvaginal ultrasound examination performed during a painful episode often reveals one or more hematometra (Figs. 11, 12) frequently accompanied by evidence of endometrial growth. Hematometra are often found centrally or at one or both uterine cornua [6,39].

Another form of CPP was first reported by Townsend et al. [53] in 1993 who described 6 women with postablation tubal sterilization



Fig. 11. Sonographic view of failed GEA procedure demonstrating small bilateral cornual hematometra.

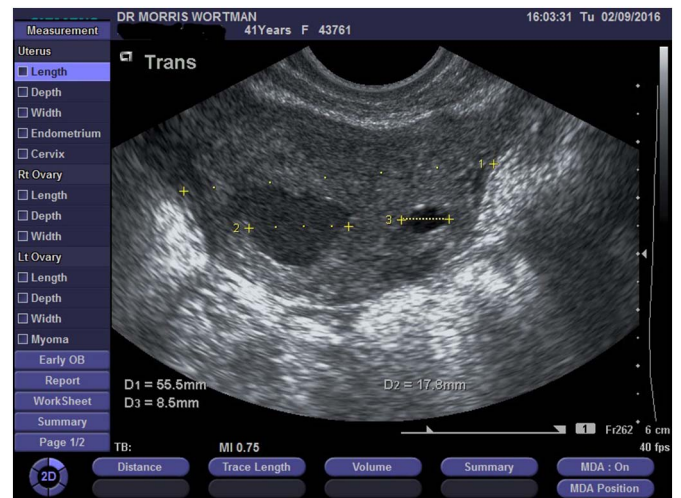


Fig. 12. Sonographic view of failed GEA procedure demonstrating large and asymmetrical cornual hematometra.

syndrome (PATSS). These subjects all presented with unilateral or bilateral CPP associated with vaginal spotting. All the subjects had undergone a tubal ligation followed by a rollerball endometrial ablation. In each case the proximal portion of 1 or both fallopian tubes was swollen and resembled the appearance of an early ectopic pregnancy. The mechanism responsible for PATSS is thought to result from sequestered endometrial tissue within the uterine cornua that is unable to pass retrograde through the distal fallopian tube causing cyclic swelling and pain.

The actual incidence of PATSS appears to be quite low. Although El-Nashar et al. [54] were able to show that a history of bilateral tubal ligation appeared to be a risk factor for LOEAF, they did not report a single case of PATSS in a group of 816 women who underwent GEA. In other larger studies of hysterectomy subsequent to EA failure, neither Shavell et al. [35] nor Longinotti et al. [4] reported a single case of PATSS in a combined total of 931 hysterectomies performed on 4850 women undergoing REA or NREA procedures.

6. Post-Ablation Endometrial Carcinoma (PAEC)

In 1987 DeCherney et al. [17] forewarned that the consequence of failing to destroy a “nest of endometrial tissue” during EA could result in a sequestered island of endometrial carcinoma (EC) inaccessible to standard biopsy techniques possibly delaying or obscuring the diagnosis. In 1993 Copperman et al. [55] described the first case of PAEC in a 56 year old who presented with postmenopausal bleeding 5 years following a resectoscopic EA. Her evaluation permitted an endometrial biopsy revealing a moderately well-differentiated (FIGO 2) adenocarcinoma. In 1995 Margolis et al. [56] reported the earliest case of an asymptomatic PAEC in a 58 year old woman 3 years following a REA. The report was disquieting inasmuch as the Stage I FIGO Grade 1 adenocarcinoma of the endometrium was discovered only as an incidental finding following a procedure for urinary stress incontinence.

In 2011 AlHilli et al. [57] reviewed the English literature and reported on 17 cases of post-ablation endometrial cancer (PAEC); the author has since reported 7 additional cases of PAEC [58,59]. These reports emphasize that PAEC may present with abnormal uterine bleeding, pelvic pain or may be entirely asymptomatic. In AlHilli's report [57], which consisted primarily of observations following REA, the average EA to EC interval was 3.9 years (3 months – 10 years). However, in our recent report of 6 women with PAEC [59]—the majority of which had been treated with GEA techniques—the average interval from EA to the diagnosis of EC was 8.8 years (95% CI 4.2–13.5 years).

An important issue for physicians to consider is how EA influences

the subsequent presentation of EC. Of the 24 cases available for analysis provided by AlHilli [57] and the author [58,59] abnormal uterine bleeding was present in 19 (79.2%) while pain was described as an important feature in 6 (25%) of the cases. Interestingly, EC can also be entirely asymptomatic as noted in 3 of AlHilli's [57] subjects raising the concern that the earliest signs of EC may be obscured.

It is now understood that traditional evaluative tools for EC—transvaginal ultrasound, diagnostic hysteroscopy and endometrial biopsy—are often inadequate in the woman with a previous EA. In our recent report of 6 women traditional endometrial biopsy was attempted in 5 cases and succeeded only once [59].

Several authors have questioned the effect of EA on the subsequent development of EC. Neuwirth et al. [60] assessed the incidence of endometrial cancer following EA in a population of 509 women with abnormal perimenopausal bleeding and detected neither an increased nor reduced risk of EC in EA-treated women compared with those in the U. S. SEER database [61]. However, Neuwirth's study investigated only resectoscopic techniques and included only women at low-risk for developing EC since subjects with a history of obesity, chronic anovulation and diabetes were excluded. Krogh et al. [62] reported 11 year follow-up data on 421 women who underwent transcervical resection of the endometrium (TRCE) between 1990 and 1996 and demonstrated a less-than-expected incidence of EC. However, the study provided an insufficient surveillance period and was comprised of a group of women whose average age was 56 ± 6 years—well short of the mean age at which EC typically presents. Finally, a more recent study by Singh et al. [63] conducted in the United Kingdom included 1521 women who underwent various types of EA procedures between 1994 and 2011 noted that none of the women in this retrospective observational study developed EC during the surveillance period. The suggestion by Singh et al. [63] suggested that endometrial ablation may even have a protective effect on the development of EC is unsupported by their data and the study's design. It appears, however, that the present literature does not indicate an obvious deleterious effect on the incidence of endometrial cancer in an EA-treated population. However, studies involving a large cohort of women undergoing GEA techniques with a sufficient period of observation have yet to be reported.

7. Risk Factors for Late-Onset Endometrial Ablation Failure (LOEAF)

Numerous risk factors for EA failure have been reported including the patient's age at the time of her EA, previous tubal ligation, an increased uterine surface area, the presence of uterine leiomyomas and endometrial polyps, anatomic distortions of the uterus and whether or not the procedure was performed in an outpatient or office setting. Other risk factors such as pelvic endometriosis, previous cesarean section and obesity are briefly considered.

7.1. Age

The inverse relationship between age and LOEAF has been well established. Longinotti et al. [4] reported that women under the age of 35 at the time of their EA have a significantly greater risk for hysterectomy (HR = 3.2; 95% CI, 2.4–4.2) compared with women aged 50 or older. According to Longinotti et al. age is more important as a predictor than the type of procedure or the presence of leiomyomas in forecasting subsequent hysterectomy following EA. Dutton et al. [64] also showed that women at least 45 years of age had a markedly decreased risk for subsequent hysterectomy (HR = 0.28; 95% CI, 0.10, 0.75; $P = 0.01$) compared with women who were younger than 35 years of age at the time of their EA. Shavel et al. [35] reported the rate of hysterectomy in the youngest quartile of women (age 21–36 years) was 20.8% compared with 10.5% for women in the oldest quartile (≥ 57 years of age) at the time of their EA.

7.2. Tubal Ligation

El-Nashar et al. [54] reported a hysterectomy hazard ratio (HR) of 2.5 (95% CI, 1.4–4.5) for women with a prior tubal ligation procedure. Istre and Langebrekke [65] also reported prior sterilization as a significant risk factor for LOEAF. However, other authors such as Shavell et al. [35], Longinotti et al. [4], Comino and Torrejon [66] and Kreider et al. [67] were unable to demonstrate such an association.

7.3. Uterine Length, Width, Surface Area and “RFA Index”

Shazly et al. [68] studied 1178 women who underwent radiofrequency ablation (RFA)—the most commonly performed EA procedure in the U. S [28,30].—and found that intraoperative measurements of uterine length, width, and an RFA Index are predictive of LOEAF in women treated with NovaSure devices (Hologic Inc., Bedford, MA). Shazly et al. also created an “RFA index” which was defined as the procedure duration (in seconds) divided by the uterine surface area (cm^2). Since the RFA device automatically terminates the procedure when 50Ω of impedance is reached (correlating to approximately 6-mm myometrial tissue depth destruction) the length of the procedure is not controlled by the surgeon. A lower RFA index, for example, indicates that less time was used per surface area of the uterus. Using these parameters Shazly et al. [68] noted that the intraoperative predictors of failure were (1) uterine sounding length > 10.5 cms (adjusted HR = 2.58; 95% CI 1.31–5.05), (2) uterine cavity length > 6 cm (adjusted HR = 2.06; 95% CI, 1.30–3.27), (3) uterine width > 4.5 cm (adjusted HR = 2.06; 95% CI, 1.29–3.28), (4) a surface area $> 25 \text{ cm}^2$ (adjusted HR = 2.02; 95% CI, 1.26–3.23), (5) procedure time < 93 s, and (6) RFA index < 3.6 .

For radiofrequency ablation failure attributed to significant AUB the strongest intraoperative predictor was a uterine sounding length > 10.5 cm (adjusted HR = 5.92; 95% CI, 2.68–13.07). In contrast for pain-related failure, uterine width and a greater RFA index were the strongest predictors (adjusted HR = 2.57; 95% CI, 1.45–4.53 and adjusted HR = 2.25; 95% CI, 1.16–4.35, respectively).

7.4. Leiomyomas, Thickened Endometrium and Endometrial Polyps

Various authors have shown that leiomyomas may increase, decrease or not influence the incidence of LOEAF. Comino and Torrejon [66] reported the presence of leiomyomas and endometrial polyps—found in half of their subjects—significantly increased the risk of hysterectomy subsequent to EA. In a retrospective cohort study Wishall et al. [69] found that preoperative ultrasound abnormalities including the presence of a thickened endometrial echo or endometrial polyps quadrupled the risk of hysterectomy following 3 separate types of GEA procedures (OR 3.96, 95% CI 1.25–12.56; $P = 0.02$). However, this study is limited by its sample size and the retrospective nature of the study. Gemer et al. [49] in a study of 128 women followed for a median period of 44 months identified the presence of submucosal myomas as a predictor of LOEAF (HR = 5.2; 95% CI, 1.63–16.73). Shamonski et al. [70] performed a retrospective analysis of 120 women who underwent EA and observed that the preoperative finding of an intramural myoma resulted in a “reduced trend toward success” (odds ratio = 0.4, $p = 0.06$) compared to women with normal preoperative transvaginal ultrasound. In contrast, Phillips et al. [71] in a large observational cohort study of 1000 consecutive endometrial laser ablations found that the presence of intrauterine pathology (e.g. polyps, fibroids and uterine shape abnormalities) decreased the risk of subsequent hysterectomy (RR = 0.26%; 95% CI 0.08–0.86; $P = 0.0082$) after adjustment for confounding due to patient's age and dysmenorrhea prior to surgery.

Longinotti et al. [4], in their study of 3681 women noted that the presence of leiomyomas did not appear to influence the risk of EA failure. This was also the conclusion drawn by Glasser and Zimmerman [72] in a study of 22 women followed for 12–20 months with

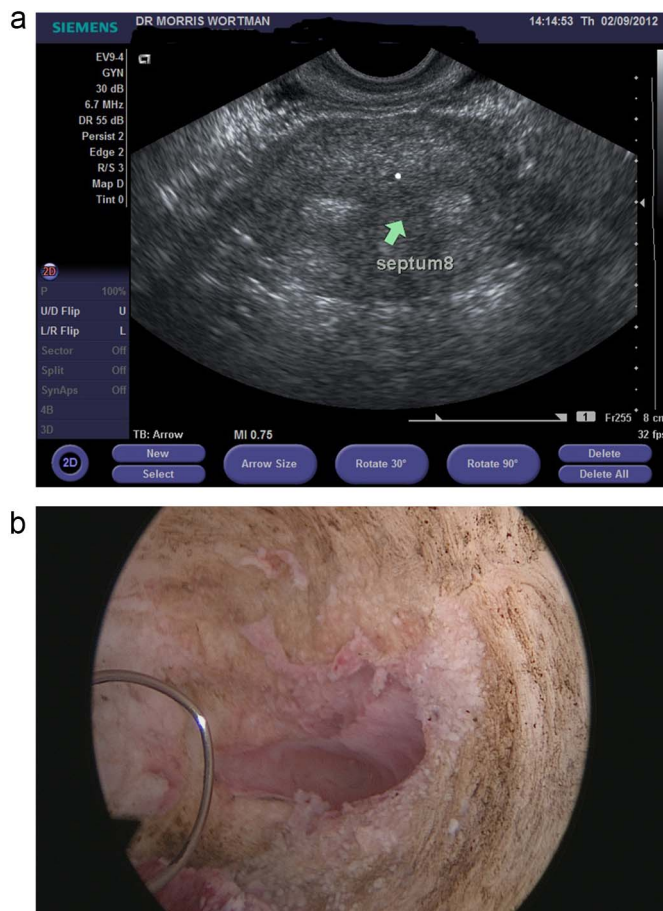


Fig. 13. a, b Sonographic and hysteroscopic view of endometrial growth following a GEA procedure in the presence of a uterine septum.

submucous leiomyomas < 4 cm.

7.5. Anatomic Distortions of the Uterus

The author has previously reported that in 12% of reoperative hysteroscopic surgeries following a GEA-associated LOEAF that a uterine septum was noted and was always accompanied by active endometrial tissue at the uterine cornua [39]. Fig. 13a and b reveals both the sonographic and hysteroscopic view of a patient with a uterine septum and endometrial growth.

7.6. Analgesia and Anesthesia

Global endometrial ablation is increasingly performed in an office setting under local anesthesia [73–76]. Although instrument manufacturers market these techniques to both physicians and patients as office-based procedures [77,78] there are scant data on whether or not the incidence of LOEAFs are affected by the administration of intravenous sedation or general anesthesia. Wishall et al. [69], in a retrospective cohort study of 300 patients who underwent EA between 2007 and 2013 found a procedure performed in the operating room decreased the risk of hysterectomy by 76% (adjusted OR 0.24, 95% CI 0.07–0.77). One may speculate that less thorough procedures are performed in the absence of adequate analgesia or anesthesia; however, randomized prospective studies on whether or not the incidence of LOEAFs are affected by the type of analgesia and sedation available have not been published.

7.7. Preoperative Bleeding Pattern

In 2011 the International Federation of Gynecology and Obstetrics adopted a standardized nomenclature for the causes of abnormal uterine bleeding in nonpregnant women of reproductive age known as the PALM-COEIN classification [79]. Within this system, AUB-O is described as irregular and heavy bleeding whereas AUB-E is a diagnosis of exclusion describing heavy and regular uterine bleeding. The American College of Obstetrics and Gynecology (ACOG) has cautioned against using EA as a first-line treatment for anovulatory uterine bleeding (AUB-O) stating that women with AUB-O treated with EA alone are at risk for development of endometrial hyperplasia and cancer because of the persistent effect of unopposed estrogen on the endometrium [80]. In addition, access to the endometrial cavity is likely to be subsequently impaired posing diagnostic challenges [38,59].

In a retrospective cohort study of 968 women who underwent endometrial ablation Smithling et al. [81] was able to compare the outcomes of EA in women with regular and irregular heavy uterine bleeding. The authors reported that women who described a regular and heavy uterine bleeding pattern ($n = 293$) were found to be at no greater risk for late-onset ablation failure than women with an irregular and heavy bleeding pattern ($n = 352$) prior to their procedure.

Hokenstad et al. [82] studied 711 women who underwent either a radiofrequency endometrial ablation (NovaSure; Hologic Inc., Bedford, MA) or thermal balloon EA (Gynecare ThermoChoice; Ethicon, Somerville, NJ). The authors compared outcomes after EA in women with AUB-O ($n = 169$) with women who had AUB-E ($n = 320$), according to the definitions of the PALM-COEIN classification [79], and found that the 5 year cumulative treatment failures were 11.7% (95% CI = 6.5%–16.9%) and 12.3% (95% CI = 8.4%–16.2%) respectively. The authors concluded that EA is effective in women with AUB-O and can be used in women as an alternative to hysterectomy or in patients with contraindications to medical management of AUB-O.

7.8. History of Dysmenorrhea

Reports by Peters et al. [83] and El-Nashar et al. [54] indicate that a history of severe dysmenorrhea is an important predictor of EA failure. Wishall et al. [69] found that a preoperative diagnosis of dysmenorrhea conferred a 74% greater risk of developing postablation pain (adjusted OR 1.74, 95% CI 1.06–2.87; $P = 0.3$) in a group 270 women following a variety of GEA techniques.

7.9. Endometriosis, the Retroverted Uterus and Other Risk Factors

There are surprisingly scarce data on the association between endometriosis and subsequent LOEAF. Although one might expect that endometriosis might be a common finding in women undergoing hysterectomy for cyclic pelvic pain following EA, this has not been reported. Longinotti et al. [4] identified endometriosis in only 51 (7%) of 774 EA failures who underwent subsequent endometriosis. Most reports of hysterectomy subsequent to EA failure rarely mention endometriosis as an intraoperative or histopathologic finding [35,42,45].

A study by Bongers et al. [84] on 130 women treated with a thermal balloon ablation (ThermoChoice; Gynecare, Somerville, NJ) revealed that women with a retroverted uterus had a 3-fold increased risk of LOEAF. Other factors such as a previous cesarean section [83] and obesity [84–86] do not appear to be associated with an increased rate of LOEAF while a history of tobacco use increases the risk of pelvic pain following EA.

8. Treatment Options for Late-Onset Endometrial Ablation Failure

The treatment strategies for LOEAF include a spectrum from simple observation, medical management, reoperative hysteroscopic surgery (RHS) and hysterectomy.

8.1. Observation

Women with a prior history of EA may develop new-onset perimenopausal vaginal bleeding. Cyclic bleeding, which is neither excessive nor associated with significant dysmenorrhea can be safely observed. A baseline ultrasound examination should be performed as it may disclose functioning endometrial tissue, leiomyomas or polyps. The physician is cautioned that blind endometrial biopsies are often misleading and that hysteroscopically-directed biopsies require a moderate level of skill in order to safely complete. AlHilli et al. [87] studied 91 patients who had radiofrequency EA and who underwent subsequent transvaginal ultrasound examinations. Symptomatic patients (69.2%) were significantly more likely than asymptomatic patients to have an endometrial thickness of 3 mm or more, a heterogeneous endometrial echotexture and leiomyomas. The most common finding in all patients was an indistinct endometrial border (83.5%).

8.2. Medical Management

A complete discussion of the medical management of LOEAF is beyond the scope of this article. If one can exclude the presence of significant endometrial or myometrial pathology medical management may be considered in the absence of any contraindication. Unfortunately, women who have undergone EA often demonstrate a poor response to medical management, and/or may find its side effects unacceptable or have developed a contraindication toward its use. Occasionally, the use of gonadotropin-releasing hormone agonists are useful for the temporary relief of pain secondary to obstructed bleeding. However, definitive management of LOEAF typically requires surgical intervention.

8.3. Reoperative Hysteroscopic Surgery (RHS)

Prior to the popularization of global endometrial ablation there were many reports of RHS. In 1992 Gimpelson and Kaigh [88] reported a series of 16 women who underwent repeat EA utilizing either the Nd:YAG laser or electro-surgical techniques and avoided hysterectomy in all subjects during the study period. In a series of 118 women who were offered RHS, Istre and Langebrekke [65] successfully averted hysterectomy in 72% of patients during a mean follow-up of 22 months. Although ultrasound guidance was not used in this series there were no intraoperative complications. Somewhat less encouraging results were obtained by MacLean-Fraser et al. [89] who compared the results of 75 women who underwent a repeat EA with 800 subjects who had a primary ablation by the same surgeon. MacLean-Fraser et al. noted a significant increase in serious perioperative complications—uterine perforation, hemorrhage, excess fluid absorption and genital tract burns—in 9.3% of repeat ablations compared with 2.05% of primary ablations ($p = 0.006$). Hansen et al. [90] reviewed the results of RHS in 65 women who presented with late onset complications related to transcervical resection of the endometrium and provided some of the longest follow-up available with a median of 56 months (range 40–110 months). In all, 57% were able to avoid hysterectomy although several subjects required 2 retreatments. Operative complications occurred in 9% and included excessive fluid absorption and uterine perforation.

In 2001, Wortman and Daggett [37] reported a series of 26 women who underwent ultrasound-guided reoperative hysteroscopic surgery (UGRHS) (Fig. 14) following EA failure and avoided hysterectomy in 88.5% during a mean follow-up of 23.2 months. A second study by the same authors in 2014 [39], included an additional 50 women undergoing UGRHS following GEA failures. The mean duration of follow-up was 18.1 months (95% CI, 13.8–22.4) with hysterectomy successfully avoided in 88.9% of subjects. Of the 76 subjects in the 2 studies, none experienced complications. Between January 1, 2007 and May 15, 2017 we have performed a total of 335 UGRHS by the same surgeon and

Ultrasound-Guided Reoperative Hysteroscopy

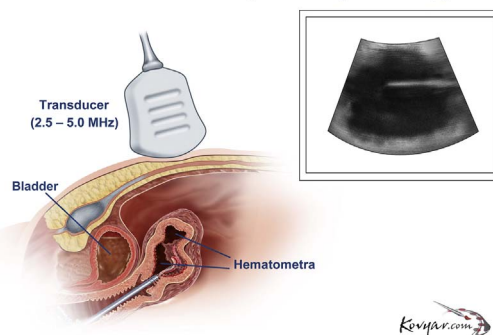


Fig. 14. Ultrasound-Guided Reoperative Hysteroscopic Surgery (UGRHS).

operating room staff and experienced a single intraoperative complication (0.3%)—a uterine perforation requiring a diagnostic laparoscopy to successfully rule out a visceral injury.

The incorporation of ultrasound-guidance into RHS provides numerous benefits. First, it is a minimally invasive approach and obviates the need for hysterectomy in the majority of properly selected candidates. Second, this technique allows for near complete exploration of the uterus and is able to disclose areas of central and cornual hematomata as well as subjacent intramural myomas (Fig. 15) and patches of adenomyosis. Third, UGRHS produces a histologic specimen, which is especially important in the evaluation and management of perimenopausal and postmenopausal women in whom an endometrial biopsy may be either unsuccessful or unreliable. Finally, in experienced hands, the procedure is safe and is associated with a very low rate of immediate postoperative complications. Fig. 16a–h demonstrates the dissection of the left cornua in a woman who presented with left lower quadrant CPP following radiofrequency endometrial ablation.

8.4. Hysterectomy

Hysterectomy is often the only available surgical option for the management of LOEAF. Most communities have not developed the expertise necessary for RHS. Even when RHS is available, other factors often determine the best course for the management of LOEAF. It is worth remembering that many of the factors that guide a physician in recommending RHS or an alternative are the same ones to be considered in recommending EA at the outset.

8.5. Choosing Between Hysterectomy and RHS

There are no well-studied guidelines for discerning whether patients would be better served with RHS or hysterectomy. A number of factors, however, are self-evident.

8.5.1. Age of the Patient

Just as age seems to be an important predictor of EA success it seems

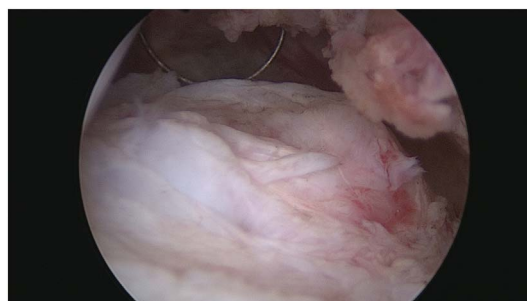


Fig. 15. An intramural leiomyoma is unroofed and removed during the course of UGRHS.

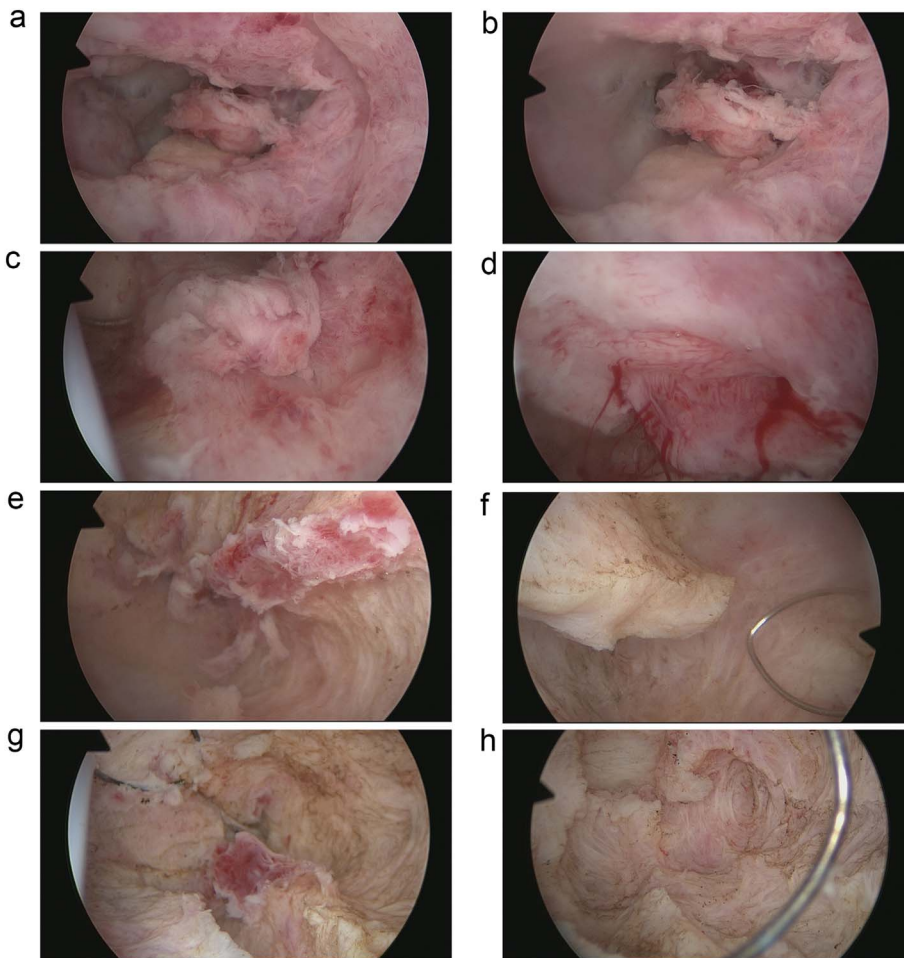


Fig. 16. a – h Dissection sequence of UGRHS in a woman with a cyclic left lower quadrant pain and abundant endometrium at the left cornua.

logical that it would be an important consideration when offering RHS. In general, women who are 45 years or older seem to be the best candidates for RHS and should expect better results.

8.5.2. Duration of the Improvement or the Latent Period

The duration improvement—the latent period—in determining successful outcomes following RHS has not been studied. The author's experience in the last 335 cases of UGRHS includes latent periods that follow REA and GEA procedures that vary from 2 months to 15 years. Women with latent periods of at least 2 years have already demonstrated a good response to EA and often benefit from the removal of small areas of sequestered endometrium. In the author's experience women with very short latent periods are often found to have uteri with one or more elongated dimension, untreated submucous leiomyomas or unrecognized uterine anomalies [39] which preclude adequate EA. These subjects often make excellent candidates for RHS provided that the untreated issue can be adequately resolved. In studying 50 women with GEA failures [39] the author has also observed that 10% of subjects had a nearly normal-appearing uterine cavity at the time of their UGRHS while another 28% had only minimal fibrosis in a cavity with abundant endometrium. These findings suggest that some GEA failures may occur because of a total or partial device failure or an inability of the device to provide proper thermal destruction to the entire endometrial cavity.

8.5.3. Ultrasound Findings

A transvaginal ultrasound examination of the patient being evaluated for LOEAF is essential in advising the best course of treatment for a late-onset complication. If possible, women with CPP should be evaluated while they are symptomatic. The presence and location of

one or more hematomata is often helpful in delineating a patient's symptoms. Ultrasound often discloses hematomata associated with a significant amount of echogenic material which may represent areas of endometrial growth. In other instances large areas of echogenic material are found at the uterine cornua and correspond to the patient's symptoms. Ultrasound may also disclose other reasons for persistent bleeding or pain such as an increased uterine surface area, leiomyomas or endometrial polyps.

8.5.4. Leiomyomas

Leiomyomas are found in nearly a quarter of GEA failures [39]. Carefully selected patients often benefit from hysteroscopic myomectomy as part of their RHS procedure.

8.5.5. Availability of Service

RHS is not commonly performed by most gynecologists. However, experienced hysteroscopists can easily manage women with untreated grade 0 and 1 leiomyomas that are < 3 cm. If the interval between the primary EA and the onset of symptoms is < 6 months, there are generally only a limited number of synechiae [52], and RHS is often no more complex than a primary resectoscopic EA.

8.5.6. Requirement for Ultrasound Guidance

An experienced sonographer offers important intraoperative support and reassurance in the presence of severe adhesions which may otherwise impede visualization and orientation. We have found this an indispensable tool in reducing the incidence of uterine perforation [39] though numerous authors have reported success without the use of sonographic guidance [65,88,91]. Other reports, however, demonstrate a significant increase in operative morbidity [89,90] suggesting that

serious consideration be given to ultrasound guidance whenever RHS is contemplated.

8.5.7. Patient Motivation

A woman who has experienced a LOEAF, particularly one that has produced little symptom relief or has resulted in CPP, is often left with little enthusiasm for anything but a definitive approach toward managing her symptoms. On the other hand women who have enjoyed several years of symptom relief following EA are often highly motivated toward RHS. As always patients must be presented with realistic data with respect to RHS so that they can make informed choices.

8.5.8. Other Factors

Numerous factors may dissuade physicians from considering hysterectomy. Issues such as multiple previous abdominal surgeries, morbid obesity and other comorbid conditions such as diabetes, cardiovascular, pulmonary, hepatic and renal disease may have a significant effect on patient counseling.

8.6. Reoperative Global Endometrial Ablation

There are no reports of repeat GEA procedures following the development of LOEAF though most device manufacturers do not specifically mention a prior endometrial ablation as a contraindication to a GEA procedure. Only the Minerva endometrial ablation system (Redwood City, CA) specifically mentions a previous endometrial ablation or resection as a contraindication toward a repeat endometrial ablation [92]. In general, a history of prior global endometrial ablation should be viewed as a contraindication to another GEA procedure.

9. Prevention of Late-Onset Endometrial Ablation Failure

9.1. Patient Selection

Proper patient selection prior to performing a primary EA procedure is critical in reducing the incidence of LOEAF. Age may be the single most objective predictor of success or failure [4,35,54]. The presence of intrauterine pathology is another important predictor of LOEAF [48,69]. Despite several reports [50,93] on the use of GEA devices for treating submucous leiomyomas these studies are poorly controlled, contain insufficient subjects and lack long term follow-up. Therefore the author suggests that all intrauterine pathology—leiomyomas and polyps—be resected prior to performing endometrial ablation. If feasible this should be accomplished concomitantly.

9.2. Procedure and Device Selection

The presence of a uterine septum or a “T-shaped” uterus should be noted before performing any GEA procedure. The efficacy of the commonly used GEA devices has not been prospectively studied in women with even mild to moderate anatomic variants. These variants may be better treated with REA as this technique, in the author's opinion, is more apt to treat endometrial tissue at the uterine cornua. In addition, GEA devices such as NovaSure are known to function suboptimally when uterine sounding length > 10.5 cm, uterine width > 4.5 cm and endometrial surface area is > 25 cm²[68]. Similar information is not available on the other fixed geometry device on the market—the Minerva Endometrial Ablation System (Redwood City, CA)—nor has it been studied for hydrothermal ablation.

In general physicians should not rely on the FDA registration data when evaluating the array of GEA devices that are available today as long-term comparative data is unavailable. Additionally, most institutions typically limit physician's choices to one or two GEA devices. This requires that physicians understand both the benefits and limitations of the EA devices and techniques that are available to them and consider this information when making patient recommendations.

9.3. The Importance of Informed Consent

In the author's experience in treating well over three-hundred EA failures the single most commonly heard complaint among patients is that they were not adequately informed of either the likelihood of a late-onset EA failure or that it could possibly present with pelvic pain. The importance of discussing both the immediate and delayed complications of EA cannot be overstated. In the presence of amenorrhea many women with pelvic pain are unaware of the possibility of hematometra, PATSS and other causes of pelvic pain.

9.4. Patient Motivation, Expectations and Availability for Follow-Up

The author believes that patient motivation is an important predictor of success. Women who are aware of the immediate and long term risks and benefits of EA appear to derive greater satisfaction from this minimally invasive approach than women who need to be persuaded that EA is the best possible approach toward resolving their particular menstrual disorder. This demands that women have proper expectations preoperatively and that physicians remind their patients, at the time of every subsequent annual examination, to contact them at the earliest signs of abnormal bleeding or unexplained pelvic pain.

9.5. Partial Endometrial Ablation

Partial endometrial ablation (PEA) was developed as a method to reduce the incidence of obstructed bleeding that often follows EA. PEA involves ablation or removal of only the anterior or posterior endometrial surface so that an injured and exposed myometrial surface is opposed by a healthy endometrial surface in order to reduce or eliminate adhesions and contracture of the uterus. In 1999 McCausland et al. [94] published a prospective study of 50 consecutive subjects treated with a rollerball PEA. After a minimum follow-up of 3 years, 76% of subjects were satisfied, 10% were partially satisfied, and 14% were unsatisfied with the results. Thirty-eight (76%) of subjects agreed to undergo diagnostic hysteroscopy and none were found to have intrauterine adhesions, contractures, or hematometra. Although hysterectomy was eventually required in 5 subjects (10%), all were found to have diffuse adenomyosis with penetration > 2.5 mm. There were no cases of CPP caused by obstructed bleeding.

Litta et al. [95] described another PEA technique in which the endomyometrium was resected to a depth of 4–5 mm throughout the uterine cavity but spared the uterine fundus and cornua. Seventy-three women were available for longitudinal analysis and underwent hysteroscopies at 3, 12, 24 and 60 months. The rates of eumenorrhea, hypomenorrhea and amenorrhea were 68.5%, 5.5% and 13.7% respectively. Persistent menorrhagia occurred in 9.6% and another 2.7% reported recurrent AUB. All of these subjects were able to undergo hysteroscopic assessment of the uterine cavity, including the cornua areas and the tubal ostia. None of the subjects reported symptoms of CPP related to obstruction. The authors noted that their modification avoids resection at the portions of the uterus most vulnerable to uterine perforation—the cornua and tubal ostia.

9.6. Combined Endometrial Ablation Procedures

In a study of 200 subjects who underwent a radiofrequency EA (NovaSure, Hologic Inc., Bedford MA) Baskett et al. [96] noted that in 10 cases, additional rollerball ablation was performed because areas of potentially viable endometrium were seen at the post-procedure hysteroscopy. This combined approach utilizing a GEA procedure as well as a conventional resectoscope has not been studied but deserves further consideration.

9.7. Combining Endometrial Ablation (EA) with the Levonorgestrel-Containing Intrauterine Device (LNG-IUD)

Papadakis et al. [97] studied a cohort of 23 women with heavy menstrual bleeding and dysmenorrhea who were treated with a combination of global endometrial ablation and a levonorgestrel-containing intrauterine device (LNG-IUD). These subjects were followed and their results were compared to a group of 65 women who were treated with EA alone. At the end of 4 years none of the women who underwent the combined EA/LNG-IUD procedure required a hysterectomy for treatment failure compared with 16 (24%) in the EA cohort. Vaughan and Byrne [98] studied 105 women with menorrhagia who were treated with one of two thermal balloon ablation systems followed by the insertion of a LNG-IUD. Overall, 96% of their subjects stated that they were satisfied with the treatment; 90.5% considered the treatment to be a “complete success” and 7.6% described it as “partly successful”. Only 2 women (1.9%) described the treatment as a failure. The authors concluded that their study supports the hypothesis that the combined EA/LNG-IUD treatment was an efficacious treatment for menorrhagia and had some distinct advantages compared to either treatment used separately. Sohn et al. [99] compared resectoscopic EA to resectoscopic EA/LNG-IUD and demonstrated that the combination procedure dramatically improved patient satisfaction and clinical outcomes in women with AUB.

Clearly the initial results of these relatively small studies is intriguing but there are at least 3 areas to be emphasized. First, the FDA had not approved the use of a levonorgestrel-containing intrauterine device as an adjunctive therapy to endometrial ablation. Second, there is a very real concern that an intrauterine device placed at the time of endometrial ablation may be entrapped, over time, by scar tissue causing its removal to be challenging if not impossible. Third, the combined EA/LNG-IUD procedure had not been studied in a long-term prospective randomized clinical trial. Nonetheless, the combined use of these modalities is intriguing and deserves additional study.

10. Summary and Conclusions

Since the introduction of GEA devices in 1997 endometrial ablation has been one of the most commonly performed gynecological procedures in the U. S. now surpassing over 500,000 units sold per year [30]. Although late-onset complications of EA have been recognized since Bauman's description in 1948 it was not until resectoscopic techniques became available that the first reports of late-onset complications emerged along with several reports of the hysteroscopic management of this entity [88–91].

Several reports [4,6,35,69] have underscored the regularity with which late-onset EA failures occur. Though it is recognized that as many as 25% [4] of women eventually undergo hysterectomy as a result of these delayed complications it is likely that the number of women who are dissatisfied with their results is greater still as women who complain of persistent bleeding unaccompanied by pain may simply resign their selves to suboptimal outcomes rather than undergo hysterectomy.

Strategies to reduce the need for hysterectomy follow EA must focus on proper patient selection, appropriate device selection, the adoption of UGRHS and the continued search for new EA techniques and devices. In addition, the author strongly recommends that practices which offer EA should develop a protocol for properly monitoring patients who have a history of EA as part of a woman's annual examination.

Appendix

Ancillary information

Ultrasound-guided reoperative hysteroscopic surgery is a technique which allows safe exploration of the uterine cavity following many late-onset endometrial ablation failures. Endometrial growth or regrowth is a common finding, particularly at the uterine cornua. This case illustrates that endometrial growth is often sequestered by intrauterine scarring. The combination of endometrial proliferation, subsequent bleeding and a blocked

Proper patient selection for EA requires a thorough consideration of non-surgical alternatives as well as a complete discussion of the immediate and late-onset complications of EA. While gynecologists routinely inform patients of the intraoperative risks and complications associated with a surgical procedure many are less accustomed to a thorough discussion of complications that may not become evident for years following a procedure. Women need to be especially aware of the association of EA with CPP since, in the absence of vaginal bleeding, acute or cyclic pain may present a confusing diagnostic challenge. Women also need to appreciate those factors that may influence their individualized risk for the development of LOEAF including age [4,64], the presence of submucous/intramural leiomyomas or other intrauterine pathology [49,69,70], increased surface area [68], and anatomic variants of the uterus [39]. Physicians need to carefully assess a woman's motivation to undergo EA and avoid hysterectomy. Women who seek predictable amenorrhea or who are unwilling to accept the possibility of a LOEAF should be discouraged from undergoing EA.

In addition to patient selection physicians must sort through a variety of EA devices and methods in order to select the most suitable approach for a particular patient. Women with symmetrically enlarged uteri may be poorly served with fixed geometry devices such as the radiofrequency ablation devices [68]. Similarly women with a significant uterine septum or with a “T-shaped” uterus are likely poor candidates for radiofrequency ablation procedures as they often fail to adequately treat the uterine cornua [39].

Reoperative Hysteroscopic Surgery has been shown to reduce the need for subsequent hysterectomy [88–91] but was more commonly performed in the era prior to the introduction of GEA devices. One of the unintended consequences of GEA device popularity seems to be a steady erosion of resectoscopic skills. Despite the proven success of RHS in reducing the need for hysterectomy following a LOEAF there seems to be little interest in fellowship training to foster the development of advanced hysteroscopic surgery under sonographic guidance.

The reduction of LOEAF will also be dependent on developing newer technologies. Presently the GEA market is dominated by fixed geometry radiofrequency ablation devices. Manufacturers will need to consider whether their devices can be modified to produce partial endometrial ablation procedures which may be more appropriate to women at increased risk for the development of LOEAF.

Finally, specialty groups such as ACOG and the American Association of Gynecologic Laparoscopists (AAGL) need to develop protocols that address the issue of standards for patient follow-up subsequent to endometrial ablation. In 1991 McLucas [100] suggested that women who underwent EA “should be encouraged to undergo a baseline ultrasound three months after ablation and then annually as part of their health maintenance.” Indeed this has been the author's (MW) practice ever since and has allowed the detection of asymptomatic areas of endometrial regrowth and hematomata. Women are reminded, as part of their annual examination to report symptoms such as a change in their menstrual pattern or new-onset pelvic pain. Whether or not annual ultrasound examinations are cost-effective and worthwhile needs to be studied. However, an annual reminder of the signs and symptoms of LOEAF is inexpensive and often helps to reduce anxiety for women who experience symptoms.

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“outflow” path often causes episodes of severe cyclic pelvic pain lasting days to weeks. Careful hysteroscopic resection of endometrial remnants is often successful in providing long term symptom relief. The following slide show illustrates the findings in a woman who underwent a commonly used GEA procedure and later developed cyclic pelvic pain (CPP).

Case presentation

The patient is a 46 year old para 2 who underwent a radiofrequency endometrial ablation (NovaSure, Hologic Inc., Bedford MA) in July 2016. In the months following her procedure she reported little improvement of her menorrhagia but began noticing some slight worsening of her menstrual cramps. In February 2017 she became amenorrheic and developed severe “labor like” suprapubic and left lower quadrant pain that lasted 2 full days. Similar episodes of pain occurred in March and April of 2017 which prompted her to contact our office.

Her initial evaluation included a transvaginal ultrasound examination which revealed echogenic changes throughout the central uterine axis and extending into both uterine cornua. The patient was asymptomatic at the time of her evaluation and there was no evidence of a hematometra.

On June 14, 2017 she was taken to our office-based surgical suite and underwent a reoperative hysteroscopic surgery (RHS) under sonographic guidance. Her cervix had been prepped by the insertion of a laminaria japonica on June 13th. Prior to the laminaria placement the cervix was dilated under ultrasound guidance to 4 mm—severe cervical stenosis was noted. The entire procedure was carried out with the adjuvant use of parenterally administered midazolam and fentanyl.

This case is representative of many ablation failures and demonstrates copious endometrial growth in both uterine cornua.



Fig. A1. The posterior distal lower segment has been removed enabling the continuous flow of distention fluid. The resectoscope, at this point, is just beyond the internal cervical os.



Fig. A2. Visualization of the left hemi-uterus.



Fig. A3. The right lateral wall has been removed in order to facilitate distention of the uterine cavity. Endometrial growth is seen along the left cornual region as well as the uterine fundus.

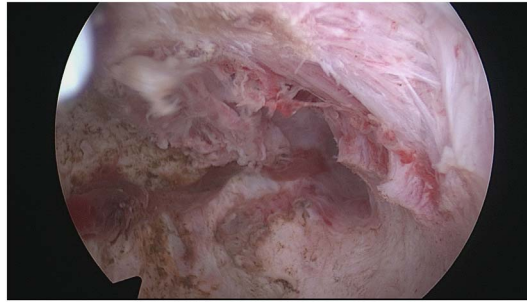


Fig. A4. Close-up of left cornua.



Fig. A5. In this view we can appreciate that the left cornua is quite deeply recessed. This suggests that there may have been a uterine septum at the outset.



Fig. A6. In addition to an excellent view of the left cornua, and some remaining endometrium, the patient's right side reveals some evidence of adenomyosis as endometrium is interlaced with myometrial tissue.



Fig. A7. This is a panoramic view of the uterine fundus in the midline after much of the left cornua has been resected. Note some hemosiderin stained tissue at the patient's right and some adenomyosis at the fundus in the center.



Fig. A8. After exploring the hemosiderin stained tissue to the right of midline some addition endometrium appears to have been uncovered.



Fig. A9. Further exploration of the right side is performed and an area of sequestration is noted toward the right cornua. At first glance this appears to be a uterine perforation. However, sonographic guidance reassures us at all times.



Fig. A10. Greater detail of the right cornua with abundant endometrial growth.

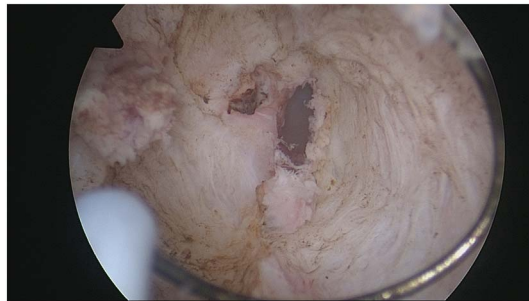


Fig. A11. Return to left cornua for inspection.



Fig. A12. Further dissection into left cornua reveals additional endometrial elements. Simultaneous ultrasound guidance reveals that the sero-muscular thickness at the left cornua is 4 mm.



Fig. A13. Return to inspect right cornua. No evidence of endometrial growth.

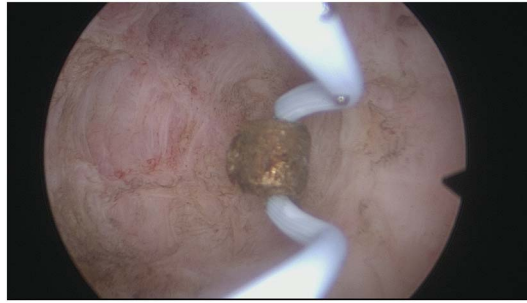


Fig. A14. Deep coagulation of the right cornua with a roller barrel electrode at 120 watts.



Fig. A15. Deep coagulation of remaining endometrial elements at the left cornua.



Fig. A16. Panoramic view of left cornua.

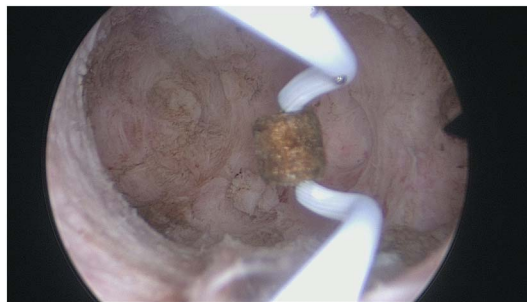


Fig. A17. Panoramic view of right cornua.

References

- [1] Leape LL, Bernstein SJ, Bohon CJ, Dickerson VM, Ling FW, Shiffman RN, Kanouse DE. Hysterectomy: Clinical Recommendations and Indications for Use. Southern California Health Policy Research Consortium. RAND.
- [2] J.D. Wright, T.J. Herzog, J. Tsui, C.V. Ananth, S.N. Lewin, Y.S. Lu, A.I. Neugut, D.L. Hershman, Nationwide trends in the performance of inpatient hysterectomy in the United States, *Obstet. Gynecol.* 122 (2013) 233–241.
- [3] M.G. Munro, ACOG practice bulletin: endometrial ablation, *Obstet. Gynecol.* 109 (2007) 1233–1247.
- [4] M.K. Longinotti, G.F. Jacobson, Y.Y. Hung, L.A. Learman, Probability of hysterectomy after endometrial ablation, *Obstet. Gynecol.* 112 (2008) 1214–1220.
- [5] J.T. Sharp, Endometrial ablation: postoperative complications, *Am. J. Obstet. Gynecol.* 207 (2012) 242–247.
- [6] A.M. McCausland, V.M. McCausland, Long-term complications of endometrial ablation: cause, diagnosis, treatment and prevention, *J. Minim. Invasive Gynecol.* (2007) 399–406.
- [7] Dührssen, Steam in the Treatment of Uterine Hemorrhage, No. 36 *Berliner klin. Wochenschrift*, 1898.
- [8] N.N. Massarweh, N. Cosgriff, D.P. Slakey, Electrosurgery: history, principles and current and future uses, *J. Am. Coll. Surg.* 202 (2006) 520–530.
- [9] F.H. Bardenheuer, Elextrokoagulation der Uterusschleimhaut zur behandlung klimakterischer blutungen, *Zbl. Gynakol.* 4 (1937) 209–211.
- [10] A. Baumann, Electrocoagulation of endometrium and cervical mucosa (for uterine hemorrhage and leukorrhea), [in German], *Geburtshilfe Frauenheilkd.* 8 (1948) 221–226.
- [11] H. Schmitz, Radium in gynecology, *Radium* 9 (1) (1917) 8–12.
- [12] W.H.B. Aikins, The value of radium in curing disease, in prolonging life, and in alleviating distressing symptoms, *Canadian Practitioner and Review*, 1919 ISBN 0665759800. Toronto CA.
- [13] M. Schulze, Menorrhagia: the results of radium treatment—a follow-up study, *Cal. West Med.* 47 (1937) 101–106.
- [14] W. Cahan, A. Brockunier, Cryosurgery of the uterine cavity, *Am. J. Obstet. Gynecol.*

- 99 (1967) 138–153.
- [15] W. Droegemueller, B. Greer, E. Makowski, Cryosurgery in patients with dysfunctional bleeding, *Obstet. Gynecol.* 38 (1971) 256–258.
- [16] M.H. Goldrath, T.A. Fuller, S. Segal, Laser photovaporization of the endometrium for treatment of menorrhagia, *Am. J. Obstet. Gynecol.* 140 (1981) 14–19.
- [17] A. DeCherney, M.L. Polan, Hysteroscopic management of intrauterine lesions and intractable uterine bleeding, *Obstet. Gynecol.* 61 (1983) 392–397.
- [18] J.J. Iglesias, A. Sporer, A.C. Gellman, J.J. Seebode, New Iglesias resectoscope with continuous irrigation, simultaneous suction and low intravesical pressure, *J. Urol.* 114 (1975) 929–933.
- [19] P.G. Brooks, F.D. Loeffler, S.P. Serden, Resectoscopic removal of symptomatic intrauterine lesions, *J. Reprod. Med.* 34 (1989) 435–437.
- [20] T.G. Vancaillie, Electrocoagulation of the endometrium with the ball-end resectoscope, *Obstet. Gynecol.* 74 (1989) 425–427.
- [21] D.E. Townsend, R.M. Richart, R.A. Paskowitz, R.E. Woolfork, “Rollerball” coagulation of the endometrium, *Obstet. Gynecol.* 76 (1990) 310–313.
- [22] A.I. Arieff, J.C. Ayus, Endometrial ablation complicated by fatal hyponatremic encephalopathy, *JAMA* 370 (1993) 1230–1232.
- [23] M.S. Baggish, A.I. Brill, Barbot J.I. Rosensweig, P.D. Indman, Fatal acute glycine and sorbitol toxicity during operative hysteroscopy, *J. Gynecol. Surg.* 9 (2009) 137–143.
- [24] J.P. Daniels, The long-term outcomes of endometrial ablation in the treatment of heavy menstrual bleeding, *Curr. Opin. Obstet. Gynecol.* 25 (2013) 320–326.
- [25] L.R. Glazerman, Endometrial ablation as treatment of heavy menstrual bleeding, *Surg. Technol. Int.* 23 (2013) 137–141.
- [26] M.H. Glasser, P.K. Heinlein, Y.Y. Hung, Office endometrial ablation with local anesthesia using the HydroThermAblator system: comparison of outcomes in patients with submucous myomas with those with normal cavities in 246 cases performed over 5½ years, *J. Minim. Invasive Gynecol.* 16 (2009) 700–707.
- [27] R.K. Kalkat, R.S. Cartmill, NovaSure endometrial ablation under local anesthesia in an outpatient setting: an observational study, *J. Obstet. Gynaecol.* 31 (2011) 152–155.
- [28] <http://investors.hologic.com/index.php?s=43&item=420>. Queried May 27, 2017.
- [29] U. S. benign uterine conditions therapy systems market. Report #A470. Bedminster, NJ: Elsevier Business Intelligence. Exhibit 1-3 Page 1-14.
- [30] Endometrial Ablation Market: Global Industry Analysis, Size, Share, Growth, Trends and Forecast, 2016–2024, Transparency Market Research, Ltd, February 2017.
- [31] P.M. Parker, The 2018–23 World Outlook for Endometrial Ablation Devices, ICON Group International, Inc., Las Vegas, NV, 2017.
- [32] M.K. Whiteman, S.D. Hillis, D.J. Jamieson, B. Morrow, et al., Inpatient hysterectomy surveillance in the United States 2000–2004, *J. Obstet. Gynecol.* 198 (1) (2008) e1–34.e7.
- [33] O. Taskin, A. Onoglu, M. Inal, et al., Long-term histopathologic and morphologic changes after thermal endometrial ablation, *J. Am. Assoc. Gynecol. Laparosc.* 9 (2002) 186–190.
- [34] A. Onoglu, O. Taskin, M. Inal, et al., Comparison of the long-term histopathologic and morphologic changes after endometrial rollerball ablation and resection: a prospective randomized trial, *J. Minim. Invasive Gynecol.* 14 (2007) 39–42.
- [35] V.I. Shavell, M.P. Diamond, J.P. Senter, M.L. Johns, Hysterectomy subsequent to endometrial ablation, *J. Minim. Invasive Gynecol.* 19 (2012) 459–464.
- [36] G.A. Vilos, B. Abu-Rafea, H.C. Eder, R. Ahmad, Indications for hysterectomy and uterine histopathology following hysteroscopic endometrial ablation, *J. Minim. Invasive Gynecol.* 12 (2005) 59.
- [37] M. Wortman, A. Daggett, Reoperative hysteroscopic surgery in the management of patients who fail endometrial ablation and resection, *J. Am. Assoc. Gynecol. Laparosc.* 8 (2001) 272–277.
- [38] S.J. Ahonkallio, A.K. Liakka, H.K. Martinkainen, et al., Feasibility of endometrial assessment after thermal ablation, *Eur. J. Obstet. Gynecol. Reprod. Biol.* 147 (2009) 69–71.
- [39] M. Wortman, A. Daggett, A. Deckman, Ultrasound-guided reoperative hysteroscopy for managing global endometrial ablation failures, *J. Minim. Invasive Gynecol.* 21 (2014) 238–244.
- [40] A. Lethaby, J. Penninx, M. Hickey, R. Garry, et al., Endometrial resection and ablation techniques for heavy menstrual bleeding, *Cochrane Database Syst. Rev.* 8 (20) (2013) (Cochrane Collaboration. John Wiley & Sons, Ltd.).
- [41] F. Tresserra, P. Grasers, A. Ubeda, M.A. Pascual, Morphological changes in hysterectomies after endometrial ablation, *Hum. Reprod.* 14 (1999) 1473–1477.
- [42] R.A. Simon, M.R. Quddus, W.D. Lawrence, C.J. Sung, Pathology of endometrial ablation failures: a clinicopathologic study of 164 cases, *Int. J. Gynecol. Pathol.* 34 (2015) 245–252.
- [43] J.R. Lisa, J.D. Gioia, I.C. Rubin, Observations of the interstitial portion of the fallopian tube, *Surg Gynecol Obstet* 92 (1954) 159–169.
- [44] L.W. Turnbull, S.J. Bowsley, A. Horsman, Magnetic resonance imaging of the uterus after endometrial resection, *Br. J. Obstet. Gynaecol.* 104 (1997) 934–938.
- [45] Riley KA, Davies MF, Harkins GJ. Characteristics of patients undergoing hysterectomy for failed endometrial ablation. *JSLs*. 1013; 17:503–7.
- [46] J.D. Seidman, K.H. Kjerulf, Pathologic findings from the Maryland Women's Health Study: practice patterns in the diagnosis of adenomyosis, *Int. J. Gynecol. Pathol.* 15 (1996) 217–221.
- [47] A.M. McCausland, V.M. McCausland, Depth of endometrial penetration in adenomyosis helps determine outcome of rollerball ablation, *Am. J. Obstet. Gynecol.* 174 (1996) 1793–1794.
- [48] M. Wortman, A. Daggett, Hysteroscopic endomyometrial resection, *JSLs* 4 (2000) 197–207.
- [49] O. Gemer, J. Kruchkovich, M. Huerta, V. Kapustian, et al., Perioperative predictors of successful hysteroscopic endometrial ablation, *Gynecol. Obstet. Invest.* 63 (2007) 205–208.
- [50] E. Hachmann-Nielsen, M. Rudnicki, Clinical outcome after hydrothermal ablation treatment of menorrhagia in patients with and without submucous myomas, *J. Minim. Invasive Gynecol.* 19 (2012) 212–216.
- [51] A. Magos, R. Baumann, G.M. Lockwood, A.C. Turnbull, Experience with the first 250 endometrial resections for menorrhagia, *Lancet* 337 (1991) 1074–1080.
- [52] M.R. Hopkins, D.J. Creedon, Radiofrequency global endometrial ablation followed by hysteroscopic sterilization, *J. Minim. Invasive Gynecol.* 104 (2007) 934–938.
- [53] D.E. Townsend, V. McCausland, A. McCausland, G. Fields, K. Kauffman, Post-ablation tubal sterilization syndrome, *Obstet. Gynecol.* 82 (1993) 422–424.
- [54] S.A. El-Nashar, M.R. Hopkins, D.J. Creedon, et al., Prediction of treatment outcomes after global endometrial ablation, *Obstet. Gynecol.* 113 (2009) 97–106.
- [55] A.B. Copperman, A.H. DeCherney, D.L. Olive, A case of endometrial cancer following endometrial ablation for dysfunctional uterine bleeding, *Obstet. Gynecol.* 82 (1993) 640–642.
- [56] M.T. Margolis, L.D. Thoen, G.M. Boike, L.J. Mercer, L.G. Keith, Asymptomatic endometrial carcinoma after endometrial ablation, *Int. J. Gynecol. Obstet.* 51 (1995) 255–258.
- [57] M.M. AlHilli, M.R. Hopkins, A.O. Famuyide, Endometrial cancer after endometrial ablation: systematic review of the medical literature, *J. Minim. Invasive Gynecol.* 18 (2011) 394–400.
- [58] M. Wortman, J.C. Dawkins, Post-ablation Endometrial Carcinoma (PAEC) following radiofrequency endometrial ablation: a case report and its implications for management of endometrial ablation failures, *Surg. Technol. Int.* XXIX (2016) 161–166.
- [59] M. Wortman, G.A. Vilos, A.G. Vilos, A. Abu-Rafea, W.A. Dwyer, et al., Post-ablation endometrial carcinoma: additional case reports and literature review, *JSLs* (2017) (In Print).
- [60] R.S. Neuwirth, F.D. Loffer, T. Trenhaile, et al., The incidence of endometrial cancer after endometrial ablation in a low-risk population, *J. Am. Assoc. Gynecol. Laparosc.* 11 (2004) 492–494.
- [61] <http://seer.cancer.gov/statfacts/html/corp.html>. Queried May 28, 2017.
- [62] R.A. Krogh, F.F. Lauszus, E. Guttorm, K. Rasmussen, Surgery and cancer after endometrial resection. Long-term follow-up on menstrual bleeding and hormone treatment by questionnaire and registry, *Arch. Gynecol. Obstet.* 280 (2009) 911–916.
- [63] M. Singh, M.M. Hosni, S.E. Jones, Is endometrial ablation protective against endometrial cancer? A retrospective observational study, *Arch. Gynecol. Obstet.* 293 (2016) 1033–1037.
- [64] C. Dutton, L. Ackerson, B. Phelps-Sandall, Outcomes after rollerball endometrial ablation for menorrhagia, *Obstet. Gynecol.* 98 (2001) 35–39.
- [65] O. Istre, A. Langebrenne, Repeat hysteroscopic surgery reduces hysterectomy rate after endometrial and myoma resection, *J. Am. Assoc. Gynecol. Laparosc.* 10 (2003) 247–251.
- [66] R. Comino, R. Torrejon, Hysterectomy after endometrial ablation-resection, *J. Am. Assoc. Gynecol. Laparosc.* 11 (2004) 495–499.
- [67] S.E. Kreider, R. Starcher, J. Hoppe, K. Nelson, et al., Endometrial ablation: is tubal ligation a risk factor for hysterectomy? *J. Minim. Invasive Gynecol.* 209 (2013) 611–619.
- [68] S.A. Shazly, A.O. Famuyide, S.A. El-Nashar, D.M. Breitkmoep, et al., Intraoperative predictors of long-term outcomes after radiofrequency endometrial ablation, *J. Minim. Invasive Gynecol.* 23 (2016) 582–589.
- [69] K.M. Wishall, J. Price, N. Pereira, S.M. Butts, et al., Postablation risk factors for pain and subsequent hysterectomy, *Obstet. Gynecol.* 124 (2014) 904–910.
- [70] M.I. Shamonski, W.F. Ziegler, G.J. Badger, C.K. Sites, Prediction of endometrial ablation success by preoperative findings, *Am. J. Obstet. Gynecol.* 182 (2000) 1005–1007.
- [71] G. Phillips, P.F. Chien, R. Garry, Risk of hysterectomy after 1000 consecutive endometrial laser ablations, *Br. J. Obstet. Gynaecol.* 105 (1998) 897–903.
- [72] M.H. Glasser, J.D. Zimmerman, The HydroThermAblator system for management of menorrhagia in women with submucous myomas: 12- to 20- month follow-up, *J. Am. Assoc. Gynecol. Laparosc.* 10 (2003) 521–527.
- [73] H. Skensved, Combining paracervical block with a complete fundal block significantly reduces patient's perception of pain during radio-frequency endometrial ablation in an office setting, *J. Minim. Invasive Gynecol.* 22 (2015) S45.
- [74] H.O. Chapa, G. Venegas, A.G. Antonetti, C.P. Van Duyne, et al., In-office endometrial ablation using a third-generation uterine balloon therapy system: 12-month prospective follow-up on menstrual patterns and dysmenorrhea impact, *J. Reprod. Med.* 54 (2009) 678–684.
- [75] H.O. Chapa, G. Venegas, Suvunrungrs L. VanDuyne, In-office thermochoice III ablation: a comparison of two anesthetic techniques, *Gynecol. Obstet. Investig.* 69 (2010) 140–144.
- [76] J.P. Penninx, M.C. Herman, R.F. Kruitwager, A.J. Ter Haar, et al., Bipolar versus balloon endometrial ablation in the office: a randomized controlled trial, *Eur. J. Obstet. Gynecol. Reprod. Biol.* 196 (2016) 52–56.
- [77] <http://novasure.com/hcp/proven-outcomes?glid=CIG5y7CA39MCFYOPswodQg8P1g> (07 May 2017). Queried 5/7/17.
- [78] <http://minervasurgical.com/patient-site/minerva-endometrial-ablation-system/> (07 May 2017). Queried 5/7/17.
- [79] M.G. Munro, H.O. Critchley, M.S. Broder, I.S. Fraser, FIGO, Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age, *Int. J. Gynaecol. Obstet.* 113 (2011) 3–13.
- [80] Committee on Practice Bulletins, Gynecology. Practice bulletin no. 136: management of abnormal uterine bleeding associated with ovulatory dysfunction, *Obstet. Gynecol.* 122 (2013) 176–185.

- [81] K.R. Smithling, G. Savella, C. Baker, K.A. Matteson, Preoperative uterine bleeding pattern and risk of endometrial ablation failure, *Am. J. Obstet. Gynecol.* 211 (556) (2014) (E1-6).
- [82] A.N. Hokenstad, S.A. El-Nashar, Z. Khan, M.R. Hopkins, et al., Endometrial ablation in women with abnormal uterine bleeding related to ovulatory dysfunction: a cohort study, *J. Minim. Invasive Gynecol.* 22 (2015) 1225–1230.
- [83] J.A. Peeters, J.P. Penninx, B.W. Mol, M.Y. Bongers, Prognostic factors for success of endometrial ablation in the treatment of menorrhagia with special reference to previous cesarean section, *Eur. J. Obstet. Gynecol. Reprod. Biol.* 167 (2013) 100–103.
- [84] M.Y. Bongers, B.W. Mol, H.A. Brolmann, Prognostic factors for the success of thermal balloon ablation in the treatment of menorrhagia, *Obstet. Gynecol.* 99 (2002) 1060–1066.
- [85] A.M. Madsen, S.A. El-Nashar, M.R. Hopkins, Z. Khan, et al., Endometrial ablation for the treatment of heavy menstrual bleeding in obese women, *Int. J. Gynaecol. Obstet.* 121 (2013) 20–23.
- [86] M.S. Thomassee, H. Curlin, A. Yunker, T.L. Anderson, Predicting pelvic pain after endometrial ablation: which preoperative patient characteristics are association? *J. Minim. Invasive Gynecol.* 20 (2013) 642–647.
- [87] M.M. AlHilli, D.J. Wall, D.L. Brown, A.L. Weaver, et al., Uterine ultrasound findings after radiofrequency endometrial ablation: correlation with symptoms, *Ultrasound Q.* 28 (2012) 261–268.
- [88] R.J. Gimpelson, J. Kaigh, Endometrial ablation repeat procedures. Case studies, *J. Reprod. Med.* 37 (1992) 629–635.
- [89] E. MacLean-Fraser, D. Penava, G.A. Vilos, Perioperative complication rates of primary and repeat hysteroscopic endometrial ablations, *J. Am. Assoc. Gynecol. Laparosc.* 9 (2002) 175–177.
- [90] B.B. Hansen, E. Dreisler, S.S. Sorensen, Outcome of repeated hysteroscopic resection of the endometrium, *J. Minim. Invasive Gynecol.* 15 (2008) 704–706.
- [91] R. Garry, D. Shelley-Jones, P.L. Mooney, G. Phillips, Six hundred endometrial laser ablation, *Obstet. Gynecol.* 85 (1995) 24–29.
- [92] https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140013c.pdf. Queried 5/15/17.
- [93] R. Sabbah, G. Desaulniers, Use of the NovaSure Impedance Controlled Endometrial Ablation System in patients with intracavitary disease: 12-month follow-up results of a prospective, single-arm clinical study, *J. Minim. Invasive Gynecol.* 13 (2006) 457–471.
- [94] A.M. McCausland, V.M. McCausland, Partial rollerball endometrial ablation: a modification of total ablation to treat menorrhagia without causing complications from intrauterine adhesions, *Am. J. Obstet. Gynecol.* 180 (1999) 1512–1521.
- [95] P. Litta, L. Nappi, P. Flori, L. Mencaglia, et al., Proposal of a modified transcervical endometrial resection (TCER) technique for menorrhagia treatment. Feasibility, efficacy and patient's acceptability, *Gynecol. Surg.* 11 (2014) 165–171.
- [96] T.F. Baskett, H. Cough, T. Scott, NovaSure bipolar radiofrequency endometrial ablation: report of 200 cases, *J. Obstet. Gynaecol. Can.* 27 (2005) 473–476.
- [97] E.P. Papadakis, S.A. El-Nashar, S.K. Laughlin-Tommaso, S.A. Shazly, M.R. Hopkins, D.M. Breikopt, A.O. Famuyide, Combined endometrial ablation and levonorgestrel intrauterine system use in women with dysmenorrhea and heavy menstrual bleeding: novel approach for challenging cases, *J. Minim. Invasive Gynecol.* (2015) 1203–1207.
- [98] D. Vaughan, P. Byrne, An evaluation of the simultaneous use of the levonorgestrel-releasing intrauterine device (LNG-IUD, Mirena®) combined with endometrial ablation in the management of menorrhagia, *J. Obstet. Gynaecol.* 32 (2012) 372–374.
- [99] B. Sohn, G.A. Vilos, A.G. Vilos, A. Ternamian, B. Abu-Rafea, A. Oraif, Resectoscopic rollerball endometrial ablation and concomitant levonorgestrel-releasing intrauterine system in women with abnormal bleeding: is the combination better? *J. Minim. Invasive Gynecol.* 20 (2013) S69.
- [100] B. McLucas, Intrauterine applications of the resectoscope, *Surg. Gynecol. Obstet.* 172 (1991) 425–431.