Medical historical notes on myoma treatment by uterine artery embolization on the occasion of its introduction 30 years ago

Medizinhistorische Anmerkungen zur Myombehandlung mittels Uterusarterienembolisation aus Anlass ihrer Einführung vor 30 Jahren

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Key words
uterus, embolization, leiomyoma

ABSTRACT
Background Since its development, uterine artery embolization (UAE) for the treatment of symptomatic fibroids has become an established minimally invasive alternative to surgical myoma treatment. Currently, more than 25,000 myoma patients worldwide are likely to be treated with UAE annually.
Method Thirty years ago, Jacques-Henri Ravina (b. 1930) and his Paris team first performed this therapy as a “substitute” for gynecologic surgery. We contacted him as part of the preparation of the present review. In addition, we performed a literature search with the aim of summarizing the current literature and data in addition to a historical account of the development of UAE.

Results and Conclusion On the occasion of this anniversary, we would like to recall the interdisciplinary roots and some facets of the history of the development of this relatively young myoma treatment method.

Key points
1. UAE is an established minimally invasive alternative to surgical myoma treatment.
2. UAE was first developed 30 years ago.
3. UAE has continuously increased in importance in recent years.

Citation Format
Psilopatis I, Fleckenstein FN, Gebauer B et al. Medical historical notes on myoma treatment by uterine artery embolization on the occasion of its introduction 30 years ago. Fortschr Röntgenstr 2023; DOI 10.1055/a-2077-1387

ZUSAMMENFASSUNG
Hintergrund Die Uterusarterienembolisation (UAE) zur Behandlung symptomatischer Myome hat sich seit ihrer Entwicklung zu einer etablierten minimalinvasiven Alternative zur operativen Myombehandlung entwickelt. Derzeit werden weltweit jährlich wahrscheinlich mehr als 25.000 Myompatientinnen mit einer UAE behandelt.

Ergebnisse und Schlussfolgerung Aus Anlass dieses Jubiläums möchten wir an die interdisziplinären Wurzeln und an einige Facetten der Entstehungsgeschichte dieser relativ jungen Myombehandlungs methode erinnern.
The early years of embolization

In the early 1970s, embolization was primarily used to treat acute (gastrointestinal) bleeding [1]. Over time, the indications were expanded to include hemoptysis, arteriovenous fistulas, arteriovenous malformations, gastroesophageal varices, varicocele, and treatment of tumors [2]. Initially, muscle fragments, metal balls, and autologous blood clots were used for embolization. In 1964, Speakman reported for the first time on the use of gelatin as an embolic agent [3]. In 1974, Tadavarthy reported on the use of polyvinyl alcohol (PVA) as embolization particles [4]. Other embolization materials, like detachable microballoons (Serbinenko, 1969) and coils (Gianturco, 1975), were also used at this time.

UAE – from a palliative treatment to a definitive treatment option for uterine fibroids

Transarterial embolization found its way into gynecology in the 1970s, particularly for the treatment of life-threatening gynecological tumor bleeding [5] and in obstetrics to treat life-threatening postpartum hemorrhages in uterine atony, placenta accreta, or complicated injuries of the birth canal with significant bleeding [6, 7].

In 1974, the French neuroradiologist Jean-Jacques Merland (born 1942) conducted the first successful UAE to treat treatment-refractory metrorrhagia in a patient with fibroids in whom surgical treatment was not possible [8]. This remained the only published report of this method for more than a decade.

In 1989, Merland and the French gynecologist Nicole Ciraru-Vigneron (born 1944) began collaborating at the “Lariboisière” hospital in Paris to further evaluate the UAE method. The French gynecologist Jacques-Henri Ravina [9] subsequently joined these efforts and his publications are considered pioneering works in the field of fibroid embolization. These gynecologists referred their fibroid patients to their colleagues in interventional radiology for preoperative bilateral UAE with the goal of minimizing perioperative blood loss and avoiding blood transfusions [10]. According to Ravina: “We originally did this just to stop uterine bleeding in women with an elevated surgical risk, e.g., in women with extreme obesity, high blood pressure, vascular injuries, thromboembolisms, and HIV infections.” [11].

In the year 1994, Ravina and his team published results of a case series of patients who underwent preoperative UAE [12]. Emmanuel Houdart (born 1961), one of the coauthors of this article and current head physician of the neuroradiology department of the “Lariboisière” hospital in Paris described the situation as follows: “Jean-Jacques Merland had the idea to use embolization to treat symptomatic fibroids that were not considered good candidates for surgery. He discovered that this could effectively stop uterine bleeding. Initially the method was only used in isolated cases. At the end of the 1980s, Professor Ravina took an interest in the idea and suggested making a small case series. At this time, Professor Ravina was no longer performing surgeries and was open to the introduction of a new technique, which, in my opinion, made it possible for this treatment method to develop. The requirements for new methods were also more flexible than today.” (personal message dated 4/11/2022).

In 1995, the article “Arterial embolisation to treat uterine myomata” was published by the same group in the “The Lancet” [13]. This publication is considered groundbreaking. Since October 1993, Ravina and his team have used UAE not only preoperatively but also as an efficient alternative to surgical fibroid treatment and as a “conservative surgical treatment of fibroids with minimal blood loss” [11]. “As a result of the rules of the French health care system, embolization in the women in his series was often performed multiple days or even weeks prior to the planned surgery. Some of these women contacted Dr. Ravina and refused the operation because they felt that embolization alone had improved their symptoms of menorrhagia and/or pressure”, according to American radiologist Robert Worthington-Kirsch (born 1960) [14]. In a personal message, Prof. Ravina referenced the foreword he wrote for a textbook about the value of interventional radiology in gynecology and obstetrics. He summarizes the development of UAE for symptomatic fibroids as follows: “When I performed surgery in these cases, I became aware of the uselessness of the surgical intervention. That was a shock. Why would you remove an inactive fibroid if embolization had already had a curative effect? [...] Only very few gynecologists were interested in this topic. They were not prepared for this new method and were very satisfied with their surgeries – they did not listen to their patients’ wishes regarding preservation of the uterus. [...] The first team that contacted us was that of John Reidy and Robert Forman from Guy’s Hospital that was working on a similar research project.” [15].

In 1995, the American gynecologist Bruce McLucas (born 1945) met Ravina at a conference in Paris and was introduced to the UAE concept. After his return to the University of California Los Angeles (UCLA), he and the interventional radiologist Scott Goodwin (born 1958) began offering UAE as a primary treatment for fibroids [14]. These initial experiences resulted in global interest in UAE as a treatment alternative for uterine fibroids.

The first reviews were published in 1998 and 1999 [16, 17]. The 80 fibroid patients successfully embolized by 1998 by Ravina et al., the 140 patients treated with UAE by the American team at UCLA, and the 88 patients treated by the British Royal Surrey County Hospital (RSCH) constituted the most comprehensive patient populations at the time [16].

In 1999, the Royal College of Obstetricians and Gynaecologists and the Royal College of Radiologists published their clinical recommendations for the use of UAE for the treatment of fibroids [18]. In the same year, the American Society of Cardiovascular & Interventional Radiology defined the training standards for performing fibroid embolization [19].

In 2002, Spies et al. published their now widely used “Uterine Fibroid Symptom and Quality of Life” (UFS-QoL) patient questionnaire [20].

The development of UAE in Germany

The “initial spark” for UAE was at the annual meeting of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) in 1999 [21]. In Heidelberg as well as Aachen and other hospitals in the Ruhr region, the method was introduced in the same year. The first workshops were held at the University Hospital Heidelberg
as early as 2001. In 2002, the first intensive, public discussion between expert radiologists and gynecologists about UAE was held in Germany after the publication of three reviews in German journals [22–24].

In 2003, survey results regarding the value of UAE at German hospitals was published: Of the 164 contacted German departments and clinics for gynecology or radiology, 33 radiology departments and 19 gynecology departments responded: Seven radiology departments reported on their own experiences with this method and two gynecology departments stated that they refer symptomatic fibroid patients to radiology for possible embolization [25].

In 2004, Richter et al. published the results of a closed prospective study including 20 patients on UAE using spherical embolization particles with a minimum duration of 12 months. This pilot study was the first UAE study, was published in the German journal “RöFo – Fortschritte auf dem Gebiet der Röntgenstrahlen und der bildgebenden Verfahren”, and reported high therapeutic efficacy and satisfaction on the part of patients after flow-guided embolization with spherical particles (under controlled study conditions) [26].

In October 2005, the interventional radiologists and gynecologists of the Charité Berlin initiated the first radiology-gynecology consensus meeting on UAE with the goal of “compiling the current knowledge regarding the fibroid embolization treatment option and to provide recommendations regarding indication, performance, and after care from an interdisciplinary, radiological-gynecological standpoint” [27].

For the seventh and last consensus meeting to date, an expert group comprised of 12 radiologists and 9 gynecologists including radiologists from Austria and Switzerland met in January 2019 in Berlin. The preamble of the recommendations approved there state: “Uterine artery embolization represents a treatment option for patients with fibroid-related symptoms and allows further treatment individualization for uterine fibroids in Germany, Austria and Switzerland [...]” [28].

**Current status of fibroid treatment with UAE**

Since its development, UAE for treating symptomatic fibroids has become an established minimally invasive alternative to the surgical treatment of fibroids. At present, probably more than 25,000 fibroid patients are treated with UAE globally each year [29]. UAE is indicated primarily in premenopausal patients with fibroid-related symptoms and no desire to become pregnant in the future [28]. Since there is a risk of fibroids becoming intraperitoneal or intracavitary after UAE, possibly resulting in sterile peritonitis or intrauterine infection, isolated submucosal (FIGO 0, 1) and pedunculated, subserosal uterine fibroids are relative contraindications [28]. Embolization is absolutely contraindicated in pregnant women and patients with suspicion of malignancy of the uterus or with acute genital infection [28]. Patients with symptomatic uterine fibroids and a desire to become pregnant should benefit from UAE without a loss of fertility even though this aspect has not yet been definitively scientifically proven [30]. The use of gelatin particles as temporary absorbable embolic agents dominated at the start of the studies but this material has been increasingly replaced by permanent PVA particles. In recent years, non-spherical PVA particles have been increasingly replaced by calibrated microspheres (spherical PVA (BOSTON Contour SE), acrylamido PVA (TERUMO Beadblock), tris-acryl gelatin microspheres (TAGM) (MERIT Embospheres), and polyzene-F hydrogel microspheres (VARIAN Embocenes)). These have a higher rate of fibroid volume reduction and may thus be able to provide better symptom control in women [31]. Moreover, the use of microcatheters has made UAE more selective and thus safer. The use of radial access for the vascular intervention is a further milestone for patients since a longer period of bed rest can be avoided.

The complication risk of this minimally invasive treatment method is very low. Particularly in the case of angiography, inguinal hernatomas, arterial embolisms, and aneurysms can occur [32]. Most patients complain of pain, nausea, and subfebrile temperatures immediately after the procedure that can be treated according to a defined pain protocol and in collaboration with the anesthesiologist via oral administration of nonsteroidal anti-inflammatory drugs (NSAIDS), analgesic infusion, or in rare cases with spinal or epi-/peridural anesthesia [24]. In recent years, protocols for pain treatment have been developed [33]. Moreover, in terms of early detection of complications, it must be noted that an increase in C-reactive protein (CRP) following UAE is normal as already shown in 2003 by a previous study [34]. A rare post-interventional complication is endomyometritis and can result in sepsis and consecutive hysterectomy [35].

Interestingly, the literature now includes numerous studies that document successful treatment response to UAE. Since the need for reintervention is considered an objective treatment failure, the rate of hysterectomies, myomectomies, and re-embolizations is examined in the majority of these studies. Thus, it was able to be shown that UAE is associated with a re-intervention rate of 18 % seven years after treatment and 25 % after nine years [36, 37]. Two additional studies report on low, long-term re-intervention rates of 11 % and 23.3 %, respectively, ten years post-UAE [38, 39]. According to current knowledge, predictive factors for re-intervention risk are patient age, myoma size, fibroid position, and fibroid infarction rate [40, 41]. However, the absolute best predictor of a poor result is unilateral embolization, e. g., in the case of unsuccessful catheterization of a uterine artery. Therefore, it is not surprising that the relative risk of a subsequent hysterectomy in one study was 2.19 after unilateral embolization compared to bilateral embolization [42].

The outcome of UAE has been examined by numerous case series and other observational studies. International study groups reported statistically highly significant improvements of symptom severity and health-related quality of life both in the short-term and in the long-term course after embolization. Subsequent multicenter observational studies confirm these results in very large cohorts. In particular, the FIBROID Registry, which evaluated the standardized fibroid-specific UFS-QoL questionnaire, stands out due to its size (3000 patients) and the great number of participating clinics and shows excellent improvement of the identified parameters (Table 1, 2) [38, 39, 43–45].

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Continuous significant improvement of the UFS-QoL categories has been seen in multiple studies even in the long term following treatment [38, 44]. Accordingly, most studies indicate a high level of satisfaction with the treatment result and a willingness on the part of fibroid patients to recommend the method [44, 46]. Interestingly, the post-interventional improvement of clinical symptoms and health-related quality of life cannot always be correlated with the degree of fibroid volume reduction determined on radiology [47].

UAE is recommended as the last resort for patients with symptomatic uterine fibroids and a desire to become pregnant [28]. Some authors have reported successful pregnancies following treatment [48]. UAE seems to be at least equivalent to surgical treatment options (myomectomy, hysterectomy) and MRI-guided focused ultrasound (MRgFUS) [32, 49]. To date, UAE is part of a comprehensive and individualized treatment concept that can ensure preservation of the organ.

Follow-up of fibroid embolization patients primarily consists of gynecological ultrasound and possibly MRI 6 months after UAE. If no clinical improvement is seen or there are abnormalities on imaging, further workup is necessary [28].

The importance of UAE for fibroid treatment has increased continuously in recent years. Already in the 1990s, embolization was identified as a promising alternative for the treatment of symptomatic fibroid patients. “In patients undergoing bilateral embolization, excellent short-term results regarding menorrhagia as well as pelvic pain can be expected with a simultaneous reduction in the size of the uterus and the fibroid volume. The method is generally well tolerated by patients and offers advantages including shorter hospital stays, possible preservation of fertility, and the option to treat all uterine fibroids in one session.” [50]. Nonetheless, it took almost two decades to overcome the skepticism on the part of gynecologists regarding UAE. Today, it can be considered an equivalent method to surgical fibroid treatment methods when performed at suitable centers (appendices A and B).

Conflict of Interest

The authors declare that they have no conflict of interest.

References


<table>
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<tr>
<th>Study</th>
<th>n</th>
<th>pre-UAE Median (25, 75.P)</th>
<th>post-UAE Median (25, 75.P)</th>
<th>p-value</th>
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<tr>
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<td>56</td>
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<td>37.5 (28.1 53.1)</td>
<td>0.0 (0.0 10.9)</td>
<td>&lt;0.001</td>
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1 n = Number of patients in the respective study population

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Table 1 Improvement in symptom severity after UAE measured by UFS-QoL questionnaires.

Table 2 Improvement in health-related quality of life after UAE measured by UFS-QoL questionnaires.


