



Italian Journal of Gynaecology & Obstetrics

March 2026 - Vol. 38 - N. 1 - Quarterly - ISSN 2385 – 0868

A new approach in the Italian landscape of chronic pelvic pain and endometriosis

Massimo Candiani¹, Lucia Lazzeri², Antonio Maiorana³, Ludovico Muzii^{4,*}, Michele Vignali⁵, Enrico Vizza⁶, Errico Zupi²

¹Gynaecology and Obstetrics Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy.

²Gynaecology and Obstetrics Clinic, Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy.

³Gynaecologic and Obstetric Unit, ARNAS Civico Di Cristina Fatebenefratelli, Palermo, Italy.

⁴Department of Mother, Child and Urological Sciences, "Sapienza" University of Rome, Rome, Italy.

⁵Department of Biomedical Sciences for Health, University of Milan, Macedonio Melloni Hospital, Milan, Italy.

⁶Gynecologic Oncology Unit, Department of Experimental Clinical Oncology, IRCCS Regina Elena National Cancer Institute, Rome, Italy.

The authors contributed equally to this work. The order of author names was alphabetically determined.

ARTICLE INFO

History

Received: 25 November 2025

Received in revised form: 12 March 2025

Accepted: 09 December 2025

Available online: 31 March 2026

DOI: 10.36129/jog.2026.258

Key words

Endometriosis; medical therapy; drug combination; GnRH antagonists; relugolix.

*Corresponding author: Ludovico Muzii, M.D., Department of Mother, Child and Urological Sciences, Sapienza University of Rome, Viale del Policlinico 155, 00161 Rome, Italy.

Email: ludovico.muzii@uniroma1.it.

ORCID: 0000-0001-7195-9583.

ABSTRACT

Endometriosis entails a huge burden: it is estimated that affects 10% of women in their reproductive age. Symptoms may be severe (chronic pelvic pain, dysmenorrhea, dyspareunia, dysuria, dyschezia and fatigue) affecting women's quality of life from a personal, familiar, social and professional point of view. Endometriosis may also affect fertility. The economic burden of endometriosis is relevant. Despite the recent improvements patients' journey before diagnosis is still long and difficult.

Different options for the treatment have been proposed: hormonal therapies that suppress ovulation and menstruation, surgical treatment or a combination of both. The most recent tools for the medical management of endometriosis are the oral GnRH antagonists with add-back therapy (ABT). Relugolix Combination Therapy (CT) (40 mg Relugolix + 1 mg estradiol as hemihydrate + 0.5 mg norethisterone acetate), one tablet daily, is licensed in adult women of reproductive age for symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis as well as for treatment of moderate to severe symptoms of uterine fibroids. The triple combination has the aim of combining the activity on endometriosis's symptoms with the maintenance of oestradiol and progesterone levels in an optimal therapeutic range, in order to minimize the adverse effects.

Nowadays oral relugolix CT may help to solve an unmet need for a condition with such a severe impact on all aspects of women's lives with an effective, well-tolerated, and convenient medical treatment for endometriosis, maintaining a long-term care on women's health, preserving their bone mass.

INTRODUCTION

Endometriosis is a very treacherous issue; even the history of the disease is matter of debate. Officially

the disease was identified by von Rokitansky [1] in 1860, but about two centuries before Daniel Shroen had described peritoneal ulcers that tended to form lesions and were susceptible to haemorrhage

in women in reproductive age [2]. In our opinion the most interesting description was provided by a Scottish physician, Louis Brotherson, in 1776: he talked about the chronic pelvic pain experienced by women. He also added that *“in its worst stages, this disease affects the well-being of the female patient totally and adversely, her whole spirit is broken, and yet she lives in fear of still more symptoms”* [3].

A cornerstone in endometriosis knowledge is that it is a polygenically inherited disease with a complex, multifactorial aetiology [4]. Several theories have been suggested to explain the development of endometrial glands and stroma within the pelvic peritoneum and other extra uterine sites, but the most intriguing aspect of endometriosis pathogenesis is that is a hormone-driven disease [5], dependent on estrogen [6], similar to that seen in eutopic endometrium, but with a lack of consistent response to progesterone or synthetic progestins [7].

CURRENT SCENARIO – THE BURDEN OF DISEASE

It is estimated that endometriosis affects 10% of women in their reproductive age [8]. In Italy a recent publication using national-level hospital data estimated endometriosis incidence in 0.839 per 1,000 women (95%CI 0.834-0.844), while the prevalence rate stood at 14.0 per 1,000 [9]. It has to be considered that this study only took into account cases intercepted by hospital admissions with a diagnosis of endometriosis (ICD-9-CM, codes 617.x), supported by the presence of a procedure code of laparoscopy or any other surgical procedure allowing for direct visualisation of the lesions; conversely according to other studies [10], it can be speculated that only one-third of women with endometriosis reach a confirmed diagnosis. Therefore, in Italy, there would be more than 500,000 women with endometriosis [9] affected by chronic pelvic pain, dysmenorrhea, dyspareunia, dysuria, dyschezia and fatigue. According to the Ministry of Health the number of women with endometriosis would be 3,000,000 [11]. Endometriosis may also affect fertility by tampering the peritoneal environment or by deforming the pelvic anatomy; about 30% of patients with endometriosis have difficulty conceiving [12].

In Italy around 300,000 women with moderate or severe endometriosis (III or IV degree according to r-ASRM [13]) have the right to benefit from certain

healthcare services free of charge [14]. The exemption is granted during a gynaecological examination at a public centre specialized in endometriosis and then submitted by the woman to the Local Health Unit [14].

Endometriosis is associated with a high burden of comorbidities [15], endometriosis-associated pelvic pain is combined with reduced HRQoL, including impaired mental and sexual functioning, as well as reduced work performance and productivity social relationships [16].

The economic burden of endometriosis should not be underestimated, both individually and for the community, as this pathology leads to a loss of productivity at work and large utilization of healthcare resources and personnel costs [15-17].

Despite the recent improvements, due to increased awareness of women and training involvement for healthcare professionals, patients' journey before diagnosis is long and difficult [15]. It is estimated a delay up to 10-years before diagnosis after the onset of symptoms [15, 18].

More and more scientific evidence is accumulating on the importance of an early diagnosis of endometriosis to limit the psychophysical damage for women [18-20] and the risk of chronic pain development [21]; it has been demonstrated that the efficacy of endometriosis therapeutical approaches due to lack of confidence in the medical profession and in treatment are inversely related to duration of untreated endometriosis [20].

CURRENT SCENARIO – SURGICAL AND MEDICAL APPROACHES

Different options for the treatment of patients with symptomatic endometriosis have been proposed: hormonal therapies that suppress ovulation and menstruation, surgical treatment or a combination of both. The management of the disease is driven by symptoms, individual risk factors and informed patient preferences. Nonsteroidal anti-inflammatory drugs may be a helpful first-line treatment for symptoms of dysmenorrhea, but no evidence suggests that they improve non menstrual symptoms [22].

Pharmacologic management of endometriosis includes therapies to decrease endogenous oestrogen, on the basis that oestradiol is a key driver of endometrial growth and local inflammation and pain [23, 24].

Hormonal contraception and progestins are strongly recommended in women suffering from endometriosis-associated symptoms [25], but few drugs are approved specifically for management of pain associated with endometriosis [26] and reimbursed by Italian National Health Services [27].

Oral contraceptives, either administered with a cycle or continuous schedule, or dienogest, a fourth-generation progestin, are generally considered as first-option medical treatment for endometriosis associated with pain symptoms or for preventing postoperative recurrences [25, 28, 29].

Gonadotropin-releasing hormone (GnRH) agonist therapy provides a profound oestradiol suppression, but due to its hypoestrogenic side effects, mainly the diminished bone density, the duration of use is limited and should require additional concomitant hormonal administration [24, 25, 30].

Surgical treatment is an option when drug therapies are contraindicated (such as for patients who are trying to conceive), are not tolerated or have failed to provide adequate relief or as for patient's choice. A minimally invasive approach with complete treatment of the disease is considered best practice by most international guidelines [25, 31, 32]. Surgical approach is mandatory when endometriosis has conducted to obstructions at ureteric or bowel level. Systematic reviews have shown a persistence or recurrence rate of 22% at 2 years and of 40%-50% at 5 years after surgery [24, 33].

NEW PHARMACOLOGICAL APPROACHES

The most recent tools for the medical management of endometriosis are the oral GnRH antagonists with add-back therapy (ABT). The efficacy is based on the fast binding to the GnRH receptor, blocking endogenous GnRH activity with suppression of LH and FSH production [34] avoiding the flare-up effects observed with GnRH agonists [35, 36]. Considering the need of a long-term use, the ABT with estrogen/progestin is an unmissable issue acting as prevention of the side effects of hypoestrogenism (mainly bone loss).

Even if oestrogens are considered the primary driver of lesion development, with the loss of progesterone signalling in these tissues [37], however, it is well known that there is a hierarchy of organ response to oestradiol [38]. The current medical position is to consider as not necessary to raise to the ground the oestrogenic concentrations to treat

in the long-term women with endometriosis, in order not to expose them to all the dangerous consequences of a prolonged oestrogen deficiency. The goal is to maintain the oestradiol concentrations in the range of 30-45 pg/ml, instead. This is the right threshold that does not stimulate endometriotic lesion to growth, and in the meantime, it can avoid the short and long-term consequences, mainly on osteocalcium metabolism and bone structure, badly affected by a profound hypoestrogenism [39]. The bone health is a major health objective since 1998, when the European Commission report on osteoporosis was published with the objective to reach a significant reduction in the incidence of osteoporosis and related fractures [40]. The burden of osteoporosis for Italian women is huge, considering the epidemiological figures and the scarce awareness among patients (only one in two women knows she is affected) and healthcare professionals [41]. Relugolix Combination Therapy (CT) (40 mg Relugolix + 1 mg estradiol as hemihydrate + 0.5 mg norethisterone acetate), one tablet daily, is licensed in adult women of reproductive age for symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis as well as for treatment of moderate to severe symptoms of uterine fibroids [42].

The pharmacodynamic properties of the combination are the following:

- Relugolix is a phenyl urea derivative, with an affinity 52 times higher for GnRH receptor in the anterior pituitary than endogenous GnRH; it has the aim of decreasing oestrogen and progesterone production [43, 44].
- Estradiol maintained at concentrations consistent to those detectable in the early follicular phase of the menstrual cycle; it has the aim of preserving bone mineral density and significantly improving the patient's quality of life [45, 46]. In the phase 3 clinical studies, in patients with endometriosis oestradiol concentrations were approximately 38 pg/mL, corresponding to estradiol concentrations in the early follicular phase of the menstrual cycle [42], thus completely within the oestrogen therapeutic window stated by the oestrogen threshold hypothesis [39].
- Norethisterone acetate a synthetic progestin; it has the aim of reducing the risk of oestrogen-induced endometrial hyperplasia [42]. Furthermore, the action this progestin on bone density is well documented [47-49].

In the phase 3 double-blind trials (SPIRIT 1 & SPIRIT 2), involving nearly 1.300 women with confirmed endometriosis, a higher proportion of the sample met the dysmenorrhea responder criteria and the non-menstrual pelvic pain responder criteria in the Relugolix CT group compared to placebo group (**Figure 1**) with a similar incidence of adverse events. The evaluation of time to response indicates benefit as early as 4 weeks after starting treatment with maximum effect at 8 weeks for dysmenorrhoea and 12 weeks for non-menstrual pelvic pain. The endometriosis Health Profile-30 pain domain, mirroring the effects of pain on daily function, improved significantly in the Relugolix CT group compared with placebo. Lastly, more women in the Relugolix CT group were opioid free at week 24 compared to the placebo group.

In addition, Relugolix CT is able to provide inhibition of ovulation in women taking the commended dose and provides adequate contraception after at least one month of use, but the median time of menses return was 31 days (IQR 21-36) after stopping treatment for the Relugolix CT [50].

Within a single cohort study, the return of ovulation after discontinuation of treatment occurred within 43 days (mean 23.5 days) in the whole sample of healthy premenopausal women participating in the study [42].

In the SPIRIT open-label extension study the proportion of responders at Week 104/End of treatment was 84.8% for dysmenorrhea and 75.8% for non-menstrual pelvic pain; both decreases in dy-

spareunia and improvement in EHP-30 pain domain were also sustained for the whole period. Eventually, at Week 104/End of treatment 75% of patients were analgesic-free and 91% were opioid-free. After initial least squares mean BMD loss <1% at Week 24, at Week 36 a BMD plateau was evident and was sustained up to 104 weeks of treatment [26] (**Figure 2**).

CONCLUSIONS

Endometriosis is a widely diffused condition; in most cases patients' journey to receive diagnosis and treatment is troublesome and exhausting. Endometriosis may cause considerable distress and can heavily affect women's lives, potentially leading to the development of chronic pelvic pain, infertility or end-organ damage. Therefore, early recognition and diagnosis are crucial to providing timely treatment: all healthcare professionals in contact with women should enhance their ability to make a prompt clinical diagnosis of endometriosis and engage their patients in the correct disease' management.

Nowadays oral relugolix CT may help to solve an unmet need for an effective, well-tolerated, and convenient medical treatment for endometriosis, maintaining a long-term care on women's health, preserving their bone mass. Thereby new efforts from our community are required to identify and tackle a condition with such a severe impact on all aspects of women's lives.

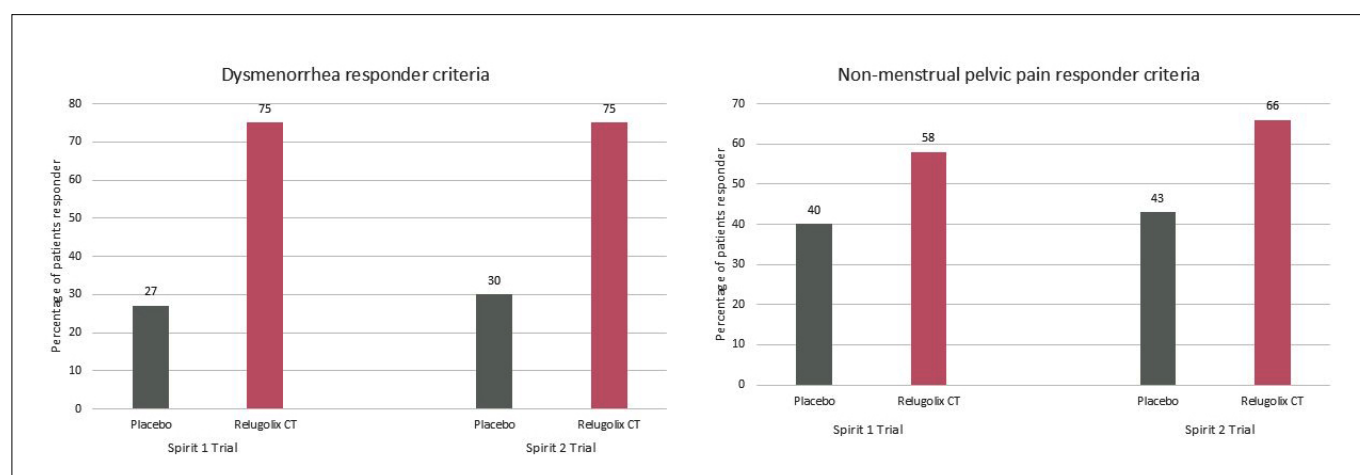


Figure 1. Clinical trials: reduction in pain symptoms

Results of the registrative trials of Relugolix-CT Spirit 1 and Spirit 2. Proportion of patients who responded to treatment (%) for dysmenorrhoea and non-menstrual pelvic pain in Spirit 1 and Spirit 2 at week 24. The responder rates are both based on Numerical Rating Scores NRS and analgesic use (Modified from Giudice et al. Once daily oral relugolix combination therapy versus placebo in patients with endometriosis-associated pain: two replicate phase 3, randomised, double-blind, studies (SPIRIT 1 and 2). *Lancet*. 2022;399(10343):2267-2279. doi: 10.1016/S0140-6736(22)00622-5).

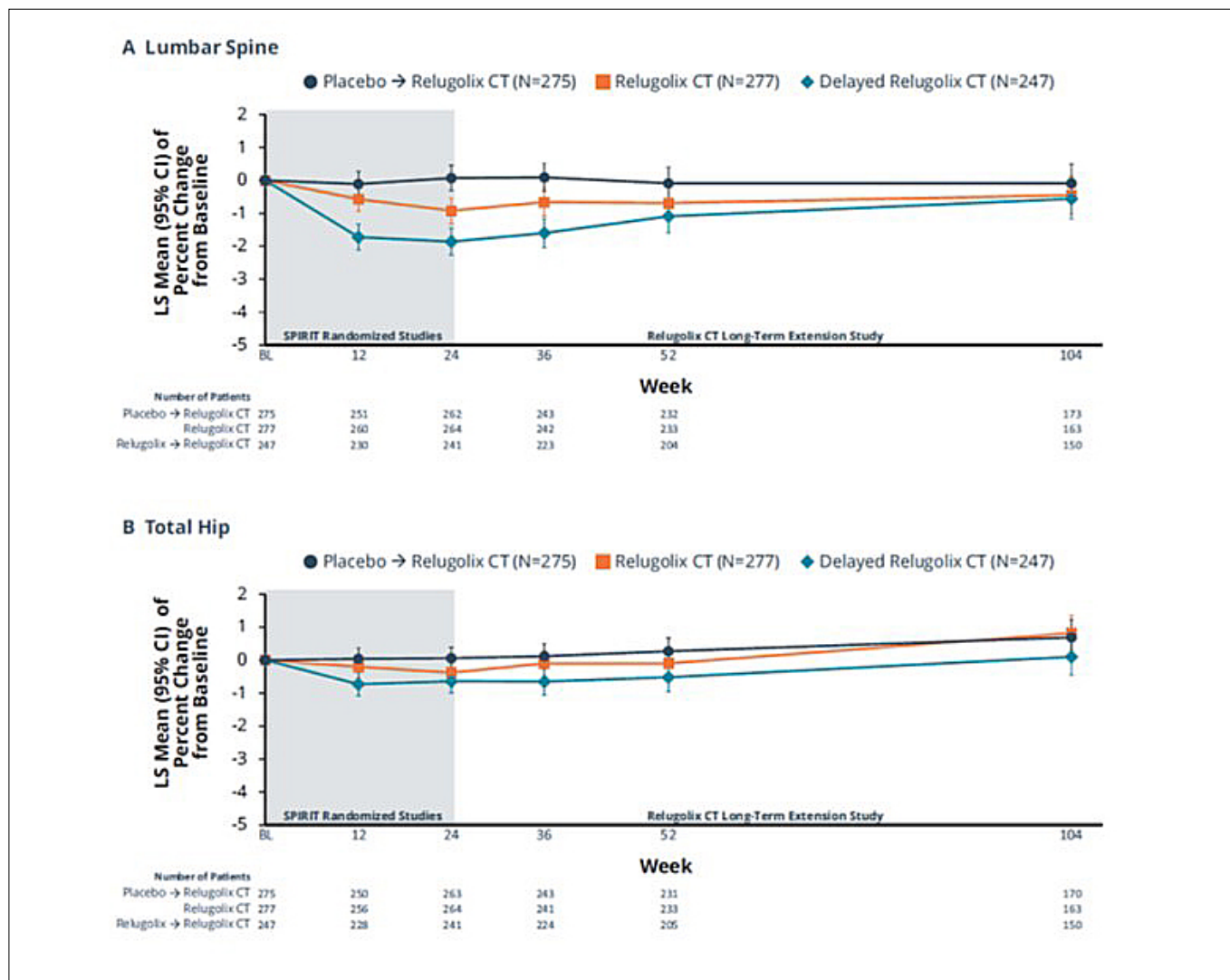


Figure 2. Clinical trials: impact on BMD.

Percentage change from baseline in bone mineral density over time for lumbar spine and total hip. During the first 24 weeks of treatment, patients receive one of three randomized treatments: relugolix CT (combination therapy), relugolix for 12 weeks +relugolix CT for 12 weeks, or placebo. At Week 24, with the beginning of the SPIRIT long-term extension study, all patients received relugolix CT. (A) Data for lumbar spine. (B) Data for hip. (Modified from Becker et al. Two-year efficacy and safety of relugolix combination therapy in women with endometriosis-associated pain: SPIRIT open-label extension study. *Hum Reprod.* 2024;39(3):526-537. doi: 10.1093/humrep/dead263).

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

All authors: conceptualization, methodology, writing – original draft, writing – review & editing.

Funding
None.

Study registration
N/A.

Disclosure of interests

The author declare that they have no conflict of interests.

Ethical approval
N/A.

Informed consent
N/A.

Data sharing
N/A.

REFERENCES

1. Benagiano G, Brosens I. The history of endometriosis: identifying the disease. *Hum Reprod.* 1991;6(7):963-968. doi: 10.1093/oxfordjournals.humrep.a137470.

2. Knapp VJ. How old is endometriosis? Late 17th- and 18th-century European descriptions of the disease. *Fertil Steril* 1999;72:10-14. doi: 10.1016/S0015-0282(99)00196-x.
3. Brotherson L. *Dissertatio medica, inauguralis, de utero inflammatione ejusdem*. 1776.
4. Olive DL, Schwartz LB. Endometriosis. *N Engl J Med*. 1993;328(24):1759-1769. doi: 10.1056/NEJM199306173282407.
5. Pant A, Moar K, Arora TK, Maurya PK. Implication of biosignatures in the progression of endometriosis. *Pathol Res Pract*. 2024;254:155103. doi: 10.1016/j.prp.2024.155103.
6. Zeitoun KM, Bulun SE. Aromatase: a key molecule in the pathophysiology of endometriosis and a therapeutic target. *Fertil Steril*. 1999;72(6):961-969. doi: 10.1016/S0015-0282(99)00393-3.
7. Bulun SE, Yilmaz BD, Sison C, Miyazaki K, Bernardi L, Liu S, et al. Endometriosis. *Endocr Rev*. 2019;40(4):1048-1079. doi: 10.1210/er.2018-00242.
8. Zondervan KT, Becker CM, Missmer SA. Endometriosis. *N Engl J Med*. 2020;382(13):1244-1256. doi: 10.1056/NEJMr1810764.
9. Maraschini A, Ceccarelli E, Giangreco M, Monasta L, Manno V, Catelan D, et al. Development of an Italian National Epidemiological Register on Endometriosis Based on Administrative Data. *J Clin Med*. 2024;13(11):3087. doi: 10.3390/jcm13113087.
10. Ferrero S, Arena E, Morando A, Remorgida V. Prevalence of newly diagnosed endometriosis in women attending the general practitioner. *Int J Gynaecol Obstet*. 2010;110(3):203-207. doi: 10.1016/j.ijgo.2010.03.039.
11. Ministero della Salute. Portale donna – Endometriosi. Ministero della Salute. Available at: <https://www.salute.gov.it/portale/donna/dettaglioContenutiDonna.jsp?id=4487&area=Salute%20donna&menu=patologie>. Accessed on December 9, 2024.
12. Prescott J, Farland LV, Tobias DK, et al. A prospective cohort study of endometriosis and subsequent risk of infertility. *Hum Reprod*. 2016;31(7):1475-1482. doi: 10.1093/humrep/dew085. doi: 10.1093/humrep/dew085.
13. Canis M, Donnez JG, Guzick DS, et al. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril*. 1997;67(5):817-821. doi: 10.1016/S0015-0282(97)81391-X.
14. Ministero della Salute. Portale esenzioni – Endometriosi. Ministero della Salute. Available at: <https://www.salute.gov.it/portale/esenzioni/dettaglioContenutiEsenzioni.jsp?lingua=italiano&id=1017&area=esenzioni&menu=vuoto> and <https://www.trovanorme.salute.gov.it/norme/renderPdf.spring?seriegu=SG&datagu=18/03/2017&redaz=17A02015&artp=13&art=1&subart=1&subart1=10&vers=1&prog=001>. Accessed on December 9, 2024.
15. Eisenberg VH, Decter DH, Chodick G, Shalev V, Weil C. Burden of Endometriosis: Infertility, Comorbidities, and Healthcare Resource Utilization. *J Clin Med*. 2022 Feb 21;11(4):1133. doi: 10.3390/jcm11041133.
16. As-Sanie S, Shafrir AL, Halvorson L, et al. The burden of pelvic pain associated with endometriosis among women in selected European countries and the United States: a restricted systematic review. *J Minim Invasive Gynecol*. 2024;31(8):653-666.e5. doi: 10.1016/j.jmig.2024.05.002.
17. Della Corte L, Di Filippo C, Gabrielli O, et al. The burden of endometriosis on women's lifespan: a narrative overview on quality of life and psychosocial wellbeing. *Int J Environ Res Public Health*. 2020;17(13):4683. doi: 10.3390/ijerph17134683.
18. Agarwal SK, Chapron C, Giudice LC, et al. Clinical diagnosis of endometriosis: a call to action. *Am J Obstet Gynecol*. 2019;220(4):354.e1-354.e12. doi: 10.1016/j.ajog.2018.12.039.
19. Márki G, Bokor A, Rigó J, et al. Physical pain and emotion regulation as the main predictive factors of health-related quality of life in women living with endometriosis. *Hum Reprod*. 2017;32(7):1432-1438. doi: 10.1093/humrep/dex091.
20. Maiorana A, Alfano P, Mercurio A, et al. Quality of life and clinical factors in women with endometriosis, the role of dienogest vs EE/dienogest over time: a single-center study. *Arch Gynecol Obstet*. 2023;307:1503-1512. doi: 10.1007/s00404-023-06942-9.
21. Brawn J, Morotti M, Zondervan KT, et al. Central changes associated with chronic pelvic pain and endometriosis. *Hum Reprod Update*. 2014;20(5):737-744. doi: 10.1093/humupd/dmu025.
22. Brown J, Crawford TJ, Allen C, Hopewell S, Prentice A. Nonsteroidal anti-inflammatory drugs

- for pain in women with endometriosis. *Cochrane Database Syst Rev.* 2017;1(1):CD004753. doi: 10.1002/14651858.CD004753.pub4.
23. Zondervan KT, Becker CM, Koga K, Missmer SA, Taylor RN, Viganò P. Endometriosis. *Nat Rev Dis Primers.* 2018;4(1):9. doi: 10.1038/s41572-018-0008-5.
 24. Zondervan KT, Becker CM, Missmer SA. Endometriosis. *N Engl J Med.* 2020;382(13):1244-1256. doi: 10.1056/NEJMra1810764.
 25. Becker CM, Bokor A, Heikinheimo O, Horne A, Jansen F, Kiesel L, et al. ESHRE guideline: endometriosis. *Hum Reprod Open.* 2022;2022(2):hoac009. doi: 10.1093/hropen/hoac009.
 26. Becker CM, Johnson NP, As-Sanie S, et al. Two-year efficacy and safety of relugolix combination therapy in women with endometriosis-associated pain: SPIRIT open-label extension study. *Hum Reprod.* 2024;39(3):526-537. doi: 10.1093/humrep/dead263.
 27. Agenzia Italiana del Farmaco (AIFA). Endometriosi – autorizzata la rimborsabilità di dienogest. *Socialfarma.* Available at: <https://www.socialfarma.it/endometriosi-aifa-autorizza-rimborsabilita-di-dienogest/>. Accessed on December 10, 2024
 28. Muzii L, Di Tucci C, Achilli C, et al. Continuous versus cyclic oral contraceptives after laparoscopic excision of ovarian endometriomas: a systematic review and metaanalysis. *Am J Obstet Gynecol.* 2016;214(2):203-211. doi: 10.1016/j.ajog.2015.08.074.
 29. Muzii L, Di Tucci C, Galati G, et al. The efficacy of dienogest in reducing disease and pain recurrence after endometriosis surgery: a systematic review and meta-analysis. *Reprod Sci.* 2023;30(11):3135-3143. doi: 10.1007/s43032-023-01266-0.
 30. Johnson NP, Hummelshoj L, Adamson GD, et al. World Endometriosis Society consensus on the classification of endometriosis. *Hum Reprod.* 2017;32(2):315-324. doi: 10.1093/humrep/dew293.
 31. Kuznetsov L, Dworzynski K, Davies M, Overton C; Guideline Committee. Diagnosis and management of endometriosis: summary of NICE guidance. *BMJ.* 2017;358:j3935. doi: 10.1136/bmj.j3935.
 32. Leyland N, Casper R, Laberge P, et al. Endometriosis: diagnosis and management. *J Obstet Gynaecol Can.* 2010;32(Suppl 2):S1-S3.
 33. Guo SW. Recurrence of endometriosis and its control. *Hum Reprod Update.* 2009;15(4):441-461. doi: 10.1093/humupd/dmp007.
 34. Di Spiezio Sardo A, Maiorana A, Muzii L, et al. It's time to make a change from a lesion-tailored to a patient-tailored approach in the management of uterine fibroids. *Ital J Gynaecol Obstet.* 2024;36(1):4-9. doi: 10.36129/jog.2023.144.
 35. Van Poppel H, Klotz L. Gonadotropin-releasing hormone: an update review of the antagonists versus agonists. *Int J Urol.* 2012;19(7):594-601. doi: 10.1111/j.1442-2042.2012.02997.x.
 36. Di Spiezio Sardo A, Ciccarone F, Muzii L, et al. Use of oral GnRH antagonists combined therapy in the management of symptomatic uterine fibroids. *Facts Views Vis Obgyn.* 2023;15(1):29-33. doi: 10.52054/FVVO.15.1.059.
 37. Zhang P, Wang G. Progesterone Resistance in Endometriosis: Current Evidence and Putative Mechanisms. *Int J Mol Sci.* 2023;24(8):6992. doi: 10.3390/ijms24086992.
 38. Chetkowski RJ, Meldrum DR, Steingold KA, et al. Biologic effects of transdermal estradiol. *N Engl J Med.* 1986;314(25):1615-1620. doi: 10.1056/NEJM198606193142505.
 39. Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. *Am J Obstet Gynecol.* 1992;166(2):740-745. doi: 10.1016/0002-9378(92)91706-G.
 40. European Community. Report on osteoporosis in the European Community: action for prevention. Available at: <http://europa.eu.int>. Accessed on September 9, 2024.
 41. Istituto Superiore di Sanità. Osteoporosi – Epicentro. Available at: <https://www.epicentro.iss.it/focus/osteoporosi/osteoporosi>. Accessed on December 10, 2024.
 42. European Medicines Agency. Relugolix – Summary of Product Characteristics (SmPC). Available at: https://ec.europa.eu/health/documents/community-register/2021/20210716152087/anx_152087_it.pdf. Accessed on December 10, 2024.
 43. Markham A. Relugolix: first global approval. *Drugs.* 2019;79(6):675-679. doi: 10.1007/s40265-019-01111-x.
 44. Rocca ML, Palumbo AR, Lico D, et al. Relugolix for the treatment of uterine fibroids. *Expert Opin Drug Metab Toxicol.* 2020;16(11):1667-1674. doi: 10.1080/14656566.2020.1787988.
 45. Al-Hendy A, Lukes AS, Poindexter AN, et al. Treatment of uterine fibroid symptoms with relugolix combination therapy. *N Engl J*

- Med. 2021;384(7):630-642. doi: 10.1056/NEJ-Moa2008283.
46. Committee for Medicinal Products for Human Use (CHMP). Ryego, INN–Relugolix–Estradiol–Norethisterone acetate. European Medicines Agency.
 47. Johansen JS, Jensen SB, Riis BJ, et al. Time-dependent variations in bone turnover parameters during 2 months' cyclic treatment with different doses of combined estrogen and progestogen in postmenopausal women. *Metabolism*. 1990;39(10):1122-1126. doi: 10.1016/0026-0495(90)90152-b.
 48. Riis BJ, Lehmann HJ, Christiansen C. Norethisterone acetate in combination with estrogen: effects on the skeleton and other organs. A review. *Am J Obstet Gynecol*. 2002;187(4):1101-1116. doi: 10.1067/mob.2002.126300.
 49. Osmanağaoğlu MA, Osmanağaoğlu S, Osmanağaoğlu T, et al. Effect of different preparations of hormone therapy on lipid and glucose metabolism, coagulation factors, and bone mineral density in overweight and obese postmenopausal women. *Fertil Steril*. 2005;84(2):384-393. doi: 10.1016/j.fertnstert.2005.02.028.
 50. Giudice LC, As-Sanie S, Arjona Ferreira JC, et al. Once daily oral relugolix combination therapy versus placebo in patients with endometriosis-associated pain: two replicate phase 3, randomised, double-blind studies (SPIRIT 1 and 2). *Lancet*. 2022;399(10333):2267-2279. doi: 10.1016/S0140-6736(22)00562-5.