Title:

Transvaginal ultrasound versus magnetic resonance imaging for diagnosing adenomyosis. A systematic review and head-to-head meta-analysis

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ABSTRACT

Objective: To compare the diagnostic accuracy of transvaginal ultrasound (TVS) and magnetic resonance imaging (MRI) for the diagnosis of adenomyosis

Methods: A search of papers comparing TVS and MRI for the diagnosis of adenomyosis was performed in Medline (Pubmed), Web of Science, Cochrane Database, Scopus and CINHAL from January 1990 to May 2022. Quality was assessed using QUADAS-2 tool. Quantitative meta-analysis was performed. Pooled sensitivity and specificity of both techniques were estimated and compared.

Results: We identified 972 citations. Ultimately, six studies comprising 595 women were included. Mean prevalence of adenomyosis was 52%. The risk of bias was high in three studies for domain “patient selection”. Risk of bias was low for “index test”, “reference test” domains for all studies. Overall, pooled estimated sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio for TVS were were 75 %, 81 %, 3.9 and 0.31, respectively. Pooled estimated sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio for MRI were were 69 %, 80 %, 3.5 and 0.39, respectively. No statistical significant differences were found (p=0.7509). Heterogeneity was moderate for both sensitivity and high for specificity.

Conclusion: MRI and TVS have similar performance for the diagnosis of adenomyosis.

Keywords. Adenomyosis, diagnosis, transvaginal ultrasound, magnetic resonance imaging.

Introduction

Adenomyosis is an oestrogen-dependent disorder, characterized by the existence of endometrial glands and stroma within the thickness of the myometrium, along with hyperplasia and hypertrophy of the smooth muscle fibers (1). The prevalence of adenomyosis is highly variable, 5 to 70%, depending on the different diagnostic criteria such as clinical, imaging or histological (2). This disease mainly affects multiparous women between 40 and 50 years of age. Clinical presentations of adenomyosis include menorrhagia, metrorrhagia, dysmenorrhea, dyspareunia, chronic pelvic pain, and infertility. Even though, adenomyosis is asymptomatic in one third of the patients (4 and its etiology and pathogenic mechanisms that cause adenomyosis are poorly understood (3).

The definitive diagnosis should be based in the histological study of the hysterectomy specimens (5). However, accurate preoperative diagnostic tools would be advisable in order to avoid unnecessary hysterectomy and, if possible, to investigate non-surgical alternatives. The role of imaging techniques in the evaluation of these patients will make it possible to establish a diagnostic approach, determine the depth and extent of myometrial penetration, and monitor the evolution of patients receiving conservative therapy (6). Both, transvaginal ultrasound (TVS and magnetic resonance imaging (RMI) are currently considered as the best imaging techniques for the non-invasive diagnosis of adenomyosis. Some previous meta-analyses concluded that the performance of TVS and MRI for diagnosing adenomyosis was similar (7-9). However, to the best of our knowledge, there is no reported any head-to-head meta-analysis comparing the diagnostic performance between TVS and MRI in the diagnosis of adenomyosis. Thus, the aim of this meta-analysis is to perform such heat-to-head meta-analysis.

Materials and methods

Protocol and registration

We elaborated on this meta-analysis following the Synthesizing Evidence from Diagnostic Accuracy Tests (SEDATE) guidelines (10) and PRISMA guidelines (11). The methodology for inclusion and exclusion criteria, data collection, and quality assessment was defined in advance. We did not register the protocol.

Data sources and searches

A search using five electronic databases (PubMed/MEDLINE, Web of Science, Cochrane, Scopus and CINHAL) was conducted in order to identify potentially eligible studies published between January 1990 and May 2022. The terms included in the search were "adenomyosis", "transvaginal ultrasound" and "magnetic resonance imaging". There was not language restriction in the search.

Study selection and data collection

Two authors (J.V., C.U.) screened the titles and abstracts obtained during the search in order to exclude clearly irrelevant articles. Full texts of those remaining were obtained to determine which were potentially relevant to our study. To do so, we applied the following inclusion criteria:

1. Prospective or retrospective cohort study including patients who underwent both MRI and TVS, as index tests, for the diagnosis of adenomyosis.

2. Histopathological analysis after hysterectomy as the reference standard.

3. Availability of the data required to construct the 2 × 2 table of diagnostic performance.

Description of the included studies was done using the Patients, Interventions, Comparator, Outcomes, and Study design (PICOS) criteria. Three of the authors (J.V., C.U., J.L.A.) retrieved diagnostic accuracy results and additional useful information about patients and procedures from selected primary studies independently. Disagreements emerging during the selection process and data collection were resolved by consensus among these three authors

Risk of bias in individual studies

In order to assess the quality of the studies included in our meta-analysis, the tool provided by the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) was adapted (12). This format includes four domains: 1) patient selection, 2) index test, 3) reference standard, and 4) flow and timing. For each domain, the risk of bias and concern about applicability (the latter one not referring to the flow and timing domain) were examined and rated as low, high, or unclear risk. The results of these analyses were used to establish the overall quality of the included studies and to assess potential sources of heterogeneity.

Three authors (J.V., C.U., J.L.A.) independently evaluated methodological quality using specific criteria. Any arising disagreement was solved by discussion between these three authors. The methodological quality criteria were based on the description of inclusion and exclusion criteria for patient selection domain, detailed explanation of how the index tests were performed and interpreted for the index test domain, histopathological study as the gold standard for the reference standard domain and, finally, specification of the time elapsed between index test implementation and reference standard result.

Statistical analysis

A random-effects model was used to determine the overall pooled sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR-). Likelihood ratios were used to characterize the clinical utility of the tests and to determine the post-test probability of disease. The mean prevalence of adenomyosis (pre-test probabilities) in each subset was used, together with the LRs extracted for each assessed technique, in order to calculate post-test probabilities and plot Fagan nomograms. The heterogeneity for sensitivity and specificity was assessed with Cochran's Q statistic and the I^2 index, setting the p-value at < 0.1 to determine heterogeneity. The I^2 values indicating the different degrees of heterogeneity were established at 25 %, 50 %, and 75 % for low, moderate, and high heterogeneity, respectively (13). Forest plots of the sensitivity and specificity including all studies were drawn. In the cases in which heterogeneity existed, a meta-regression was used to assess covariates that could explain it. The covariates that were analysed were the year the study took place in, study design (prospective or retrospective), sample size, prevalence of adenomyosis and number of observers for the index test (single or multiple). Summary receiver-operating characteristics (sROC) curves were plotted to visually describe the relationship between sensitivity and specificity. The area under the curve was estimated. TVS and MRI diagnostic performance for detecting adenomyosis were compared using the bivariate method. Publication bias was assessed using Deek's method (14)

All analyses were performed using Meta-analytical Integration of Diagnostic Accuracy Studies (MIDAS) and METANDI commands in STATA version 12.0 for Windows (Stata Corporation, College Station, TX, USA). A p-value < 0.05 was considered statistically significant

Results

Search results

The electronic search provided 972 citations. After removal of 343 duplicate records, 629 papers remained. Of these, 608 were excluded because of they were not relevant to the review (reviews, case reports, papers not assessing diagnostic performance or not related to the topic). We examined the full text of the remaining 21 studies. Finally, 16 articles were also excluded because they did not meet the any of the inclusion criteria. Thus, the remaining six studies were ultimately included in the meta-analysis (15-20).

Characteristics of included studies

Six studies published between 1990 and 2022 reporting data on 595 patients were included in the final analyses. In 270 patients, adenomyosis was identified in the surgical specimen. The mean prevalence of adenomiosis was 52%, ranging from 21% to 85%. Patients' age ranged from 20 to 88 years. The PICOS features of the included studies are given in Table 1.

Methodological quality of included studies

The study design was clearly stated as prospective in three studies and as retrospective in one, while the data collection in the other two studies was not described as prospective or retrospective. The QUADAS-2 method used for the assessment of the risk of bias and concerns regarding the applicability of the selected studies is shown in figure. 2.

With regard to the risk of bias in the domain of patient selection, one study was unclear about its inclusion and exclusion criteria (15) and three studies were considered high risk due to inappropriate exclusion (for example,. excluding patients with poor quality TVS or MRI images) (16,18,19). Two studies had a low risk of bias (17,20). Concerning the index test domain, focusing on TVS, all the studies comprehensively described the method as well as how it was performed and interpreted. Regarding MRI, most of the studies adequately outlined how the index test was performed and interpreted. Only one study was classified as unclear as the diagnosis criteria were described but not the MRI method (19).

Every study compared the imaging findings to the histopathology of the surgical specimen. Therefore, we can consider all of them to have a low risk of bias concerning the reference standard domain, although only four studies specifically stated that the pathologists were blinded to the imaging results. Regarding the flow and timing domain, the time lapse between the index tests and the reference standard was low risk in two studies, because less than 2 weeks passed between the index tests and histopathological confirmation of the findings (16,17). In the remaining four studies, the flow timing was unclear.

In reference to applicability, for the patient selection domain, index test domains and reference test, was low risk for all the studies included.

Diagnostic performance of TVS and MRI for the detection of adenomyosis

Overall, the pooled sensitivity, specificity, LR+, and LR- of TVS for detecting adenomyosis were 75 % (95 % confidence interval [CI] = 63 %–84 %), 81 % (95 % CI = 60 %–92 %), 3.9 (95 % CI = 1.7– 9) and 0.31 (95 % CI = 0.21–0.47), respectively. High heterogeneity was

found for both specificity (I2 = 87.78 %; Cochran Q = 40.58; p < 0.001), and for sensitivity (I2 = 76.38 %; Cochran Q = 21.17; p < 0.001). Univariate meta-regression analysis was done, but none of the variables assessed were found to explain the heterogeneity.

On the other hand, the pooled sensitivity, specificity, LR+, and LR- of MRI to adenomyosis involvement were 69 % (95 % CI = 54 %–80 %), 80 % (95 % CI = 67 %–89 %), 3.5 (95 % CI = 1.9– 6.2), 0.39 (95 % CI = 0.25–0.6), respectively. High heterogeneity was found for both sensitivity (I2 = 83.54 %; Cochran Q = 30.38; p < 0.001) and specificity (I2 = 85.55 %; Cochran Q = 34.59; p < 0.001). Univariate meta-regression analysis was done but none of the variables assessed were found to explain the heterogeneity. Figure 3 shows the forest plots for both methods. When comparing both methods, no statistical differences were found (p = 0.7509.)

The sROC curves depicted in Figure 4 show that both techniques had almost identical areas under the curve for sROC curves, with very similar 95 % prediction contours. The result for TVS was AUC 0.83 (95% CI: 0.79-0.86) and for MRI the AUC was 0.81 (95% CI: 0.54-0.80).

The Fagan nomograms showed that a positive test for TVS and MRI significantly increases the pre-test probability for adenomyosis, from 52% to 81 % in the case of TVS and from 52 % to 79 % in the case of MRI. Whereas a negative test result significantly decreases the pre-test probability for adenomyosis from 52% to 25 % in the case of TVS and from 52 % to 30 % in the case of MRI (Figure 5). There was no risk of bias neither for TVS (p = 0.38) nor for MRI (p= 0.51)

Discussion

Summary of Evidence

There are no many studies comparing the diagnostic performance of TVS and MRI for detecting uterine adenomyosis in the same set of patients. In the present meta-analysis we have found out that TVS and MRI have a similar performance for diagnosing adenomyosis. The quality of studies assessed is good except for the case of patient selection as high risk of bias was observed for half of studies evaluated.

Interpretation of Results

Our data indicate that both techniques show a high specificity and moderate sensitivity for the diagnosis of adenomyosis. No statistically significant differences were found between one method and the other for the diagnosis of adenomyosis However, we observed a significant heterogeneity. This implies that our results should be interpreted with caution.

According to our results, both methods could be used interchangeably. However, on clinical grounds, the use of ultrasound would imply lower costs and this technique is more widely available. Therefore, it should be considered as the first choice.

Limitations and Strengths

The main strength of our study is that, to the best of our knowledge, this meta-analysis is the first head-to-head comparison study addressing this issue. There are some previously reported meta-analysis comparing TVS and MRI for the diagnosis of adenomyosis (7-9). These meta-analyses found similar results than ours (Table 2), what confirm the concept that TVS and MRI have similar diagnostic performance for this entity. The main difference between those studies and ours is that we did a formal statistical comparison and the others did not..

Despite this, our study also has some limitations. We consider that the main limitation of this meta-analysis is mainly the few studies currently available comparing TVS and MRI in the diagnosis of adenomyosis. In fact, is interesting to note that only six studies with direct comparison of both techniques have been reported in 28 years. In addition, more interesting is observing the fact that no apparent improvement on diagnostic performance is observed along these years, in spite of significant improvements in technical quality imaging for TVS and MRI.

These facts combined with the high heterogeneity we have observed make to us thinking there is a need for more studies assessing this issue.

Future Research Agenda

As mentioned above, more prospective studies with better selection criteria are needed. Probably, prospective comparative studies using MUSA criteria would be advisable (21) On the other hand, there is a need to establish good and global criteria for the diagnosis of adenomyosis. Moreover, the need to train sonographers for a better diagnosis is also a point to consider.

Conclusion

No statistically significant differences were found between MRI and TVS for the diagnosis of adenomyosis.

Conflict of Interest

The authors declare that they have no conflict of interest

Bibliography

1. Zhai J, Vannuccini S, Petraglia F, Giudice LC. Adenomyosis: Mechanisms and Pathogenesis. Semin Reprod Med. 2020 May;38(2-03):129-143. doi: 10.1055/s-0040-1716687.
2. Habiba M, Benagiano G. Classifying Adenomyosis: Progress and Challenges. Int J Environ Res Public Health. 2021 Nov 25;18(23):12386. doi: 10.3390/ijerph182312386.
3. Guo SW. The Pathogenesis of Adenomyosis vis-à-vis Endometriosis. J Clin Med. 2020 Feb 10;9(2):485. doi: 10.3390/jcm9020485.
4. Harada T, Khine YM, Kaponis A, Nikellis T, Decavalas G, Taniguchi F. The Impact of Adenomyosis on Women's Fertility, Obstet Gynecol Survey. 2016; 71 (9): 557-568. doi: 10.1097/OGX.0000000000000346
5. Bergholt T, Eriksen L, Berendt N, Jacobsen M, Hertz JB. Prevalence and risk factors of adenomyosis at hysterectomy. Human Reproduction. 2001;16(11):2418-21. DOI:10.1093/humrep/16.11.2418
6. Dashottar S, Singh AK, Debnath J, Muralidharan CG, Singh RK, Kumar S. Comparative analysis of changes in MR imaging of pre and post intrauterine progesterone implants in adenomyosis cases. Med J Armed Forces India. 2015 Apr;71(2):145-51. doi: 10.1016/j.mjafi.2015.01.008.
7. Champaneria R, Abedin P, Daniels J, Balogun M, Khan KS. Ultrasound scan and magnetic resonance imaging for the diagnosis of adenomyosis: systematic review comparing test accuracy. Acta Obstet Gynecol Scand. 2010;89(11):1374-84.

8. Tellum T, Nygaard S, Lieng M. Noninvasive Diagnosis of Adenomyosis: A Structured Review and Meta-analysis of Diagnostic Accuracy in Imaging. J Minim Invasive Gynecol. 2020;27(2):408-418.e3
9. Liu L, Li W, Leonardi M, Condous G, Da Silva Costa F, Mol BW, Wong L. Diagnostic Accuracy of Transvaginal Ultrasound and Magnetic Resonance Imaging for Adenomyosis: Systematic Review and Meta-Analysis and Review of Sonographic Diagnostic Criteria. J Ultrasound Med. 2021 Nov;40(11):2289-2306. doi: 10.1002/jum.15635. Epub 2021 Jan 27. PMID: 33502767.
10. Sotiriadis A, Papatheodorou SI, Martins WP. Synthesizing Evidence from Diagnostic Accuracy TEsts: the SEDATE guideline. Ultrasound Obstet Gynecol 2016; 47: 386–395. doi:10.1002/uog.15762
11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71. doi: 10.1136/bmj.n71.
12. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529-36.
13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.

14. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005;58:882-93.
15. Ascher SM, Arnold LL, Patt RH, Schruefer JJ, Bagley AS, Semelka RC, Zeman RK, Simon JA. Adenomyosis: prospective comparison of MR imaging and transvaginal sonography. Radiology. 1994 Mar;190(3):803-6. doi: 10.1148/radiology.190.3.8115630.
16. Reinhold C, McCarthy S, Bret PM, Mehio A, Atri M, Zakarian R, Glaude Y, Liang L, Seymour RJ. Diffuse adenomyosis: comparison of endovaginal US and MR imaging with histopathologic correlation. Radiology. 1996 Apr;199(1):151-8. doi: 10.1148/radiology.199.1.8633139.
17. Dueholm M, Lundorf E, Hansen ES, Sørensen JS, Ledertoug S, Olesen F. Magnetic resonance imaging and transvaginal ultrasonography for the diagnosis of adenomyosis. Fertil Steril. 2001 Sep;76(3):588-94. doi: 10.1016/s0015-0282(01)01962-8.
18. Bazot M, Cortez A, Darai E, Rouger J, Chopier J, Antoine JM, Uzan S. Ultrasonography compared with magnetic resonance imaging for the diagnosis of adenomyosis: correlation with histopathology. Hum Reprod. 2001 Nov;16(11):2427-33. doi: 10.1093/humrep/16.11.2427.
19. Alborzi S, Askary E, Khorami F, Poordast T, Abdulwahid Hashim Alkhalidi B, Hamedi M, Alborzi S, Shahraki HR. A Detailed Study in Adenomyosis and Endometriosis: Evaluation of the Rate of Coexistence Between Uterine Adenomyosis and DIE According to Imaging and Histopathology Findings. Reprod Sci. 2021 Aug;28(8):2387-2397. doi: 10.1007/s43032-021-00527-0.

20. Anwar, J., Tariq, M., Amin, N., Gul, B., Niaz, A., Nawaz, K. Diagnostic Accuracy of Ultrasound and MRI for Diagnosis of Adenomyosis Taking Histopathology as Gold Standard. *PAFMJ 2022; 72*(SUPPL-2):S346-49.

21. Van den Bosch T, Dueholm M, Leone FP, Valentin L, Rasmussen CK, Votino A, Van Schoubroeck D, Landolfo C, Installé AJ, Guerriero S, Exacoustos C, Gordts S, Benacerraf B, D'Hooghe T, De Moor B, Brölmann H, Goldstein S, Epstein E, Bourne T, Timmerman D. 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;46(3):284-98.