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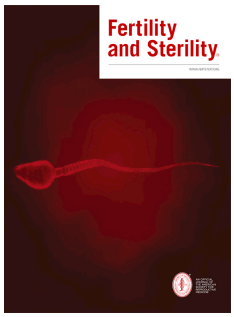

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Eduard Mension, MD PhD, Francisco Carmona, MD PhD, Silvia Vannuccini, MD PhD, Charles Chapron, MD PhD

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Clinical signs and diagnosis of fibroids from adolescence to menopause

Eduard Mension MD PhD[1], Francisco Carmona MD PhD[1], Silvia Vannuccini MD PhD[2], Charles Chapron MD PhD[3]

1. Department of Obstetrics and Gynecology, Hospital Clínic of Barcelona, Spain, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Facultad de Medicina, Universidad de Barcelona, Barcelona, España.
2. Obstetrics and Gynecology, Dept. Experimental, Clinical and Biomedical Sciences, University of Florence, Careggi University Hospital, Florence, Italy
3. Département de Gynécologie, Obstétrique et Médecine de la Reproduction, AP-HP, Centre Hospitalier Universitaire (CHU) Cochin, F-75014, Paris, France.

Corresponding author: F Carmona MD PhD
Email address: fcarmona@clinic.cat
Department of Obstetrics and Gynecology, Hospital Clínic of Barcelona, Spain.

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Uterine fibroids, leiomyomas, diagnosis, personalized.

ABSTRACT

The aim of this review was to provide an updated assessment of the present diagnostic tools and clinical symptoms and signs to evaluate uterine fibroids (UFs) based on current guidelines, recent scientific evidence and a PubMed and Google Scholar search for peer-reviewed original and review articles related to clinical signs and diagnosis of UFs. Around 50-75% of UFs are considered non-clinically relevant. When present, the most common symptoms are abnormal uterine bleeding, pelvic pain and/or bulk symptoms and reproductive failure. Transvaginal ultrasound (TVUS) is recommended as the initial diagnostic modality due to its accessibility and high sensitivity, although magnetic resonance imaging appears to be the most accurate diagnostic tool to date in certain cases. Other emerging techniques such as saline infusion sonohysterography, elastography and contrast-enhanced ultrasonography may contribute to improving the diagnostic accuracy in selected cases. Moreover, artificial intelligence has begun to demonstrate its ability as a complementary tool to improve the efficiency of UF diagnosis. Therefore, it is critical to standardize descriptions of TVUS images according to updated classifications and to individualize the use of the different complementary diagnostic tools available to achieve a precise uterine mapping able to lead targeted therapeutic approaches according to the clinical context of each patient.

During the last years important advances in the pathophysiology of uterine fibroids (UFs) have been made, revealing potential new diagnostic and therapeutic approaches that may provide a paradigmatic change in the management of this disease.

Traditionally, UFs have been associated with classical risk factors, such as race, aging and obesity, but it's been suggested that uterine stem cells of all women may have an intrinsic risk for the development of UFs, that can be increased by several "hits" to the hormonal stem cell pathways along their lifetime (1)-(2–4). Therefore, UFs may be presented throughout the lifetime of a woman, being more frequent during the reproductive age from adolescence to menopause when hormonal inputs are greater (5). Nonetheless, many women presenting UFs do not present clinical symptoms or signs, with 50-75% of UFs being considered as non-clinically relevant (2,6,7).

According to the literature, the incidence of UFs among the population is variable, ranging from 5.4% to 77% in women of reproductive age. The upper limit of the incidence of UFs seems to be at around 50 years of age, with women at this age presenting a 10-fold increased risk of developing UFs compared to those in their 30s. However, this increased risk disappears after the age of 60 (5), since UFs are responsive to estrogens and progestins, and thus, when menopause occurs, UF-associated symptoms may spontaneously resolve and cease (8,9).

The aim of this review was to provide an updated overview of the clinical symptoms to evaluate UFs and the current diagnostic tools available.

1. CLINICAL SYMPTOMS OF UTERINE FIBROIDS

The most common symptoms of the presence of UFs are heavy menstrual bleeding (HMB) or abnormal uterine bleeding (AUB), pelvic pain and/or bulk symptoms and reproductive failure.

Abnormal Uterine Bleeding

Although the association between AUB and UFs has been reported, its pathophysiological mechanisms are not yet clearly established, since many women with UFs may present entirely normal bleeding patterns. Once bleeding is defined as being abnormal, the well-known acronym PALM-COEIN (Polyp, Adenomyosis, Leiomyoma, Malignancy (and hyperplasia), Coagulopathy, Ovulatory disorders, Endometrial, Iatrogenic and Not otherwise classified) is usually used for categorizing causes (10).

When AUB is present, in 45.7% of the cases there is a UF associated causing the bleeding (11). However, when a UF is diagnosed, it does not exclude the presence of other causes of AUB, that may co-exist with UF, such as adenomyosis, and thus its presence should be assessed (12). In addition, hormonal dysfunction in the premenopausal period may represent a confounding factor in the diagnosis of AUB associated with UFs (13) (14).

Regarding the location of UFs, it has been thought that women with submucosal fibroids, particularly with those distorting the uterine cavity, were more likely to present AUB (15). However, there is current debate assessing the main possible causes provoking AUB apart from the location itself. One of the main theories explaining the cause of AUB in patients presenting UFs seems to be the presence of increased microscopic myometrial venous dilatations in the uterine tissue surrounding UFs. These dilatations are produced

by increased production of vascular endothelial growth factor, epidermal growth factor and platelet-derived growth factor in the microenvironment, inducing increased angiogenesis, endometrial decidualization and reduced hemostasis. Moreover, abnormal myometrial contractions have been related to induced AUB through a cascade of cytokines in the extracellular matrix cells surrounding UFs.

Finally, in many cases, AUB may lead to chronic iron deficiency and chronic anemia, although the women may be asymptomatic due to the chronic nature of this condition (13,16–19).

Pain and Bulk symptoms

Other symptoms related to UFs include complaints of chronic pelvic pain, dysmenorrhea, premenstrual pelvic pain, intercourse pain and bladder pressure. However, an interesting international survey showed that women diagnosed with UFs compared to women without UFs significantly more often reported pain symptoms such as pressure on the bladder (32.6% vs. 15.0%), chronic pelvic pain (14.5% vs. 2.9%), painful sexual intercourse (23.5% vs. 9.1%) and pain occurring mid-cycle, after and during menstrual bleeding (31.3%, 16.7%, 59.7%, vs. 17.1%, 6.4%, 52.0%) (20). Although these are common symptoms, their correlation with the size, number, or position of UFs have yet to be clearly established (21), and some authors suggest that the characteristics of UFs may not correlate with bulk symptoms (22).

Reproductive failure

Reproductive failure is another clinical sign related to the presence of UFs. Some mechanisms of association between fibroids and infertility have been proposed, and

epidemiological studies have shown that women with infertility had a 2.18 higher incidence of UFs (23).

Fibroid-related infertility may be caused by several mechanisms, such as uterine cavity deformation, impaired endometrial-myometrial blood supply, disturbed uterine contractility, hormonal, paracrine and molecular changes, and impaired endometrial receptivity and gene expression. All these mechanisms were reviewed by *Donnez et al* in the same series of Views and reviews. (4) (24). The disruption of physiological myometrial contractility may interfere with both spermatozoa progression and embryo implantation (25), and moreover UFs may alter the pelvic anatomy and impair the function of the fallopian tubes (26) (27). On the other hand, serosal UFs that have no impact on the uterine cavity do not seem to be related to reproductive failure or to affect IVF results (29,32).

Fibroids during pregnancy

In relation to how UFs may change during pregnancy, some imaging studies have shown an increase of leiomyoma volume at any time during pregnancy, but others have noted size reduction or no change (33,34). In addition, in late pregnancy and puerperium the tendency is of volume reduction (35). The growth of UFs during pregnancy may occur mainly in the first 7 gestational weeks, because of increased estrogen levels and also human chorionic gonadotropin, angiogenic and growth factors. The growth of UFs has a nonlinear trend in pregnancy, with a median change in volume up to 140% in early gestation. Conversely, in the postpartum, sustained ischemia and apoptosis promoted by uterine remodeling during its involution contribute to the shrinkage of UFs (36).

2. DIAGNOSTIC TOOLS AND CLASSIFICATION OF UTERINE FIBROIDS

Transvaginal ultrasound

When clinical symptoms or signs suggest the possible presence of UFs, the first line diagnostic technique that should be performed is transvaginal ultrasound (TVUS) due to its accessibility and low cost (10) as well as its high sensitivity and specificity comparable to magnetic resonance imaging (MRI) (37), offering the possibility of a precise mapped description of the UFs present in the uterus (39).

Comparison of UF detection accuracy between TVUS and MRI (38) is reported in Table 1.

UFs affecting the JZ seem to present fewer cytogenetic abnormalities, presenting a different pattern of vascularization and being more responsive to GnRH analogues and with fewer recurrences after surgery (17). Thus, adequate description of the presence of JZ involvement is essential since it may influence symptoms and its response to treatments. In addition, different patterns and scores of myometrial vascularization provide important information regarding the growth of UFs (45,46). The high diagnostic accuracy of these factors contributes to helping clinicians select better targeted treatments or the clinical management of patients according to the different myometrium involvement and vascularization.

Furthermore, adequate description of the inner myometrium (corresponding to the JZ), the middle myometrium (extending from the JZ to the venous and arterial arcuate vessels of the uterus), and the outer myometrium (located between the arcuate vessels

and the uterine serosa) helps to achieve precise uterine mapping of the location of UFs**.** The vascular arcuate, observed in the sagittal plane in 2D TVUS with the application of color or power Doppler, serves as a reference for the differentiation of uterine layers, which have been correlated with the presence of different symptoms (41).

An example of uterine vascular arcuate is visible in Figure 1.

The MUSA description reports the sonographic features of the myometrium using gray-scale sonography, color/power Doppler and three-dimensional ultrasound imaging, highlighting important characteristics of UFs, such as: number, size, localization, echogenicity, acoustic shadow, vascularization, fibroid type, minimal distance to serosa and minimal distance to mucosa. On the other hand, specific classifications of submucosal UF, such as the STEPW/Lasmar Classification, provide information on the expected difficulty and complexity of hysteroscopic UF resection according to the size, topography, extension, penetration, and wall of submucous UFs (49). The Lasmar-Score is usually obtained by diagnostic hysteroscopy, despite some authors suggesting that TVUS may be able to provide the score when performed in the luteal phase of the menstrual cycle, avoiding office hysteroscopy without a loss of diagnostic accuracy (50). International validation of this classification for predicting hysteroscopic UF removal among a total population of 465 women showed that STEPW less than or equal to 4 presented 100% of UF hysteroscopic resection success, while successful resection was achieved in 77.2% of women with a score greater than 4 (51).

Furthermore, when UFs present an atypical appearance by TVUS a differential diagnosis between UFs, uterine smooth muscle tumors of uncertain malignant potential (STUMP)

and leiomyosarcomas is necessary. No specific characteristics of TVUS have proven to be effective for differentiating "typical myoma" from "STUMP" and leiomyosarcomas due to the lack of large series describing TVUS characteristics of diagnosed leiomyosarcomas. Nonetheless, some authors have attempted to identify and define atypical signs by TVUS that might be suspicious of an atypical UF with a possible increased risk of finally becoming a STUMP or a leiomyosarcoma (52).

Typical UFs may present changes in morphology in response to different triggers. When UFs grow, the vascularization might be compromised, presenting, in some cases, partial necrosis classified as different kinds of pathologic degeneration (hyaline, myxoid, cystic, red or dystrophic degeneration). Initially, these degenerations are difficult to detect by TVUS, with the only sign being a hyperechoic border without detection of power doppler flow in the UF core. It is only in the late phase of internal UF necrosis, that the resulting edema might present as a mixed echogenicity with hypoechoic cystic areas inside the UF (53,54). These hypoechoic internal cystic areas with increased core vascularization, visualized by power doppler as large UF-like uterine masses, can be suggestive of malignant myometrial tumors (55,56).

Magnetic Resonance Imaging

MRI is the other remarkable imaging technique to assess UFs, presenting a high sensitivity and specificity (Table 1) and according to some authors, is the most accurate diagnostic test to assess UFs (52). Notwithstanding, in cases of women presenting large UFs or a uterus that rises out the pelvis, some authors showed up to 36% of discrepancies between clinicians in the classification of these cases when assessing UFs by TVUS, and thus concluding that MRI appears to be superior to TVUS when assessing

more than four fibroids or a uterus larger than 375 cm^3 (31). Moreover, MRI is a helpful complementary imaging technique to TVUS when assessing women presenting coexisting endometriosis and adenomyosis (38). MRI allows differentiation between UF and adenomyosis despite both appearing as hypointense lesions on T2-weighted images, since adenomyosis usually shows poorly defined margins and an irregular shape contrary to UFs. However, some studies have demonstrated that 2D-TVUS has a similar sensitivity and specificity for the diagnosis of adenomyosis compared to MRI (57).

Table 2 shows the comparison of the advantages and disadvantages between TVUS and MRI as tools for the diagnosis of UFs.

Despite the better reproducibility of MRI, its interpretation might be more difficult than TVUS images. When degeneration is seen by TVUS, it is usually visualized as hypoechoic internal cysts and calcifications. However, when assessed by MRI, different patterns of signal intensity are seen depending on the pathologic degeneration subtype. T2-weighed images may show from hypointensity in typical UFs to marked hyperintensity in cystic degenerated UFs and hypercellular fibroids, while many cases may present iso-hypointensity on T1-weighted images (52).

Nonetheless, differential diagnosis between UFs and uterine sarcoma is another indication for the use of MRI to assess uterine masses. According to a recent meta-analysis, MRI seems to be superior to TVUS in differentiating UFs from uterine sarcomas, presenting a sensitivity of 90% and a specificity of 96% , with a pooled accuracy of 97% (58), while TVUS a sensitivity and specificity of 76% and 89%, respectively (59). Some of the image characteristics associated with an increased risk of malignancy are the

absence of a clear myometrial origin, the lack of a normal endometrial stripe, intermediate signal intensity on T2-weighted images, T2-weighted signal heterogeneity, signs of intratumoral hemorrhage, heterogeneous contrast enhancement, hyperintensity on high-b-value diffusion-weighted images, and low apparent diffusion coefficient values (52).

Despite these possible associations, there is still a lack of consensus due to contradictory findings in different studies and overlap of these associations between benign and malignant lesions (60). Nevertheless, key points are starting to flourish, as Sato *et al. (61)* reported that UF-like mases, seen as hypointense in diffusion-weighted imaging, should be considered benign with a 100% sensitivity and 94% specificity.

Therefore, indications for MRI to evaluate UFs comprise these cases with uncertainty regarding the anatomical origin of the mass, in cases of large uterus with the presence of multiple leiomyomas, in cases with clinical suspicion of coexistence of endometriosis or adenomyosis and in cases in which atypical signs have been seen by TVUS to assess the risk of malignancy.

Other techniques

During the last decade, other complementary techniques have been tested and others have been developed to provide help for precise uterus mapping in specific cases.

Techniques such as hysteroscopy and saline infusion sonohysterography (SIS) may help in cases in which TVUS presents doubts of an intrauterine image and in planning submucosal UF surgical interventions. Hysteroscopy remains the gold standard tool for

the detection of intrauterine abnormalities, but SIS is a highly sensitive and specific test for the diagnosis of uterine polyps, submucous myomas and intrauterine anomalies, being comparable to hysteroscopy with a sensitivity of 88% [85–90%] and specificity of 94% [93–96%] (62,63). SIS provides intracavity images of submucosal UFs with a high level of accuracy and is less invasive than hysteroscopy (64), and some studies have suggested that SIS may avoid hysteroscopy in some cases (42,43) (44). One of its main uses is the study of infertility, since SIS combines the features of hysteroscopy and TVUS and can simultaneously visualize tubal patency, the uterine cavity, and other pelvic pathologies.

Elastography is an ultrasound technique that measures the stiffness of uterine tissue based on differences in elasticity on response to compression or vibration (65). Although it is still in the research stage, elastography is a promising tool and may have a role in the diagnosis of UFs due to its low cost and non-invasiveness. It has mainly been tested in the differential diagnosis with adenomyosis, observing that UFs and adenomyosis may have different elastographic characteristics with different color patterns, with UFs, in most cases, being darker than adjacent myometrium, compared to a brighter appearance in cases of adenomyosis (66,67). Elastography has also been compared to MRI in the assessment of UFs, obtaining a Cohen's kappa of 1.0 with MRI (65). Furthermore, some studies have also suggested a role of elastography in the diagnosis of malignant uterine tumors, since these tumors are known to present increased stiffness due to biomechanical modifications in uterine tissue (68).

Moreover, contrast enhanced ultrasound (CEUS) is a technique that uses endovenous gas-filled microbubbles with diameters less than 8 μm, and a lipid, protein, or a polymer shell as ultrasound contrast agents (UCAs) to enhance the microvasculature of the myometrium (69). Thus, CEUS provides additional details compared to TVUS and SIS in terms of the pseudo-capsule of fibroids, central necrosis, and intra-lesion vascularity patterns (70). Previous studies using CEUS have already assessed the normal behavior of UFs, showing that they tend to enhance earlier than the surrounding myometrium and the peak of intensity differs depending on the degree of fibroid degeneration, and most fibroids (94.5%) present a more rapid UCA wash-out than the surrounding myometrium (71). A recent systematic review reported a diagnostic accuracy for CEUS of 97.5% for intramural fibroids and 96.3% for other types (72), and some authors compare its high accuracy to MRI in uterine mass assessment, with a correlation of $R = 0.97$ ($p < 0.001$) (73). Despite its high accuracy, there are no data regarding uterine malignancies with CEUS. Nonetheless, CEUS may be a useful future tool due to its ability to better assess UF vascularization patterns than TVUS doppler and the visualization of micro-vessels seems to be helpful to differentiate UFs from malignant uterine tumors (72).

Figure 2 shows the future diagnostic tools for complete evaluation of UFs.

On the other hand, the use of older techniques, such as computerized tomography (CT), have also been assessed in the diagnosis of UFs, but do not seem to be useful for the assessment of UFs. However, incidental UFs are sometimes found on CT, appearing as diffuse uterine enlargement or lobulated uterine contours demonstrating a density similar to that of normal uterine myometrium or in the form of uterine calcifications. Some authors assessed the imaging of UFs by 18F-fuorodeoxyglucose (FDG) positron

emission tomography (PET) imaging, with UFs showing physiological FDG uptake in 10.4% of premenopausal and 1.2% of post-menopausal women, with maximum standard uptake values (SUVmax) values ranging between 3.0 and 10.0, and in degenerated UFs, SUV may be higher compared to non-degenerated lesions (74).

Finally, artificial intelligence (AI) is currently being evaluated for different uses in the diagnosis of uterine alterations. For example, an artificial intelligence-assisted method to assist junior ultrasonographers in improving the diagnosis of UFs was evaluated, with AI improving the results and being comparable to those of senior clinicians (75). Even more significantly, other authors have used AI as a complementary diagnostic tool to existing 3D TVUS images or for real-time automatic-assisted detection, presenting an average accuracy of 90-95% for detecting UFs and achieving a detection speed of 0.28 seconds per image using deep learning -based algorithms, demonstrating that AI may be a helpful tool to improve the efficiency of the diagnosis and follow-up of UFs, and may change the way UFs are diagnosed in the near future (76,77).

4. CONCLUSIONS AND ESSENTIAL POINTS

UFs manifest throughout a woman's life, with increased frequency during reproductive years, yet many cases remain asymptomatic.

It is critical to be aware of the symptoms and signs which may lead to a possible diagnosis of the presence of UFs. When a UF is suspected, the first diagnostic tool chosen is TVUS for its high sensitivity and specificity, low cost, and good accessibility.

Standardized descriptions of TVUS images according to updated classifications are decisive for achieving individualized therapeutic approaches within the clinical context of each patient.

MRI has also shown to be a helpful complementary imaging technique to TVUS for the assessment of women presenting coexisting endometriosis and adenomyosis. In cases of multiple UFs (>4), large uterus (>375cm^3) or doubts of malignancy, MRI appears to be superior to TVUS.

New techniques, which are still mainly in the research stage, may contribute to improving diagnostic accuracy in certain situations in the near future. These techniques include SIS to complement intrauterine images visualized by TVUS, and elastography and CEUS for the differential diagnosis between UFs, adenomyosis and uterine malignancies. Finally, AI-assisted techniques may improve the efficiency in the diagnosis and follow-up of UFs, and may change the way UFs are diagnosed in the near future.

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6. AUTHOR CONTRIBUTIONS

All authors contributed in the bibliographic search, data analysis, data interpretation and study writing.

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8. CONFLICTS OF INTEREST

The authors declare no conflict of interest.

9. REFERENCES

1. Day Baird D, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: Ultrasound evidence. Am J Obstet Gynecol. 2003 Jan;188(1):100–7.
2. Pavone D, Clemenza S, Sorbi F, Fambrini M, Petraglia F. Epidemiology and Risk Factors of Uterine Fibroids. Best Pract Res Clin Obstet Gynaecol. 2018 Jan;46:3–11.
3. Dolmans MM, Petraglia F, Catherino WH, Donnez J. Pathogenesis of uterine fibroids: current understanding and future directions. Fertil Steril. 2024 Mar;S0015028224001699.
4. Donnez J, Taylor HS, Marcellin L, Dolmans MM. Uterine fibroid–related infertility: mechanisms and management. Fertil Steril. 2024 Mar;S0015028224001705.
5. Stewart E, Cookson C, Gandolfo R, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. BJOG Int J Obstet Gynaecol. 2017 Sep;124(10):1501–12.
6. Reis FM, Bloise E, Ortiga-Carvalho TM. Hormones and pathogenesis of uterine fibroids. Best Pract Res Clin Obstet Gynaecol. 2016 Jul;34:13–24.
7. Ulin M, Ali M, Chaudhry ZT, Al-Hendy A, Yang Q. Uterine fibroids in menopause and perimenopause. Menopause. 2020 Feb;27(2):238–42.
8. Hale GE, Manconi F, Luscombe G, Fraser IS. Quantitative Measurements of Menstrual Blood Loss in Ovulatory and Anovulatory Cycles in Middle- and Late-Reproductive Age and the Menopausal Transition. Obstet Gynecol. 2010 Feb;115(2):249–56.
9. Fuldeore M, Soliman A. Patient-reported prevalence and symptomatic burden of uterine fibroids among women in the United States: findings from a cross-sectional survey analysis. Int J Womens Health. 2017 Jun;Volume 9:403–11.
10. Munro MG, Critchley HOD, Fraser IS. The FIGO classification of causes of abnormal uterine bleeding: Malcolm G. Munro, Hilary O.D. Crithcley, Ian S. Fraser, for the FIGO Working Group on Menstrual Disorders. Int J Gynecol Obstet. 2011 Apr;113(1):1–2.
11. Ni P, Wu M, Guan H, Yuan Y, Zhang L, Zhang F, et al. Etiology distribution of abnormal uterine bleeding according to FIGO classification system: A combined study of ultrasound and histopathology. J Obstet Gynaecol Res. 2022 Jul;48(7):1913–20.
12. Munro MG. Classification of menstrual bleeding disorders. Rev Endocr Metab Disord. 2012 Dec;13(4):225–34.
13. Vannuccini S, Jain V, Critchley H, Petraglia F. From menarche to menopause, heavy menstrual bleeding is the underrated compass in reproductive health. Fertil Steril. 2022 Oct;118(4):625–36.
14. Treloar AE, Boynton RE, Behn BG, Brown BW. Variation of the human menstrual cycle through reproductive life. Int J Fertil. 1967;12(1 Pt 2):77–126.
15. Stewart E. Leiomyoma-related bleeding: a classic hypothesis updated for the molecular era. Hum Reprod Update. 1996 Jul 1;2(4):295–306.
16. Bereza T, Lis G, Mitus J, Sporek M, Chmielewski P, Kolber W, et al. Blood vessels of the intratumoral septa in uterine leiomyomata. Folia Med Cracov. 2013;53(2):99–106.
17. Don EE, Middelkoop MA, Hehenkamp WJK, Mijatovic V, Griffioen AW, Huirne JAF. Endometrial Angiogenesis of Abnormal Uterine Bleeding and Infertility in Patients with Uterine Fibroids—A Systematic Review. Int J Mol Sci. 2023 Apr 10;24(8):7011.
18. Nelson AL, Ritchie JJ. Severe anemia from heavy menstrual bleeding requires

heightened attention. Am J Obstet Gynecol. 2015 Jul;213(1):97.e1-97.e6.
19. Donnez J, Carmona F, Maitrot-Mantelet L, Dolmans MM, Chapron C. Uterine disorders and iron deficiency anemia. Fertil Steril. 2022 Oct;118(4):615–24.
20. Zimmermann A, Bernuit D, Gerlinger C, Schaefers M, Geppert K. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. BMC Womens Health. 2012 Dec;12(1):6.
21. David M, Pitz CM, Mihaylova A, Siedentopf F. Myoma-associated pain frequency and intensity: a retrospective evaluation of 1548 myoma patients. Eur J Obstet Gynecol Reprod Biol. 2016 Apr;199:137–40.
22. Ferrero S, Abbamonte LH, Giordano M, Parisi M, Ragni N, Remorgida V. Uterine myomas, dyspareunia, and sexual function. Fertil Steril. 2006 Nov;86(5):1504–10.
23. Somigliana E, Reschini M, Bonanni V, Busnelli A, Li Piani L, Vercellini P. Fibroids and natural fertility: a systematic review and meta-analysis. Reprod Biomed Online. 2021 Jul;43(1):100–10.
24. Nishino M, Togashi K, Nakai A, Hayakawa K, Kanao S, Iwasaku K, et al. Uterine contractions evaluated on cine MR imaging in patients with uterine leiomyomas. Eur J Radiol. 2005 Jan;53(1):142–6.
25. Orisaka M, Kurokawa T, Shukunami KI, Orisaka S, Fukuda MT, Shinagawa A, et al. A comparison of uterine peristalsis in women with normal uteri and uterine leiomyoma by cine magnetic resonance imaging. Eur J Obstet Gynecol Reprod Biol. 2007 Nov;135(1):111–5.
26. Somigliana E, Vercellini P, Daguati R, Pasin R, De Giorgi O, Crosignani PG. Fibroids and female reproduction: a critical analysis of the evidence. Hum Reprod Update. 2007 Jun 21;13(5):465–76.
27. Ikhena DE, Bulun SE. Literature Review on the Role of Uterine Fibroids in Endometrial Function. Reprod Sci. 2018 May;25(5):635–43.
28. Bai X, Lin Y, Chen Y, Ma C. The impact of FIGO type 3 fibroids on in-vitro fertilization outcomes: A nested retrospective case-control study. Eur J Obstet Gynecol Reprod Biol. 2020 Apr;247:176–80.
29. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril. 2009 Apr;91(4):1215–23.
30. Dolmans MM, Isaacson K, Zhang W, Gordts S, Munro MG, Stewart EA, et al. Intramural myomas more than 3–4 centimeters should be surgically removed before in vitro fertilization. Fertil Steril. 2021 Oct;116(4):945–58.
31. Sunkara SK, Khairy M, El-Toukhy T, Khalaf Y, Coomarasamy A. The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. Hum Reprod. 2010 Feb 1;25(2):418–29.
32. Pritts EA. Fibroids and Infertility: A Systematic Review of the Evidence: Obstet Gynecol Surv. 2001 Aug;56(8):483–91.
33. Hammoud AO, Asaad R, Berman J, Treadwell MC, Blackwell S, Diamond MP. Volume change of uterine myomas during pregnancy: Do myomas really grow? J Minim Invasive Gynecol. 2006 Sep;13(5):386–90.
34. Neiger R, Sonek JD, Croom CS, Ventolini G. Pregnancy-related changes in the size of uterine leiomyomas. J Reprod Med. 2006 Sep;51(9):671–4.
35. Coutinho LM, Assis WA, Spagnuolo-Souza A, Reis FM. Uterine Fibroids and Pregnancy: How Do They Affect Each Other? Reprod Sci. 2022 Aug;29(8):2145–51.
36. Vitagliano A, Noventa M, Di Spiezio Sardo A, Saccone G, Gizzo S, Borgato S, et al. Uterine fibroid size modifications during pregnancy and puerperium: evidence

from the first systematic review of literature. Arch Gynecol Obstet. 2018 Apr;297(4):823–35.
37. Woźniak A, Woźniak S. Ultrasonography of uterine leiomyomas. Menopausal Rev. 2017;16(4):113–7.
38. Dueholm M, Lundorf E, Hansen ES, Ledertoug S, Olesen F. Accuracy of magnetic resonance imaging and transvaginal ultrasonography in the diagnosis, mapping, and measurement of uterine myomas. Am J Obstet Gynecol. 2002 Mar;186(3):409–15.
39. Van Den Bosch T, Dueholm M, Leone FPG, Valentin L, Rasmussen CK, Votino A, et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. Ultrasound Obstet Gynecol. 2015 Sep;46(3):284–98.
40. Laughlin-Tommaso SK, Hesley GK, Hopkins MR, Brandt KR, Zhu Y, Stewart EA. Clinical limitations of the International Federation of Gynecology and Obstetrics (FIGO) classification of uterine fibroids. Int J Gynecol Obstet. 2017 Nov;139(2):143–8.
41. Van Den Bosch T, De Bruijn AM, De Leeuw RA, Dueholm M, Exacoustos C, Valentin L, et al. Sonographic classification and reporting system for diagnosing adenomyosis. Ultrasound Obstet Gynecol. 2019 May;53(5):576–82.
42. Grimbizis GF, Tsolakidis D, Mikos T, Anagnostou E, Asimakopoulos E, Stamatopoulos P, et al. A prospective comparison of transvaginal ultrasound, saline infusion sonohysterography, and diagnostic hysteroscopy in the evaluation of endometrial pathology. Fertil Steril. 2010 Dec;94(7):2720–5.
43. Bingol B, Gunenc Z, Gedikbasi A, Guner H, Tasdemir S, Tiras B. Comparison of diagnostic accuracy of saline infusion sonohysterography, transvaginal sonography and hysteroscopy. J Obstet Gynaecol. 2011 Jan;31(1):54–8.
44. Short J, Sharp B, Elliot N, McEwing R, McGeoch G, Shand B, et al. Does the addition of saline infusion sonohysterography to transvaginal ultrasonography prevent unnecessary hysteroscopy in premenopausal women with abnormal uterine bleeding? Aust N Z J Obstet Gynaecol. 2016 Aug;56(4):432–5.
45. Nieuwenhuis L, Keizer A, Stoelinga B, Twisk J, Hehenkamp W, Brölmann H, et al. Fibroid vascularisation assessed with three-dimensional power Doppler ultrasound is a predictor for uterine fibroid growth: a prospective cohort study. BJOG Int J Obstet Gynaecol. 2018 Apr;125(5):577–84.
46. Keizer AL, Niewenhuis LL, Hehenkamp WJK, Twisk JWR, Brölmann HAM, Huirne JAF. Fibroid vascularisation assessed with 3D Power Doppler as predictor for fibroid related symptoms and quality of life; a pilot study. Facts Views Vis ObGyn. 2021 Dec;13(4):387–94.
47. Munro MG, Critchley HOD, Fraser IS, the FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. Int J Gynecol Obstet. 2018 Dec;143(3):393–408.
48. Harmsen MJ, Van Den Bosch T, De Leeuw RA, Dueholm M, Exacoustos C, Valentin L, et al. Consensus on revised definitions of Morphological Uterus Sonographic Assessment (MUSA) features of adenomyosis: results of modified Delphi procedure. Ultrasound Obstet Gynecol. 2022 Jul;60(1):118–31.
49. Lasmar RB, Barrozo PRM, Dias R, De Oliveira MAP. Submucous myomas: A new presurgical classification to evaluate the viability of hysteroscopic surgical treatment—Preliminary report. J Minim Invasive Gynecol. 2005 Aug;12(4):308–11.
50. Camanni M, Bonino L, Tessarolo M, Migliaretti G, Ferrero B, Deltetto F. Is it

possible to obtain a presurgical Lasmar score for hysteroscopic myomectomy by ultrasound alone? Ultrasound Obstet Gynecol. 2012 Jul;40(1):106–11.
51. Lasmar RB, Xinmei Z, Indman PD, Celeste RK, Di Spiezio Sardo A. Feasibility of a new system of classification of submucous myomas: a multicenter study. Fertil Steril. 2011 May;95(6):2073–7.
52. Testa AC, Di Legge A, Bonatti M, Manfredi R, Scambia G. Imaging techniques for evaluation of uterine myomas. Best Pract Res Clin Obstet Gynaecol. 2016 Jul;34:37–53.
53. Nicholson TA, Pelage JP, Ettles DF. Fibroid Calcification after Uterine Artery Embolization: Ultrasonographic Appearance and Pathology. J Vasc Interv Radiol. 2001 Apr;12(4):443–6.
54. Szabó I, Szánthó A, Csabay L, Csapó Z, Szirmai K, Papp Z. Color Doppler ultrasonography in the differentiation of uterine sarcomas from uterine leiomyomas. Eur J Gynaecol Oncol. 2002;23(1):29–34.
55. Testa AC, Pomini F, Fattorossi A, Battaglia A, Ferrandina G, Mansueto D, et al. Doppler Velocimetry and Cytofluorimetric Analysis inUterine Myomas. Gynecol Obstet Invest. 2003;56(3):139–42.
56. Exacoustos C, Romanini ME, Amadio A, Amoroso C, Szabolcs B, Zupi E, et al. Can gray-scale and color Doppler sonography differentiate between uterine leiomyosarcoma and leiomyoma? J Clin Ultrasound. 2007 Oct;35(8):449–57.
57. Bazot M, Daraï E. Role of transvaginal sonography and magnetic resonance imaging in the diagnosis of uterine adenomyosis. Fertil Steril. 2018 Mar;109(3):389–97.
58. Raffone A, Raimondo D, Neola D, Travaglino A, Giorgi M, Lazzeri L, et al. Diagnostic accuracy of MRI in the differential diagnosis between uterine leiomyomas and sarcomas: A systematic review and meta-analysis. Int J Gynecol Obstet. 2023 Sep 21;ijgo.15136.
59. Raffone A, Raimondo D, Neola D, Travaglino A, Raspollini A, Giorgi M, et al. Diagnostic Accuracy of Ultrasound in the Diagnosis of Uterine Leiomyomas and Sarcomas. J Minim Invasive Gynecol. 2024 Jan;31(1):28-36.e1.
60. Bonneau C, Thomassin-Naggara I, Dechoux S, Cortez A, Darai É, Rouzier R. Value of ultrasonography and magnetic resonance imaging for the characterization of uterine mesenchymal tumors. Acta Obstet Gynecol Scand. 2014 Mar;93(3):261–8.
61. Sato K, Yuasa N, Fujita M, Fukushima Y. Clinical application of diffusion-weighted imaging for preoperative differentiation between uterine leiomyoma and leiomyosarcoma. Am J Obstet Gynecol. 2014 Apr;210(4):368.e1-368.e8.
62. Kumar K, Pajai S, Baidya GR, Majhi K. Utility of Saline Infusion Sonohysterography in Gynecology: A Review Article. Cureus [Internet]. 2023 Feb 24 [cited 2024 Apr 8]; Available from: https://www.cureus.com/articles/114759-utility-of-saline-infusion-sonohysterography-in-gynecology-a-review-article
63. Seshadri S, El-Toukhy T, Douiri A, Jayaprakasan K, Khalaf Y. Diagnostic accuracy of saline infusion sonography in the evaluation of uterine cavity abnormalities prior to assisted reproductive techniques: a systematic review and meta-analyses. Hum Reprod Update. 2015 Mar 1;21(2):262–74.
64. Bittencourt CA, Dos Santos Simões R, Bernardo WM, Fuchs LFP, Soares Júnior JM, Pastore AR, et al. Accuracy of saline contrast sonohysterography in detection of endometrial polyps and submucosal leiomyomas in women of reproductive age with abnormal uterine bleeding: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2017 Jul;50(1):32–9.
65. Stoelinga B, Hehenkamp WJK, Brölmann HAM, Huirne JAF. Real-time elastography for assessment of uterine disorders. Ultrasound Obstet Gynecol. 2014

Feb;43(2):218–26.
66. Tessarolo M, Bonino L, Camanni M, Deltetto F. Elastosonography: a possible new tool for diagnosis of adenomyosis? Eur Radiol. 2011 Jul;21(7):1546–52.
67. Pongpunprut S, Paburana P, Wibulpolprasert P, Waiyaput W, Sroyraya M, Chansoon T, et al. A Comparison of Shear Wave Elastography between Normal Myometrium, Uterine Fibroids, and Adenomyosis: A Cross-Sectional Study. Int J Fertil Steril [Internet]. 2022 Jan [cited 2024 Apr 8];16(1). Available from: https://doi.org/10.22074/ijfs.2021.523075.1074
68. Wang X li, Lin S, Lyu G rong. Advances in the clinical application of ultrasound elastography in uterine imaging. Insights Imaging. 2022 Sep 4;13(1):141.
69. Torkzaban M, Machado P, Gupta I, Hai Y, Forsberg F. Contrast-Enhanced Ultrasound for Monitoring Non-surgical Treatments of Uterine Fibroids: A Systematic Review. Ultrasound Med Biol. 2021 Jan;47(1):3–18.
70. Stoelinga B, Dooper AMC, Juffermans LJM, Postema AW, Wijkstra H, Brölmann HAM, et al. Use of Contrast-Enhanced Ultrasound in the Assessment of Uterine Fibroids: A Feasibility Study. Ultrasound Med Biol. 2018 Aug;44(8):1901–9.
71. Zhang XL, Zheng RQ, Yang YB, Huang DM, Song Q, Mao YJ, et al. The use of contrast-enhanced ultrasound in uterine leiomyomas. Chin Med J (Engl). 2010 Nov;123(21):3095–9.
72. Stoelinga B, Juffermans L, Dooper A, De Lange M, Hehenkamp W, Van Den Bosch T, et al. Contrast-Enhanced Ultrasound Imaging of Uterine Disorders: A Systematic Review. Ultrason Imaging. 2021 Sep;43(5):239–52.
73. Chhabra P, Daugherty R, LeNoir AM, Grilli C, Makai G, Patel N, et al. Comparison of CONTRAST-ENHANCED Ultrasound Versus Magnetic Resonance Imaging in the Detection and Characterization of Uterine Leiomyomas. J Ultrasound Med. 2021 Jun;40(6):1147–53.
74. Nishizawa S, Inubushi M, Kido A, Miyagawa M, Inoue T, Shinohara K, et al. Incidence and characteristics of uterine leiomyomas with FDG uptake. Ann Nucl Med. 2008 Nov;22(9):803–10.
75. Huo T, Li L, Chen X, Wang Z, Zhang X, Liu S, et al. Artificial intelligence-aided method to detect uterine fibroids in ultrasound images: a retrospective study. Sci Rep. 2023 Mar 6;13(1):3714.
76. Shahzad A, Mushtaq A, Sabeeh AQ, Ghadi YY, Mushtaq Z, Arif S, et al. Automated Uterine Fibroids Detection in Ultrasound Images Using Deep Convolutional Neural Networks. Healthcare. 2023 May 20;11(10):1493.
77. Yang T, Yuan L, Li P, Liu P. Real-Time Automatic Assisted Detection of Uterine Fibroid in Ultrasound Images Using a Deep Learning Detector. Ultrasound Med Biol. 2023 Jul;49(7):1616–26.

Legend of figures and tables:

Figure 1. Uterine vascular arcuate observed in the sagittal plane in two-dimensional (2D) transvaginal ultrasound (TVUS) with the application of color or power Doppler and description of the endometrium (blue), inner myometrium/junctional zone (red), the middle myometrium (orange: extending from the JZ to the venous and arterial arcuate vessels of the uterus), the outer myometrium (yellow: located between the arcuate vessels and the uterine serosa) and uterine serosa (green).

Figure 2. Future diagnostic tools for complete evaluation of UFs.

Table 1. Comparison of UF detection accuracy between TVUS and MRI.

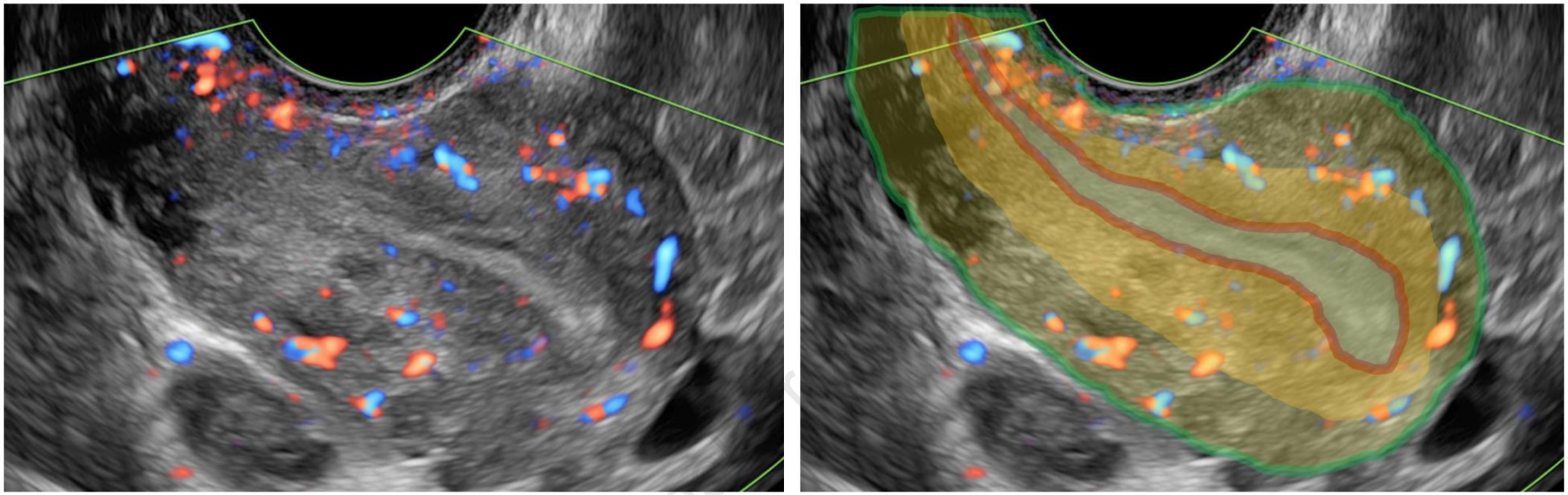
Table 2. Comparison of the advantages and disadvantages between TVUS and MRI as tools for the diagnosis of UFs. S= sensitivity, Sp= specificity.

	TRANSVAGINAL ULTRASOUND	MAGNETIC RESONANCE IMAGING
SENSITIVITY	99% [92-100%]	99% [92-100%]
SPECIFICITY	91% [75-98%]	86% [71-94%]
POSITIVE PREDICTIVE VALUE	96% [88-99%]	92% [93-97%]
NEGATIVE PREDICTIVE VALUE	97% [82-100%]	97% [85-100%]

Table 1. Comparison of UF detection accuracy between TVUS and MRI.

	ADVANTAGES	DISADVANTAGES
TVUS	High S and Sp Faster Lower cost Better accessibility	Efficacy decreases when uterus >375 mL and presenting >4 UFs Operator-dependent
MRI	High S and Sp Better efficacy when uterus >375 mL and presenting >4 UFs Not operator-dependent Reproducibility	Higher false findings rate compared to TVUS Increased cost Time consuming

Table 2. Comparison of the advantages and disadvantages between TVUS and MRI as tools for the diagnosis of UFs. S= sensitivity, Sp= specificity.



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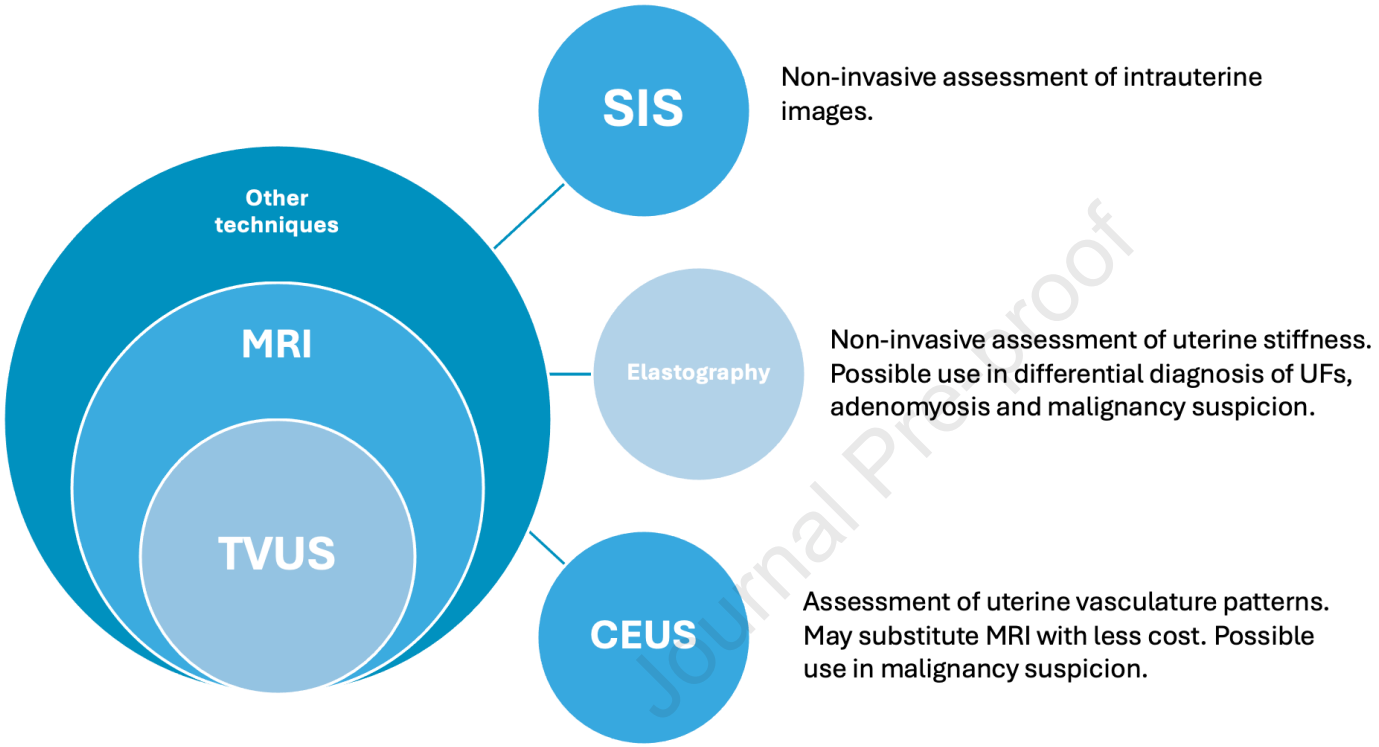

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