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**A Systematic Review of Tissue Sampling Techniques for the Diagnosis of Adenomyosis.**

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**Short Title:** Tissue Sampling Techniques for Adenomyosis.

**Key Words:** Adenomyosis, Biopsy, Tissue Sampling.

**Conflicts of Interest**: Dr. Keith Isaacson is a consultant for Karl Storz and Medtronic. Dr. Peter Movilla and Dr. Stephanie Morris have no conflicts of interest.

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**Institutional Review Board:** Systematic Review is exempt from IRB approval.

**Precis:** Uterine tissue sampling for the confirmatory diagnosis of adenomyosis is feasible, however currently it has limited clinical application and is more appropriate in an established research setting.

**Abstract:**

*Objective:* Evaluate the accuracy of tissue sampling techniques for the diagnosis of adenomyosis.

*Data Source:* Systematic Review via MEDLINE and the Cochrane Library searches.

*Methods of Study Selection:* Review performed utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, utilizing MeSH terms and keywords including "Adenomyosis/diagnosis" or "Adenomyosis/pathology" or "Myometrium/pathology" and "Biopsy" or "Hysteroscopy" or "Laparoscopy". Articles initially screened by title and abstract to include pertinent studies with reference lists cross-referenced to find additional studies. Articles related to the diagnosis of uterine malignancy or studies in which tissue sampling was obtained via excisional surgical procedures were excluded from review.

*Tabulation:* Fourteen studies were identified describing tissue sampling techniques for the purpose of diagnosing adenomyosis, with a total of 1909 patients, from 12 different countries, involving 6 different continents. Tissue sampling techniques were categorized based on (1) biopsy approach as either intra-uterine and extra-uterine, and (2) techniques that were validated or not validated with a confirmatory hysterectomy pathology.

*Integration and Results:* Overall, there was significant heterogeneity in the tissue sampling techniques including intra-uterine sampling obtained via hysteroscopic biopsy or resection and extra-uterine tissue sampling obtained via needle biopsy by a percutaneous, transvaginal, laparoscopic or ex-vivo approach. Sensitivity of these techniques varied greatly based on technique, tissue sampling location and the number of biopsies obtained, and was as low as 22.2% via an ultrasound guided transvaginal biopsy of suspicious uterine lesions with 4 biopsies per patient and was as high as 97.8% via a laparoscopic guided myometrial biopsy of suspicious uterine lesions with 10 biopsies per patient. Specificity for the identified tissue sampling techniques were more homogeneous ranging from 78.5% - 100.0% for all methods identified. The positive predictive value and negative predictive value ranges were 75.9% - 100.0% and

46.4% - 80.0% respectively amongst all tissue sampling techniques identified with confirmatory hysterectomy pathology.

*Conclusion:* Due to the heterogeneity of the tissue sampling techniques, diverse patient populations, and significant conflicting recommendations, no conclusive recommendation on the optimal tissue sampling technique can be made. However, it is of the authors opinion that it would be reasonable to limit uterine tissue sampling for confirmatory diagnosis of adenomyosis in those patients with a suspicion of adenomyosis based on both symptom profile and pelvic ultrasound, where a planned diagnostic laparoscopy for either infertility or pelvic pain has already been contemplated and scheduled, and where the confirmatory results may be of clinical benefit in discussing the prognosis of post-operative recurrent symptoms and guide any future treatment recommendations.

**Introduction:**

Adenomyosis is a gynecologic condition found in up to 20.9% of women based on pelvic ultrasound findings and may lead to significant symptoms such as dysmenorrhea, pelvic pain, dyspareunia, heavy menstrual bleeding and infertility in up to one third of these patients[1, 2]. The common presenting pelvic symptoms associated with adenomyosis make it difficult to distinguish on initial presentation from other gynecologic disorders.



Since its discovery by German pathologist Carl von Rokitansky in 1860, fertility sparing treatment of adenomyosis has been a challange[3]. Advances have been limited by the inability to obtain a confirmatory diagnosis of adenomyosis without the performance of a hysterectomy.

Pelvic ultrasound or MRI are the mainstay diagnostic modalities for making a presumed diagnosis of adenomyosis, yet histologic confirmation is still required for definitive diagnosis. Pelvic ultrasound and pelvic magnetic resonance imaging (MRI) have a sensitivity for detecting adenomyosis of up to 72.0% and 77.0% respectively; and a specificity for detecting adenomyosis of 81.0% and 89.0% respectively[4]. However, the varied appearance of adenomyosis on pelvic ultrasound in addition to the variation in radiologist experience significantly impacts the diagnosis of adenomyosis via pelvic ultrasound, with sensitivity falling to as low as 12.0% when read by a non-gynecologic specialized radiologist[5,6].

Conservative management of adenomyosis related symptoms are often initially treated hormonally with either oral contraceptive pills, progestin only pills, or a levonorgestrel intrauterine device. However, as this once neglected diagnosis gains more spotlight in the gynecologic world, more disease specific

treatment options for adenomyosis are becoming of increased interest. Several cycles of leuprolide acetate have become a common practice prior to embryo transfer in an attempt to improve endometrial receptivity in patients with adenomyosis[7,8]. Uterine artery embolization (UAE) and high intensity focused ultrasound (HIFUS) have been trialed for management of persistent dysmenorrhea and heavy menstrual bleeding associated with adenomyosis in patients who have failed medical management[9]. In select patients, open or laparoscopic surgical resection of adenomyosis have be used for symptom relief and to improve pregnancy outcomes after recurrent pregnancy loss[10,11]. As more interest and research develops in the realm of uterine transplant, it is not unfeasible to one day see uterine transplant as a treatment option for uterine-related infertility in patients with significant adenomyosis[12,13].

In an effort to optimize appropriate patient selection for these treatment options, it is it important to ensure accurate diagnosis. In addition, future medical technologies may allow for personalization of therapies for specific symptoms and individuals with adenomyosis. Thus, identifying fertility sparing techniques for more accurate and definitive diagnosis and therapies are needed, and may require direct tissue sampling of the uterine myometrium.



The first described tissue sampling technique for the diagnosis of adenomyosis without a hysterectomy was presented by Pasquinucci in 1991[14], with subsequent case reports and trials describing methods for collecting uterine biopsies to diagnose adenomyosis via hysteroscopy, laparoscopy, percutaneous needle and transvaginal approaches[15, 16]. Here we systematically review the current literature for all tissue sampling techniques for the diagnosis of adenomyosis. We describe the reported tissue sampling techniques for the diagnosis of adenomyosis, and review the sensitivity, specificity, positive predictive value, and negative predictive value of each of the techniques described and confirmed with hysterectomy pathology.

**Methods:**

This systematic review was conducting following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This systemic review was submitted for registration with PROSPERO, the international prospective of systematic reviews; entitled “A systematic review of tissue sampling techniques for the diagnosis of adenomyosis” (ID 135071). We queried the MEDLINE and the Cochrane Central Register of Controlled Trials databases to identify relevant literature.

We used a combination of available MeSH terms and keywords including “Adenomyosis/diagnosis” or “Adenomyosis/pathology” or “Myometrium/pathology” and “Biopsy” or “Hysteroscopy” or “Laparoscopy”, to identify pertinent studies. We included all studies available in English that were

identified from the search query performed on April 20th, 2019. Studies were initially screened by title and abstract to include pertinent interventional studies, observational studies, and cases reports. Expert opinions and review articles were excluded from qualitative synthesis. The reference list of the included studies as well as relevant reviews were cross-referenced to find additional studies.

Studies that included patients with uterine malignancy or studies in which tissue sampling was obtained via excisional surgical procedures such as adeno-myomectomy, uterine wedge resection, the Osada procedure or hysterectomy alone were excluded from review.

The studies remaining for qualitative synthesis where then categorized based on biopsy approach as either intra-uterine and extra-uterine, and then subcategorized by techniques that were either validated or not validated with a confirmatory hysterectomy.

Two reviewers (P.M. and K.I.) evaluated the eligibility of candidate articles by reviewing the full text manuscripts of the screened papers. These two reviewers abstracted the details of the study characteristics, tissue sampling methods, and outcomes for each of the papers screened.



All studies were additionally evaluated based on the NIH quality assessment guidelines designed for case series studies and given an assessment of either good, fair or poor based on this assessment. A good assessment would be provided for studies that demonstrated a clear objective, well defined study population, clearly described intervention, consistently measured outcome, and well described methods and results.

**Results:**

The search strategy identified a total of 182 citations. After assessing the citation titles and abstracts for topic relevance, identifying additional articles from cross-references, applying exclusion criteria, and removing duplicates there was a total of 14 studies remaining for analysis (Figure 1). Of these 14 studies, 5 studies described an intra-uterine hysteroscopic approach for tissue sampling via biopsy or resection (Table 1); 8 studies described an extra-uterine needle biopsy approach for tissue sampling via either percutaneous, transvaginal, laparoscopic or ex-vivo biopsy (Table 2).; 1 study described tissue sampling techniques with both intra-uterine hysteroscopic and extra-uterine needle biopsy approaches (Table 2).

Of these final 14 studies, six described adenomyosis tissue sampling techniques with confirmatory hysterectomy pathology for comparison, while eight studies described adenomyosis tissue sampling techniques without confirmatory hysterectomy pathology for comparison. The studies within this systematic review evaluated a total of 1909 patients, with a total of 12 different countries involved, from 6 different continents.

*Intra-Uterine Hysteroscopic Tissue Sampling Techniques*

Only 1 study by Dakhly, demonstrated a hysteroscopic tissue sampling approach for the diagnosis of adenomyosis with subsequent confirmatory hysterectomy pathology. In this study a single hysteroscopic biopsy was taken from the posterior uterine wall utilizing hysteroscopic scissors and graspers alone and demonstrated a 54.3% sensitivity and a 78.5% specificity for diagnosing adenomyosis amongst 292 premenopausal women undergoing hysterectomy for dysmenorrhea and heavy menstrual bleeding symptoms[17].

The remaining 5 studies that described a hysteroscopic tissue sampling approach for the diagnosis of adenomyosis did not have subsequent hysterectomy pathology to assist in calculating the diagnostic sensitivity or specificity of the technique[16, 18, 19, 20, 21]. Two studies by Gordts and Fernandez respectively, described hysteroscopic tissue sampling techniques in a total of 3 patients with presumed adenomyosis, based on symptoms and ultrasound findings suggestive of adenomyosis. Both studies succeeded in obtaining a 100.0% diagnosis rate of adenomyosis amongst the three patients sampled[18, 19]. 3 studies by Goswami, Wood, and Mccausland, all described hysteroscopic resection techniques for diagnosing adenomyosis amongst patients with suspicious symptoms alone (dysmenorrhea and/or HMB), reporting a diagnosis rate via histologically confirmed adenomyosis of 60.0% (30 patients), 100.0% (9 patients), and 66.0% (50 patients) respectively[16, 20, 21].





Amongst the total of 6 intra-uterine tissue sampling studies, the hysteroscopic resectoscope was utilized in 4 of the studies, with a cutting loop depth ranging from 4 – 5 mm, with tissue samples taken either directed at suspicious lesions identified on pelvic ultrasound or blindly from the posterior uterine wall, with up to 1.5 – 3.0 cm length tissue strips extracted for evaluation. In the cases series presented by Gordts, a unique hysteroscopic instrument called a Utero-spirotome was utilized, carrying a 1 cm length helical cutting tip that was carefully manipulated into the intrauterine cavity and imbedded into the uterus to obtain a uterine sample with both endometrial and myometrial tissue.

All of the intra-uterine hysteroscopic tissue sampling studies discussed here received an NIH Quality Assessment rating of “Good” by the authors, with the exception of the Gordts and Fernandez papers.

These two studies received a "Fair" assessment primary do to the low sample sizes included in the evaluation of their tissue sampling study.

*Extra-Uterine Needle Biopsy Tissue Sampling Techniques*

A total of 5 studies described an extra-uterine tissue sampling technique with a needle biopsy for obtaining myometrial tissue samples with subsequent confirmatory hysterectomy pathology, for a total of 391 patients[22, 23, 24 ,25, 26]. Of these 5 studies, one described an extra-uterine needle biopsy by means of ultrasound guided transvaginal biopsy, one via laparoscopic guided myometrial biopsy and three with extra-uterine needle biopsy techniques performed ex-vivo after the a hysterectomy was completed.

The sensitivity of extra-uterine needle biopsies varied significantly and appeared dependent on the route of biopsy and total number of biopsies performed per patient. Extra-uterine needle biopsy sensitivity ranged from 22.2% when performed by transvaginal ultrasound guided needle biopsy with 4 biopsies per patient targeted at suspicious adenomyosis lesions identified via pelvic ultrasoind[22] up to 97.8% via laparoscopic needle biopsy with 10 biopsies performed per patient targeted at suspicious adenomyosis lesions identified via preoperative pelvic ultrasound[23].



In all three studies performing extra-uterine needle biopsy on ex-vivo uterine specimens following hysterectomy, samples were not collected based on any pelvic ultrasound suspicious lesions of adenomyosis, but rather collected either routinely from a preselected area of the uterus or by blind biopsy. The sensitivity from these 3 studies ranged from 44.8% - 62.5%[24, 25, 26].

All 5 studies demonstrated a high specificity via extra-uterine needle biopsy, ranging from 95.9% - 100.0% for all of routes of the extra-uterine needle biopsy described[17, 22, 23, 24, 25, 26].

All of these studies utilized a biopsy cutting needle, although from varying manufacturing companies. The range of needle size utilized was 14 – 20 gauge, with a 14-gauge needle utilized solely in 3 of the 5 studies[17, 22, 23, 24, 25, 26].

There were an additional 3 studies that described an extra-uterine tissue sampling technique with needle biopsy for obtaining myometrial tissue samples but without subsequent confirmatory hysterectomy pathology, totaling an additional 1,134 patients[15, 27, 28]. As a hysterectomy was not

performed for patients within these studies, they did not report a sensitivity or specificity of their techniques; rather they reported the diagnosis rate of adenomyosis from patients with either suspicious symptoms and/or pelvic ultrasound findings.

Nam and Walker both described ultrasound guided transvaginal uterine biopsy for diagnosing adenomyosis without confirmatory hysterectomy for suspected adenomyosis based on sonographic findings with a 92.2% - 100.0% diagnosis rate of adenomyosis amongst all of their patients sampled[27, 28]. Wood described an ultrasound guided abdominal percutaneous uterine biopsy with a 100.0% diagnosis rate of adenomyosis amongst patients sampled[16].

Vercellini and Wood both also described laparoscopic guided uterine biopsy approaches for patients with symptoms of adenomyosis alone without confirmation hysterectomy with a 18.1% - 100.0% diagnosis rate of adenomyosis on final pathological evaluation of the biopsy samples[15, 16].

All of the extra-uterine needle biopsy tissue sampling studies discussed here received an NIH Quality Assessment rating of “Good” by the authors, with the exception of the Walker and Wood studies. These two studies received a “Fair” assessment as it was deemed that they had low sample sizes for the respective interventions they described.





**Discussion:**

The ability to obtain a diagnosis of adenomyosis via histologic pathology without hysterectomy has been of great interest for the past three decades, with several techniques described in the literature. There is a large variance in the sensitivity amongst tissue sampling techniques with confirmatory hysterectomy pathology, with most papers reporting a suboptimal and low sensitivity for the diagnosis of adenomyosis. The number of biopsies, the location of the biopsy and the optimal biopsy technique are all potential modifiable factors that impact the sensitivity in detecting adenomyosis.

It makes sense that the more uterine biopsy samples obtained, the higher the sensitivity of any given tissue sampling technique. Brosens, Popp, and Nam all discussed the significant variation in sensitivity of detecting adenomyosis based on the number of biopsies obtained. Brosens demonstrated that sensitivity was as low as 2.3% - 56.0% with two biopsy samples and increased to 9.0% - 100.0% when 8 biopsy samples were obtained. Popp reported the sensitivity was 8.0% - 18.7% with one biopsy samples, but as high as 40.0% - 73.0% with 10 biopsy samples. Nam demonstrated 100.0% concordance between

sonographic diagnosis of adenomyosis with core needle biopsy diagnosis when greater than or equal to 6 biopsy samples were obtained.

Another significant factor that impacted the sensitivity of the tissue sampling technique was the location tissue samples. In many of the early studies, the posterior uterine wall was exclusively sampled due to the historically accepted hypothesis that the majority of adenomyosis burden is in the posterior uterine wall[15, 17]. Alternatively, tissue sampling could be obtained via targeted areas on the uterus based on sonographic lesions that were suspicious for adenomyosis[22, 23]. Although no consensus was made amongst all of the studies reported, the highest sensitivity recorded by Jeng was following tissue sampling of lesions suspicious for adenomyosis based on preoperative pelvic ultrasound.

The disease burden of adenomyosis also plays a significant role in the overall sensitivity of adenomyosis tissue sampling. Brosens concluded that tissue sampling sensitivity was highly dependent on the disease burden of adenomyosis with sensitivity of detecting adenomyosis restricted to the inner third of the myometrium to be only 2.3% - 9.0% via extra-uterine tissue sampling, but the sensitivity of detecting severe adenomyosis located in the outer one third of the myometrium being 56.0% - 100.0% via extra-uterine tissue sampling. Along these lines, Jeng hypothesized that their studies high sensitivity and specificity, 97.8% and 100.0% respectively, via the laparoscopic guided myometrial biopsy approach was due to their technique's unique ability to get a biopsy orientation perfectly perpendicular to the uterine serosa. This technique was believed to enable an adequate cross-section that would include uterine serosa, complete myometrium, the junctional zone and endometrium, minimizing the false negative findings of patients with minimal disease burden of their adenomyosis presumably close to the junctional zone. This may have been a limiting factor in the Tellum paper where the transvaginal biopsy approach, which demonstrated a low sensitivity of 22.0%, as the transvaginal approach would not obtain a biopsy from such a perpendicular orientation and potentially miss areas of adenomyosis during tissue sampling.





There were no serious complications reported amongst any of the fourteen studies evaluated. The concern for potential uterine bleeding during in-vivo tissue sampling was discussed by several authors and each time they recommended the use of prophylactic local vasopressin injection into the biopsy site as a means of decreasing any significant uterine bleeding[23,26].

There were contrary opinions amongst the reported papers on the future optimization and utility of tissue sampling for the diagnosis of adenomyosis. Vercellini and Brosens both strongly recommended against routine myometrial tissue sampling for the diagnosis of adenomyosis citing that it does not add

useful information over a transvaginal ultrasound and the need for multiple biopsies for a respectable sensitivity as a clinical impracticality. Dakhly recommended a novel two step diagnostic approach with a transvaginal ultrasound be utilized as a screening test for adenomyosis due to its higher sensitivity with a hysteroscopic uterine biopsy of the posterior uterine wall utilized performed as a confirmatory test due to its higher specificity. Tellum and Nam recommended the use of transvaginal myometrial biopsy in vivo, however Tellum recommended biopsy samples be obtained only in research settings, and not clinical use until further evaluations of benefits and long-term adverse events are evaluated. Jeng and Popp were the only two authors supporting the routine use of that tissue sampling within the clinical realm. They separately discussed the minimal additional risk of uterine tissue sampling specifically if performed during diagnostic laparoscopy for the final step of an infertility workup or for treatment of pelvic pain for ruling out pelvic endometriosis and here for additionally confirming adenomyosis.

In conclusion, tissue sampling for the purposes of making a confirmatory diagnosis is possible. This systematic review provides a detailed summary of the known publications highlighting the known various tissue sampling techniques, all identified in accordance with the PRISMA guidelines. There was significant heterogeneity amongst the studies tissue sampling approach, patient selection, biopsy location and number of biopsies obtained making it difficult to make a conclusive statement regarding the best tissue sampling technique for diagnosing adenomyosis. As future research and personalized medical and surgical treatment modalities are created and implemented specifically for adenomyosis, the role of confirmatory diagnosis will be of great value. Until that time, it would be reasonable to limit uterine tissue sampling for confirmatory diagnosis of adenomyosis in those patients with preliminary suspicion of adenomyosis based on symptom profile and pelvic ultrasound, where a planned invasive procedure is already contemplated such as a diagnostic laparoscopy for infertility or pelvic pain. In these circumstances biopsy samples can be collected via a laparoscopic means with a 14-guage needle, as this has the highest proven sensitivity and specificity profile and can aide in prognosis of possible recurrent symptoms and guide any future surgical treatment recommendations. Pelvic imaging via either pelvic ultrasound or pelvic MRI currently have very acceptable sensitivity, specificity, and reproducibility in detecting adenomyosis without an invasive procedure, thus utilizing either diagnostic imaging modality over obtaining a definitive diagnosis via tissue sampling should be considered very appropriate prior to the management of the majority of patients with suspected adenomyosis[29, 30]. Limiting utilization of tissue sampling for the confirmatory diagnosis of adenomyosis to the subset of patients described above would ensure that no unnecessary diagnostic interventions are taken for patients who would potentially gain little to no clinical benefit, until there are one day more efficacious and specific treatment options available for the management of adenomyosis." However, for research purposes under proper IRB protocols, obtaining tissue samples from patients desiring to keep their uterus is extremely valuable to better understand this enigmatic disease and should be pursued in the proper research setting.

**References:**


1. Naftalin J, Hoo W, Pateman K, Mavrelos D, Holland T, Jurkovic D; How common is adenomyosis? A prospective study of prevalence using transvaginal ultrasound in a gynaecology clinic. Hum Reprod. 2012 Dec;27(12):3432-9. doi: 10.1093/humrep/des332. Epub 2012 Sep 20.

2. Jones, Howard W, and John A. Rock. Te Linde's Operative Gynecology. Chapter 22: Endometriosis, Section: Adenomyosis. 2015. Print.

3. Benagiano G, Brosens I; History of adenomyosis. Best Pract Res Clin Obstet Gynaecol. 2006 Aug;20(4):449-63. Epub 2006 Mar 2.

4. 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 Nov;89(11):1374-84. doi: 10.3109/00016349.2010.512061. Epub 2010 Oct 8.

5. Tamhane N, McDowell M, Oliva M, Tanner JP, Hochberg L, Baker M, Imudia AN, Mikhail E; Association between preoperative adenomyosis detection rate during pelvic ultrasonography and the specialty of the reading physician. J Minim Invasive Gynecol. 2019 Apr 17. pii: S1553-4650(19)30193-1. doi: 10.1016/j.jmig.2019.04.015.

6. Tellum T, Nygaard S, Skovholt EK, Qvigstad E, Lieng M; Development of a clinical prediction model for diagnosing adenomyosis. Fertil Steril. 2018 Oct;110(5):957-964.e3. doi: 10.1016/j.fertnstert.2018.06.009.

7. Zhou LM, Zheng J, Sun YT, Zhao YY, Xia AL; Study on leuprorelin acetate in treatment of uterine adenomyosis with infertility; Zhonghua Fu Chan Ke Za Zhi. 2013 May;48(5):334-7.

8. Guo S, Li Z, Yan L, Sun Y, Feng Y; GnRH agonist improves pregnancy outcome in mice with induced adenomyosis by restoring endometrial receptivity. Drug Des Devel Ther. 2018 Jun 7;12:1621-1631. doi: 10.2147/DDDT.S162541. eCollection 2018.

9. Jin-Jiao Li, Jacqueline P. W. Chung, Sha Wang, Tin-Chiu Li, and Hua Duan; The Investigation and Management of Adenomyosis in Women Who Wish to Improve or Preserve Fertility. BioMed Research International

10. Nezhat C, Wood M, Kennedy Burn M, Nezhat A; A patient with severe adenomyosis requests uterine-sparing surgery. OBG Manag. 2019 February;31(2):28-30, 32-34, 36-37, 49. Article updated March 15, 2019.

11. Osada H. Uterine adenomyosis and adenomyoma: the surgical approach. Fertil Steril. 2018;109:406-417.

12. Akar M; Might uterus transplantation be an option for uterine factor infertility. Journal of the Turkish German Gynecological Association. Publish 2015 March 1. PMID 25788850

13. Johannesson L, Jarvholm S; Uterus transplantation: current progress and future prospects. Inernational Journal of Women's Health. Published 2016 Feb 5. PMID 26917976

14. Pasquinucci C, Pittino R, Carcione R, Corbo A; Adenomyosis: trans-myometrial biopsy. Ann Ostet Ginecol Med Perinat. 1991 Mar-Apr;112(2):91-4.

15. Vercellini P, Trespidi L, Panazza S, Bramante T, Mauro F, Crosignani PG; Laparoscopic uterine biopsy for diagnosing diffuse adenomyosis. J Reprod Med. 1996 Apr;41(4):220-4.

16. Wood C, Maher P, Hill D; Biopsy diagnosis and conservative surgical treatment of adenomyosis. J Am Assoc Gynecol Laparosc. 1994 Aug;1(4 Pt 1):313-6.

17. Dakhly DM, Abdel Moety GA, Saber W, Gad Allah SH, Hashem AT, Abdel Salam LO; Accuracy of Hysteroscopic Endomyometrial Biopsy in Diagnosis of Adenomyosis. J Minim Invasive Gynecol. 2016 Mar-Apr;23(3):364-71. doi: 10.1016/j.jmig.2015.11.004. Epub 2015 Nov 12.

18. Gordts S, Campo R, Brosens I; Hysteroscopic diagnosis and excision of myometrial cystic adenomyosis. Gynecol Surg. 2014;11(4):273-278. Epub 2014 Oct 3.

19. Fernández C, Ricci P, Fernández E; Adenomyosis visualized during hysteroscopy. J Minim Invasive Gynecol. 2007 Sep-Oct;14(5):555-6.

20. Goswami A, Khemani M, Logani KB, Anand R. Adenomyosis: diagnosis by hysteroscopic endomyometrial biopsy, correlation of incidence and severity with menorrhagia. J Obstet Gynaecol Res. 1998 Aug;24(4):281-4.

21. McCausland AM. Hysteroscopic myometrial biopsy: its use in diagnosing adenomyosis and its clinical application. Am J Obstet Gynecol. 1992 Jun;166(6 Pt 1):1619-26; discussion 1626-8.

22. Tellum T, Qvigstad E, Skovholt EK, Lieng M; In Vivo Adenomyosis Tissue Sampling Using a Transvaginal Ultrasound-guided Core Biopsy Technique for Research Purposes: Safety, Feasibility, and Effectiveness. J Minim Invasive Gynecol. 2019 Feb 8. pii: S1553-4650(19)30088-3. doi: 10.1016/j.jmig.2019.02.002.

23. Jeng CJ, Huang SH, Shen J, Chou CS, Tzeng CR; Laparoscopy-guided myometrial biopsy in the definite diagnosis of diffuse adenomyosis. Hum Reprod. 2007 Jul;22(7):2016-9. Epub 2007 Apr 11.

24. Vercellini P, Cortesi I, De Giorgi O, Merlo D, Carinelli SG, Crosignani PG; Transvaginal ultrasonography versus uterine needle biopsy in the diagnosis of diffuse adenomyosis. Hum Reprod. 1998 Oct;13(1O):2884-7.

25. Brosens JJ, Barker FG; The role of myometrial needle biopsies in the diagnosis of adenomyosis. Fertil Steril. 1995 Jun;63(6):1347-9.

26. Popp LW, Schwiedessen JP, Gaetje R; Myometrial biopsy in the diagnosis of adenomyosis uteri. Am J Obstet Gynecol. 1993 Sep;169(3):546-9.

27. Nam JH, Lyu GS; Abdominal ultrasound-guided transvaginal myometrial core needle biopsy for the definitive diagnosis of suspected adenomyosis in 1032 patients: a retrospective study. J Minim Invasive Gynecol. 2015 Mar-Apr;22(3):395-402. doi: 10.1016/j.jmig.2014.08.006. Epub 2014 Aug 11.

28. Walker, Jones; Transvaginal ultrasound guided biopsies in the diagnosis of pelvic lesions. Minim Invasive Ther Allied Technol. 2003 Sep;12(5):241-4.

29. Van den Bosch T, de Bruijn AM, de Leeuw RA, Dueholm M, Exacoustos C, Valentin L, Bourne T, Timmerman D, Huirne JAF. Sonographic classification and reporting system for diagnosing adenomyosis. Ultrasound Obstet Gynecol. 2019 May;53(5):576-582.

30. Lazzeri L, Morosetti G, Centini G, Monti G, Zupi E, Piccione E, Exacoustos C. A sonographic classification of adenomyosis: interobserver reproducibility in the evaluation of type and degree of the myometrial involvement. Fertil Steril. 2018 Nov;110(6):1154-1161

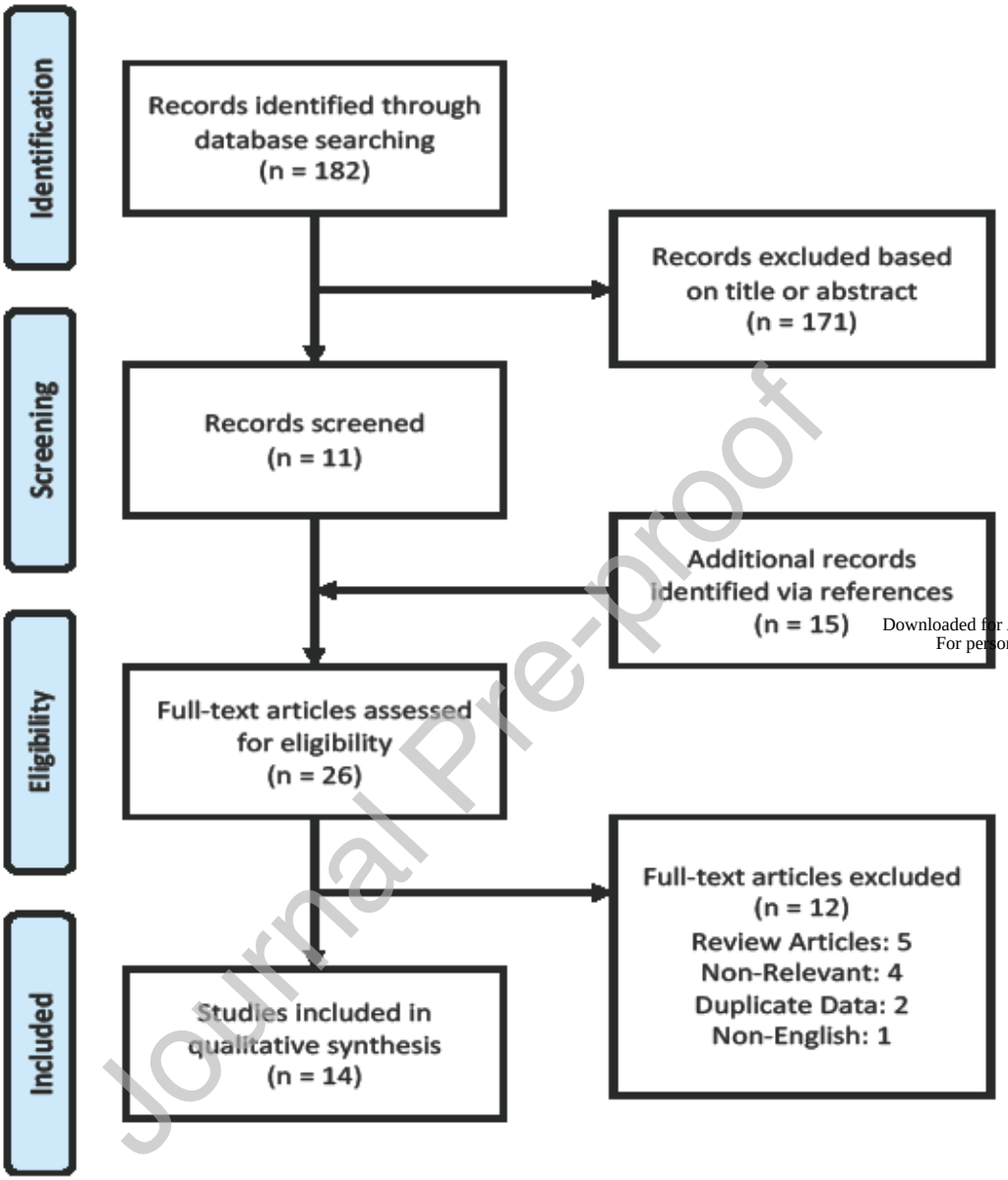






Figure 1: PRISMA flow diagram of included studies

Table 1: Intra-Uterine/Hysteroscopic Tissue Sampling Techniques.

| Study | Country | Number of Patients | Confirmatory Hysterectomy Pathology | Approach | Biopsy Quantity | Biopsy Location | Instrument | Sampling Success Rate | Biopsy Diagnosis Rate of Adenomyosis | Sensitivity | Specificity | Positive Predictive Value | Negative Predictive Value | Serious Complications | NIH Quality Assessment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dakhly (2016) | Egypt | 292 | Yes | Hysteroscopic biopsy | Single | Posterior uterine wall | Hysteroscopic scissors and grasper<br><br>5-mm rigid hysteroscope Tekno-Medical Optik Chirurgie Case 1: 5-Fr sciss ors Case 2: Utero-Spirotome<br><br>4.4- | 100% (292/292 patients) | N/A | 54.3% (88/162 patients) | 78.5% (102/130 patients) | 75.9% (88/116 patients) | 58.0% (102/172 patients) | None | Good |
| Gordts (2014) | Belgium | 2 | No | Hysteroscopic biopsy | Single | Suspicious lesions | | 100% (2/2 patients) | 100% (2/2 patients) | N/A | N/A | N/A | N/A | None | Fair |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | mm hysteroscope Karl Stroz | | | | | | | |
| Fernandez (2007) | Chile | 1 | No | Hysteroscopic resection | Single | Suspicious lesion | Hysteroscopic resectoscope | 100% (1/1 patient) | 100% (1/1 patient) | N/A | N/A | N/A | N/A | None | Fair |
| Goswami (1998) | India | 30 | No | Hysteroscopic resection | Single | Posterior uterine wall | Hysteroscopic resectoscope 4-mm cutting loop | 100% (30/30 patients) | 60.0% (18/30 patients) | N/A | N/A | N/A | N/A | None | Good |
| Mccausland (1992) | United States | 50 | No | Hysteroscopic resection | Single | Posterior uterine wall | Hysteroscopic resectoscope 5-mm cutting loop | 100% (50/50 patients) | 66.0% (33/50 patients) | N/A | N/A | N/A | N/A | None | Good |

Table 2: Extra-Uterine Needle Biopsy Tissue Sampling Techniques.

| Study | Country | Number of Patients | Confirmatory Hysterectomy Pathology | Approach | Biopsy Quantity | Biopsy Location | Instrument | Sampling Success Rate | Biopsy Diagnosis Rate of Adenomyosis | Sensitivity | Specificity | Positive Predictive Value | Negative Predictive Value | Serious Complications | NIH Quality Assessment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tellum (2019) | Norway | 81 | Yes | Ultrasound-guided Transvaginal biopsy | Multiple (4 biopsies per patient) | Suspicious lesions | BIP-Histo Core needle BIP Biomed Instrumente Gauge: 14 - 20 G | 98.8 % (80/81 patients) | N/A | 22.2 % (10/45 patients) | 97.0 % (32/33 patients) | 90.1 % (10/11 patients) | 47.8% (32/67 patients) | None | Good |
| Jeng (2007) | Taiwan | 100 | Yes | Laparoscopic biopsy | Multiple (10 biopsies per patient) | Suspicious lesions | Tru-cut needle Gauge: 14 G | 100.0 % (100/100 patients) | N/A | 97.8 % (90/92 patients) | 100.0 % (8/8 patients) | 100.0 % (90/90 patients) | 80.0 % (8/10 patients) | None | Good |
| Vercellini (1998) | Italy | 102 | Yes | Ex-vivo uterine biopsy | Single | Posterior uterine wall | Biocut cutting needle Sterylab Prod | 100.0 % (102/102 patients) | N/A | 44.8 % (13/29 patients) | 95.9 % (70/73 patients) | 81.3 % (13/16 patients) | 81.4 % (70/86 patients) | None | Good |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ucts Gauge: 14 G | | | | | | | | |
| Brosens (1995) | United Kingdom | 40 | Yes | Ex-vivo uterine biopsy | Multiple (8 biopsies per patient) | Half posterior uterine wall, Half anterior uterine wall | Pro-Mag cutting needle Man Medical Products Gauge: 14 G | 100.0 % (40/40 patients) | N/A | 44.4 % (12/27 patients) | 100.0 % (13/13 patients) | 100.0 % (12/12 patients) | 46.4 % (13/28 patients) | None | Good |
| Popp (1993) | Germany | 68 | Yes | Ex-vivo uterine biopsy | Multiple (10 biopsies per patient) | Blind | Tru-cut needle Gague: 14 G - 18 G | 100.0 % (68/68 patients) | N/A | 62.5 % (25/40 patients) | 100.0 % (28/28 patients) | 100.0 % (25/25 patients) | 65.1 % (28/43 patients) | None | Good |
| Nam (2015) | South Korea | 1032 | No | Ultrasound-guided Transvagi | Multiple (1 - 13 biopsies | Suspicious lesions | Biopsy Needle 7650 Medical Devi | 100 % (1032/1032 patients | 92.2 % (951/1032 patients) | N/A | N/A | N/A | N/A | None | Good |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | nal biopsy | per patient) (2596 total biopsies) | | ces Technology Gauge: 14 G | ) | | | | | | |
| Walker (2003) | United Kingdom | 8 | No | Ultrasound-guided Transvaginal biopsy | Single | Suspicious lesions | Biopsy Needle Gauge: 14 G - 18 G | 100% (8/8 patients) | 100% (8/8 patients) | N/A | N/A | N/A | N/A | None | Fair |
| Vercellini (1996) | Italy | 72 | No | Laparoscopic biopsy | Single | Posterior uterine wall | Tru-cut needle Gauge: 14 G | 100% (72/72 patients) | 18.1% (13/72 patients) | N/A | N/A | N/A | N/A | None | Good |
| Wood (1994) | Australia | 31 | No | Ultrasound-guided Percutaneous biopsy (10 patients) & Laparosc | Single | Variable | Biopty cutting needle Bard Products Gauge: 18 G & Hysteroscopic rese | 100% (31/31 patients) | 100% (31/31 patients) | N/A | N/A | N/A | N/A | None | Fair |

| | | | |
|---|---|---|---|
| | opic biopsy (12 patients) & Hysteroscopic biopsy (9 patients) | ctoscope | |