Asian Journal of Health Research
Journal Homepage: https://a-jhr.com
Published by Ikatan Dokter Indonesia Wilayah Jawa Timur

OPEN ACCESS

Systematic Review

Prevalence of Endometriosis in Postmenopausal Women: A Systematic Review

Ghinantia Athaya Putri*, Emiliana Da Costa Margarida, M.Faisal Azis

Medical Study Program, Faculty of Medicine, Universitas Brawijaya/dr. Saiful Anwar Hospital, Malang, East Java, Indonesia

ARTICLE HISTORY
Received: 26 August 2024
Revised: 17 September 2024
Accepted: 11 November 2024

CORRESPONDING AUTHOR*
Ghinantia Athaya Putri
ghinantiaathaya@student.ub.ac.id
Medical Study Program, Faculty of Medicine, Universitas Brawijaya/ dr. Saiful Anwar Hospital, Malang, East Java, Indonesia

KEYWORDS
Endometriosis; Menopause

ABSTRACT

Introduction: Endometriosis is generally known as a condition that occurs in reproductive-age women, but cases in menopausal women have also been reported, especially in those who have received postmenopausal hormone therapy. The prevalence of endometriosis in menopausal women can reach 2.2% of all diagnosed cases of endometriosis.

Material and Methods: There are 4 articles included from 3 databases. Several databases used included PubMed, ScienceDirect, and Taylor & Francis. The sample population included postmenopausal patients with endometriosis. Exclusion criteria included non-peer-reviewed journals, non-human research study designs, and grey literature. 4 articles are showing that endometriosis can occur in postmenopausal women. The articles show that the prevalence of endometriosis in postmenopausal women is around 2-20% where the diagnosis is made based on a combination of laparoscopic visualization and histological confirmation.

Results: The occurrence of endometriosis in postmenopausal women can occur due to various risk factors, including the use of hormone replacement therapy (HRT) and obesity because it can increase estrogen levels, which results in the development of endometriosis. Therefore, it is important to recognize that endometriosis is not only limited to women of productive age but can also occur in those who have passed menopause because they are often suspected of being malignant.

Conclusion: In general, patients with endometriosis have a higher risk of developing ovarian cancer. But, the clinical picture of endometriosis in menopausal patients is nonspecific. This makes endometriosis often experience a delay in diagnosis, especially in elderly patients. Postmenopausal women with endometriosis should be treated with surgery.

This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

Cite this as: Putri GA, Margarida EDC, Azis MF (2024) Prevalence of Endometriosis in Postmenopausal Women: A Systematic Review. *Asian J Heal Res.* 3 (3): 297–303. doi: 10.55561/ajhr.v3i3.192

INTRODUCTION

Endometriosis is generally known as a condition that occurs in women of reproductive age, but cases in postmenopausal women have also been reported [1]. This condition is often difficult to diagnose in postmenopausal women because the symptoms can resemble those of other conditions and are often overlooked. Additionally, the limited data makes it challenging to determine the exact prevalence of endometriosis in this group. This indicates that although it is less common, endometriosis remains a relevant health issue for postmenopausal women [2–4].

The prevalence of endometriosis in postmenopausal women can reach 2.2% of all diagnosed cases of endometriosis [5]. This study highlights the importance of recognizing that endometriosis is not only limited to women of reproductive age but can also occur in those who have gone through menopause [6].

This is also supported by a report from *The American Journal of Obstetrics and Gynecology*, which mentions that although less common, endometriosis can still occurin postmenopausal women, especially in those who have received postmenopausal hormone therapy [7–9].

Receiving hormone therapy can trigger or worsen endometriosis, indicating that close monitoring and accurate diagnosis are crucial for effective management [10,11].

MATERIAL AND METHODS

This review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.

Inclusion-exclusion Criteria

Inclusion criteria included interventional and observational studies published in the last ten years using English. The sample population included postmenopausal patients with endometriosis. The PICO format used consisted of 1) Problem: endometriosis; 2) Exposure: postmenopausal women; 3) Comparison: premenopausal women; 4) Outcome: incidence of endometriosis in postmenopausal women. Exclusion criteria included: 1) non-peer-reviewed journals; 2) non-human research study designs; and 3) grey literature.

Search Strategy

A literature search was conducted on July 15, 2024. Several databases used included PubMed, ScienceDirect, and Taylor & Francis. The keywords used were ("Endometriosis") AND ("Menopause"), adjusted according to the characteristics of each database. Article screening was performed in two stages: an initial screening was performed based on the title and abstract to exclude irrelevant studies, followed by a full-text review to assess compliance with the inclusion criteria. This rigorous screening was performed independently. In cases of articles that raised disagreement or uncertainty, a third reviewer acted as an arbitrator to resolve conflicts, ensuring an unbiased selection of studies based on the PRISMA pathway.

Data Extraction and Analysis

Data extraction by three authors into a Google Sheet, to assess its eligibility and accuracy. The Google sheet was designed to record the main characteristics of the studies, including authors, year of publication, study design, sample size, patient demographics, and outcomes. Each author then cross-verified the extracted data to ensure data accuracy. The data were then analyzed and reported by the authors. Differences of opinion that occurred during the writing process were resolved through discussion.

Risk of Bias Assessment

Risk of bias assessment was carried out on studies using the Newcastle Ottawa risk of bias tool by the authors and another author who supervised the process. Risk of bias assessment used the Newcastle Ottawa risk of bias tool. The domains assessed in each article were based on 3 main domains, namely: 1) selection related to how researchers selected research subjects including the number and tools used in obtaining data; 2) comparability related to researchers' efforts in controlling confounding variables; 3) outcome related to the results of data analysis. To describe the quality of the research, the domains were categorized into three groups: low (7-9), moderate (3-6), and high risk of bias (0-3).

Qualitative Analysis

The collection of articles included in the writing of the literature using the systematic review design method was analyzed qualitatively by all authors involved. Qualitative assessments were still based on the PICO format and previously designed inclusion-exclusion criteria

RESULTS

Identification and Selection of Studies

After conducting the literature search, a total of 512 articles were retrieved from three databases. Some articles were automatically excluded by the databases as they did not align with the study design. A total of 351 articles were excluded because they did not meet the criteria, such as review articles, books, and paid articles. Additionally, 157 articles were excluded as they did not meet the inclusion criteria. **Fig. 1** shows the PRISMA flowchart. Ultimately, 4 articles were included in this study.

Risk of Bias Assessment

The risk of bias was assessed using the Newcastle Ottawa risk of bias tool, as the included studies had a cross-sectional design. Based on the risk of bias assessment, all four studies received a score of 8 because, in the comparability domain, the researchers did not mention any efforts to control for confounding variables. All included studies were classified as having a low risk of bias (**Fig. 2**).

Included Studies

This systematic review includes four studies, selected based on predefined inclusion criteria related to the incidence of endometriosis in postmenopausal women. The incidence of endometriosis in postmenopausal women is summarized in this article, with the following findings: one study conducted in Germany examined the prevalence of endometriosis in

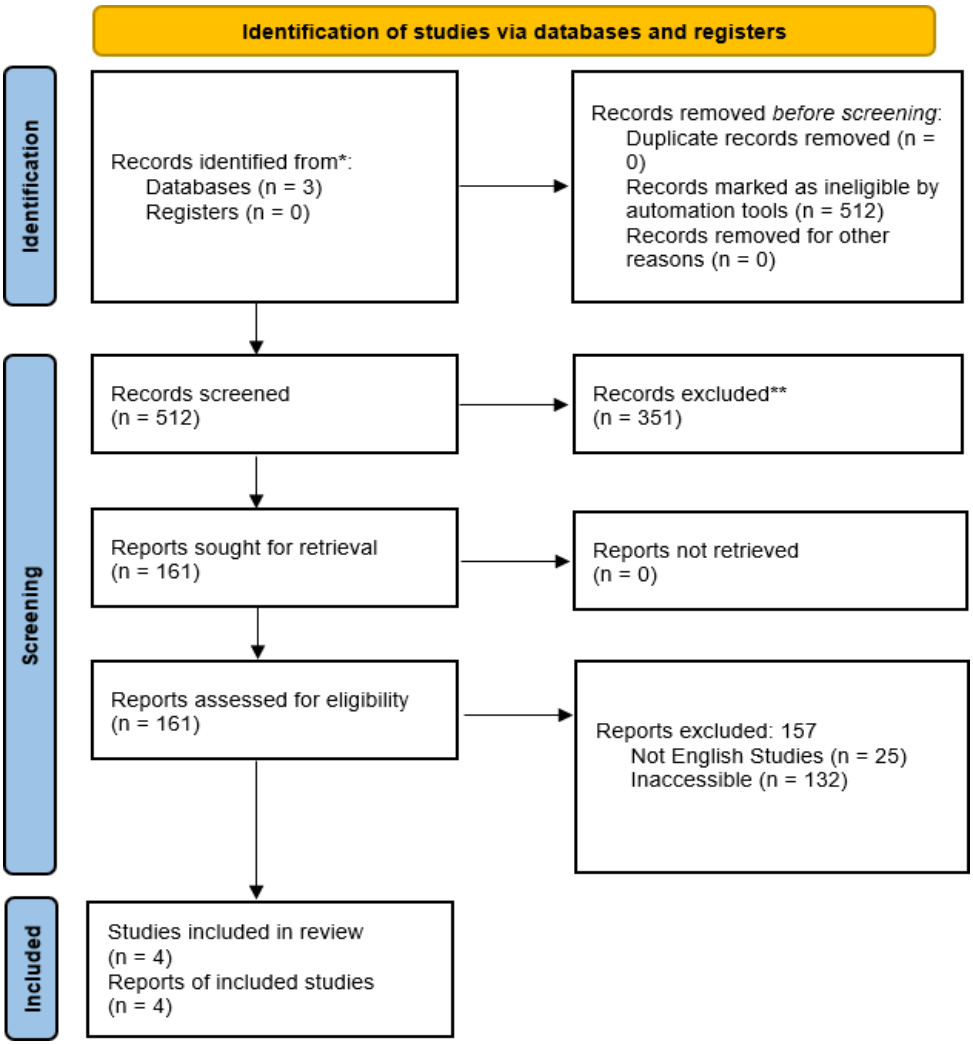


Fig. 1. PRISMA Flowchart

Newcastle - Ottawa	Selection				Comparability	Outcome		Total
	1	2	3	4	1	1	2	
Haas, 2012	*	*	*	**		**	*	8
Morassutto, 2016	*	*	*	**		**	*	8
Matalliotakis, 2019	*	*	*	**		**	*	8
Oral, 2020	*	*	*	**		**	*	8

Fig. 2. Newcastle Ottawa Scale (Risk of Bias tool)

premenopausal, perimenopausal, and postmenopausal women; two studies conducted in Italy and Turkey focused on the prevalence of endometriosis in premenopausal and postmenopausal women; and one study conducted in the US and Greece explored the prevalence of endometriosis in perimenopausal and postmenopausal women. Table 1 presents the included studies.

DISCUSSION

Endometriosis in postmenopausal women is a rare condition. There are 4 articles showing that endometriosis can occur in postmenopausal women [12–15]. One of the risk factors for endometriosis in

postmenopausal patients is hormone replacement therapy (HRT) which stimulates endometrial deposits by exogenous estrogen [16]. This effect is even greater in estrogen therapy without progesterone components. In addition, obesity is another risk factor that can increase estrogen levels, which results in the development of endometriosis [17–19]. The use of tamoxifen as a therapy for breast cancer is also associated with the emergence of endometriosis [20,21]. Tamoxifen, a selective estrogen receptor modulator, is known to have an agonist effect on endometrial tissue and is responsible for endometrial abnormalities, such as endometriosis [22,23].

Postmenopausal endometriosis is considered to have a more complex pathophysiology than premenopausal endometriosis. At menopause, estrogen production at the ovarian level stops, but is balanced by peripheral estrogen production from androgen conversion (especially in adipose tissue and skin). Cyclooxygenase type 2 enzyme production is induced by estrogen, leading to increased levels of prostaglandin E2, a known stimulator of aromatase activity, suggesting a positive feedback loop supporting sustained local estradiol production in endometriotic tissue [24–26]. In addition to peripheral estrogen production, high circulating estrogen levels may also be responsible. External sources are mainly hormone replacement therapy (HRT) [27].

The clinical picture of endometriosis in menopausal patients is nonspecific. This makes endometriosis often experience a delay in diagnosis, especially in elderly patients [28]. Currently, laparoscopy and biopsy for histological confirmation are the gold standard for the diagnosis of endometriosis, regardless of age. Although laparoscopy and biopsy remain the gold standard, non-invasive testing for early diagnosis is still preferred [29, 30]. Transvaginal ultrasound is a first-line imaging technique that is very useful in the diagnosis of endometriosis. Meanwhile, MRI is the best non-invasive method for diagnosing endometriosis. However, there is no imaging technique that can provide absolute confirmation of the diagnosis of endometriosis [31]. USG and MRI are important, but their findings are more difficult to interpret in postmenopausal patients than in younger patients because of the higher suspicion of neoplastic lesions. As a general consideration, all postmenopausal patients should be evaluated for malignancy if a new suspicious structure is found on USG [32].

Given the age of postmenopausal patients with endometriosis, they are often suspected of being malignant [33]. In general, patients with endometriosis have a higher risk of developing ovarian cancer. The incidence of transformation from endometrioma to ovarian cancer is estimated to be around 2-3%. In addition, another potential risk factor for malignancy is the increasing age of the patient, especially in the postmenopausal population. This increases the risk of ovarian cancer in postmenopausal patients. The concept of atypical endometriosis is defined as a precursor lesion to the development of clear cell ovarian carcinoma and endometrioid ovarian carcinoma. Hyperestrogenic environment, oxidative stress, genetic mutations, and cytokines may play a role in carcinogenesis and the evolution of benign endometriosis to atypical endometriosis and then ovarian cancer [34].

Postmenopausal women with endometriosis should be treated with surgery, namely the removal of all visible endometriotic tissue because of the risk of recurrence and the higher risk of malignancy [31,35]. Medical therapy can be used if there is the recurrence of pain after surgery or if surgery is contraindicated. Aromatase inhibitors may be an option that works by reducing extra-ovarian estrogen production [36,37]. Aromatase inhibitors were first used for postmenopausal treatment because of their ability to reduce estrogen production by inhibiting cytochrome P450, the enzyme that catalyzes the conversion of andostenendione and testosterone to estrone and estradiol [38]. Letrozole and anastrozole are triazole derivatives that are reversible and competitive AIs and at doses of 1-5 mg/day inhibit estrogen levels by 97% to more than 99% [39]. However, the most important risks associated with AI administration are osteoporosis and increased fracture risk. To reduce this, bisphosphonates can be given together with AIs during long-term treatment [40].

CONCLUSION

Endometriosis is generally known as a condition that occurs in women of reproductive age; however, cases in menopausal women have also been reported. Studies indicate that about 2-20% of diagnosed endometriosis cases occur in menopausal women. Although it is less common than in women of reproductive age, thepresence of endometriosis in this group highlights the need for further attention and research. Risk factors that increase the likelihood of endometriosis in menopausal women include the use of hormone therapy and obesity. Postmenopausal hormone therapy, in particular, can trigger or exacerbate existing endometriosis. Understanding these factors is crucial for the effective diagnosis and management of endometriosis in menopausal women, as well as for the development of better prevention and treatment strategies.

ACKNOWLEDGMENT

We thank all the authors of the articles reviewed in this article

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

REFERENCES

1. Parasar P, Ozcan P, Terry KL. (2017) Endometriosis: Epidemiology, Diagnosis and Clinical Management. Curr Obs Gynecol Rep. 6(1):34–41.
2. Jakson I, Hirschberg AL, Gidlöf SB. (2023) Endometriosis and menopause—management strategies based on clinical scenarios. Acta Obstet Gynecol Scand. 102(10):1245–423.
3. OXHOLM D. (2007) Postmenopausal endometriosis. Acta Obstet Gynecol. 86:1158–64.
4. Secosan C, Balulescu L, Brasoveanu S, Balint O, Pirtea P, Dorin G, et al. Endometriosis in Menopause—Renewed Attention on a Controversial Disease. Diagnostics. 2020;10(3).
5. Gemmell LC, Webster KE, Kirtley S, Vincent K, Zondervan KT, Becker CM. (2017) The management of menopause in women with a history of endometriosis: a systematic review. Hum Reprod Update. 23(4):481–500.
6. Vallée A, Carbonnel M, Ceccaldi P-F, Feki A, Ayoubi J-M. (2024) Postmenopausal endometriosis: a challenging condition beyond menopause. Menopause. 31(5):447–56.
7. Jeon D-S, Kim T-H, Lee H-H, Byun DW. (2013) Endometriosis in a Postmenopausal Woman on Hormonal Replacement Therapy. J Menopausal Med. 19(3):151–153.
8. Zanello M, Borghese G, Manzara F, Esposti ED, Moro E, Raimondo D, et al. (2019) Hormonal Replacement Therapy in Menopausal Women with History of Endometriosis: A Review of Literature. Med. 55(8):477.
9. Cassani C, Tedeschi S, Cucinella L, Morteo V, Camnasio CA, Tiranini L, et al. (2024) Menopause and endometriosis. Maturitas. 190.
10. Dinu M-D, Hamoud BH, Amza M, Gorecki G-P, Sima R-M, Gică N, et al. (2024) Endometriosis in Menopausal Women—A New Age Is Coming? Literature Review. Life. 14(4):485.
11. Palep-Singh M, Gupta S. (2009) Endometriosis: associations with menopause, hormone replacement therapy and cancer. Menopause Int. 15(4).
12. Haas D, Chvatal R, Reichert B, Renner S, Shebl O, Binder H, et al. (2012) Endometriosis: a premenopausal disease? Age pattern in 42,079 patients with endometriosis. Arch Gynecol Obstet. 286(3):667–670.
13. Morassutto C, Monasta L, Ricci G, Barbone F, Ronfani L. (2016) Incidence and Estimated Prevalence of Endometriosis and Adenomyosis in Northeast Italy: A Data Linkage Study. PLoS One. 11(4).
14. Matalliotakis M, Matalliotaki C, Trivli A, Zervou MI, Kalogiannidis I, Tzardi M, et al. (2019) Keeping an Eye on Perimenopausal and Postmenopausal Endometriosis. Diseases. 7(1):29.
15. Oral E, Sozen I, Uludag S, Demirkiran F, Ilvan S, Oncul M, et al. (2020) The prevalence of endometrioma and associated malignant transformation in women over 40 years of age. J Gynecol Obstet Hum Reprod. 2020;49.
16. Chiu L, Nanayakkara P. (2024) An Examination of the Association Between Types of Menopausal Hormone Therapy (Estrogen-Only Hormone Therapy Versus Combined-Hormone-Therapy Versus Tibolone) and Endometriosis Progression in Peri/Postmenopausal Women With a Previous Hysterectomy. J Clin Gynecol Obstet. 13(1):23–4.
17. Hong J, Yi KW. (2022) What is the link between endometriosis and adiposity? Obs Gynecol Sci. 25(3):227–233.
18. Rowlands IJ, Hockey R, Abbott JA, Montgomery GW, Mishra GD. (2022) Body mass index and the diagnosis of endometriosis: Findings from a national data linkage cohort study. Obes Res Clin Pract. 16(3):235–41.
19. Jegasothy, Abdalla, Elengoe, Kutty (2021) Obesity and Endometriosis. In: Obesity and its Impact on Health. Springer, Singapore; 2021.
20. Nishiyama S, Hayashi S, Abe N, Kira S, Oda M, Lee L, et al. (2022) Bilateral ovarian endometriomas after laparoscopic hysterectomy following adjuvant tamoxifen therapy for breast cancer: A case report. Case Reports Women's Heal. 2022;36.
21. Grisdale M, Alghamdi S, Boutross-Tadross O, Luketic L. (2021) Asymptomatic Atypical Hyperplasia and Endometriosis Following Treatment with Tamoxifen: A Case Report and Review of the Literature. J Obstet Gynaecol Canada. 43(1):85–7.
22. Ryu K-J, Kim MS, Lee JY (2022) Risk of Endometrial Polyps, Hyperplasia, Carcinoma, and Uterine Cancer After Tamoxifen Treatment in

Premenopausal Women With Breast Cancer. JAMA Netw Open. 5(11).

23. Emons G, Mustea A, Tempfer C (2020) Tamoxifen and Endometrial Cancer: A Janus-Headed Drug. Cancers (Basel). 12(9).
24. Vercellini, Vigano, Somigliana, Fedele (2020) Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol. 10(5):261–75.
25. Streuli I, Gaitzsch H, Wenger J-M, Petignat P (2017) Endometriosis after menopause: physiopathology and management of an uncommon condition. Climateric. 20(2):138–43.
26. Chauhan S, More A, Chauhan V, Kathane A (2022) Endometriosis: A Review of Clinical Diagnosis, Treatment, and Pathogenesis. Cureus. 14(9).
27. Ladanyi C, Boyd S, Sticco P, Mohling S (2019) Postmenopausal endometriosis, where are we now? Wolters Kluwer Health
28. Agarwal SK, Chapron C, Giudice LC, Missmer SA, Singh SS, Taylor HS (2019) Clinical diagnosis of endometriosis: a call to action. Am J Obstet Gynecol. 220(4).
29. Wibowo N, Irwinda R, Frisdiantiny E, Karkata MK, Mose JC, Chalid MT, et al. (2016) Pedoman Nasional Pelayanan Kedokteran: DIAGNOSIS DAN TATALAKSANA PRE-EKLAMSIA. Perkumpulan Obstetri dan Ginekologi Indonesia: Himpunan Kedokteran Feto Maternal
30. Bafort C, Beebeejaun Y, Tomassetti C, Bosteels J, Duffy JM (2020) Laparoscopic surgery for endometriosis. Cochrane Database Syst Rev. 10(10).
31. Cope AG, VanBuren WM, Sheedy SP (2019) Endometriosis in the postmenopausal female: clinical presentation, imaging features, and management. Abdom Radiol. 45:1790–1799.
32. Chen-Dixon K, Uzuner C, Mak J, Condous G. (2022) Effectiveness of ultrasound for endometriosis diagnosis. Curr Opin Obs Gynecol. 34(5):324–31.
33. Giannella L, Marconi C, Giuseppe J Di, Carpini GD, Fichera M, Grelloni C, et al. (2021) Malignant Transformation of Postmenopausal Endometriosis: A Systematic Review of the Literature. Cancers (Basel). 13(16).
34. Chen B, Zhao L, Yang R, Xu T (2024) New insights about endometriosis-associated ovarian cancer: pathogenesis, risk factors, prediction and diagnosis and treatment. Frontiers (Boulder). 2024;14.
35. Ozyurek ES, Yoldemir T, Kalkan U (2018) Surgical challenges in the treatment of perimenopausal and postmenopausal endometriosis. Climacteric. 21(4):385–90.
36. Słopień R, Męczekalski B (2016) Aromatase inhibitors in the treatment of endometriosis. Prz Menopauzalny. 15(1):43–7.
37. Peitsidis P, Tsikouras P, Laganà AS, Laios A, Gkegkes ID, Iavazzo C (2023) A Systematic Review of Systematic Reviews on the Use of Aromatase Inhibitors for the Treatment of Endometriosis: The Evidence to Date. Drug Des Devel Ther. 2023(17):1329–1346.
38. Rispoli E, Gardella B, Dominoni M, Pasquali MF, Mauria M (2023) Aromatase inhibitors in the pharmacotherapy of endometriosis. Expert Opin Pharmacother. 24(9):1067–73.
39. Hashim HA (2014) Potential role of aromatase inhibitors in the treatment of endometriosis. Int J Womens Heal. 21(6):671–680.
40. Polyzos NP, Fatemi HM, Zavos A, Grimbizis G, Kyrou D, Velasco J-G, et al. (2011) Aromatase inhibitors in post-menopausal endometriosis. Reprod Biol Endocrinol. 9(1):90.

Table 1. Included Studies

DOI	No	Author, Year	Country	Design Study	Time of Survey	Sample	Sample Age	Diagnose Method	Results
10.1007/s00404-012-2361-z	1	Haas et al., 2012 [4]	Germany	Descriptive study	2005-2006	42,079	1-95	Combination of laparoscopy visualization and histologic confirmation	• In the premenopausal group(age 0–45 years), there were33,814 patients with endometriosis (80.36 %) • In the perimenopausal group (45–55 years), there were 7,191 patients with endometriosis (17.09 %) • In the postmenopausal group (55–95 years), there were 1,074 patients with endometriosis (2.55 %)
10.1371/journal.pone.0154227	2	Morassutto et al., 2016 [5]	Italy	Descriptive study	2011-2013	1,415	15-83	Combination of laparoscopy visualization and histologic confirmation	• In premenopausal women (15–50 years of age), there were 900 cases without histological confirmation and535 with histological confirmation • In postmenopausal women (>50 years of age), there were 117 cases without histological confirmation and 91 with histological confirmation
10.3390/diseases7010029	3	Matalliotakis *et al.*, 2019 [6]	US and Greece	Descriptive study	1990-2015	1,100	NA	Confirmed bytissue biopsy and laparotomy orlaparoscopy	• There were 184 (16.7%) patients with perimenopausalendometriosis (age 45–54 years) • There were 46 (4.2%) patients with postmenopausal endometriosis (55–80 years).
10.1016/j.jogoh.2020.101725	4	Oral *et al.*,2020 [7]	Turkey	Descriptive study	2006-2016	1,100	40-91	NA	• Premenopausal women with endometrioma (n = 238/79.6%) • Postmenopausal women with endometrioma (n = 61/20.4%).