Long Term Management of Endometriosis

By Dr. Meenakshi Ahuja

About the speaker

Dr. Meenakshi Ahuja

Senior Director Obstetrics & Gynecology

Fortis La Femme GK

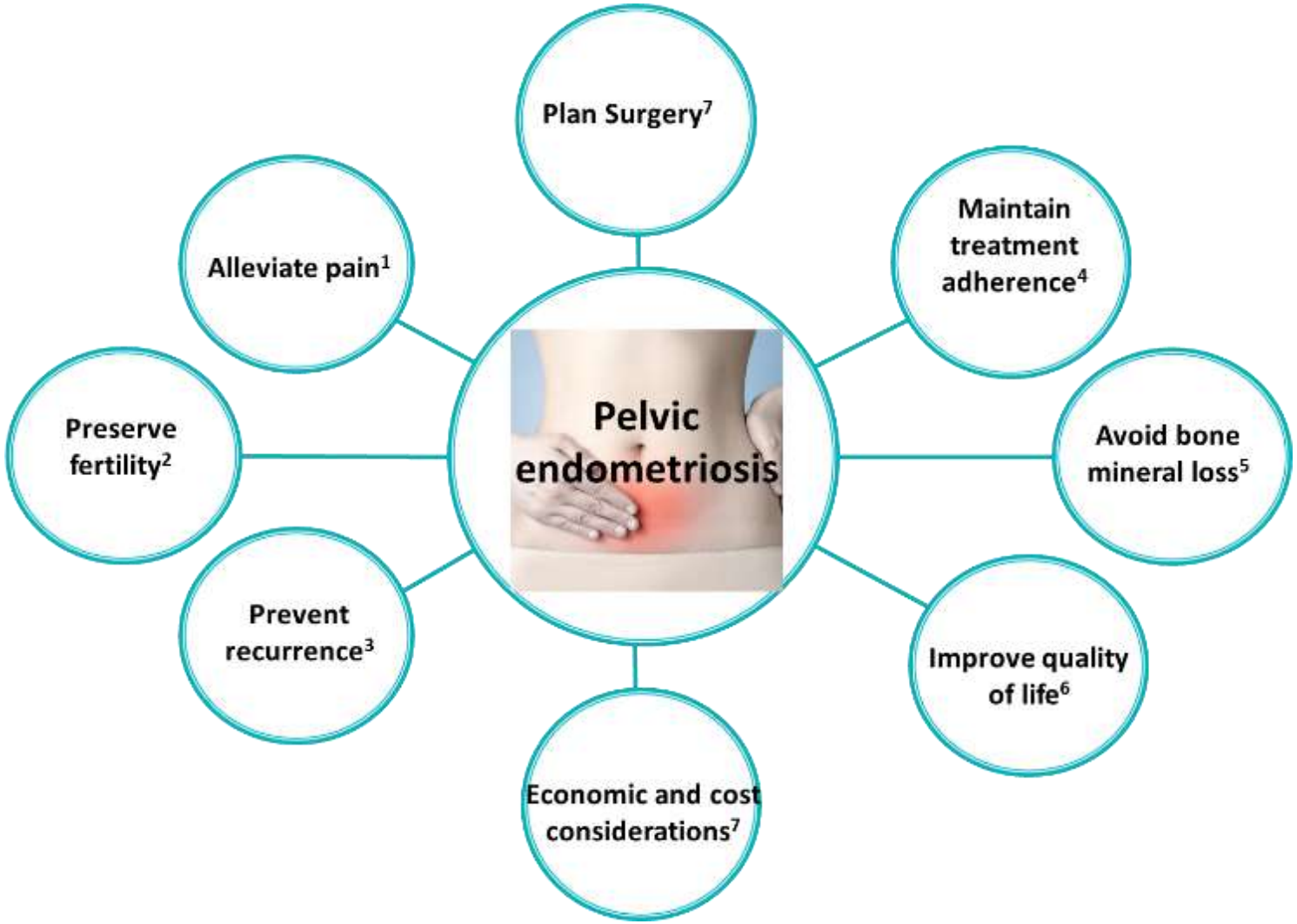
- Leading gynecologist with **~30 years of clinical practice** in South Delhi's premier hospitals.
- **Founding member & Senior Director** at Fortis La Femme, GK-II.
- **Leadership roles**:
  - President – Delhi Menopausal Society
  - Academic Secretary – Delhi Gynae Forum
  - President – Delhi North India Gynae Forum
- **Research & Publications**:
  - Multiple publications in **national & international journals**.
  - Author of thesis: *"The Role of Carbon Dioxide Laser in Benign Cervical Lesions"*.
  - Article in *Indian Journal of Obstetrics & Gynecology* (1992): *Laser Vaporization in Cervical Lesions*.
  - Contributor to **Training Module for Medical Officers at Post-Partum Centers**, MoHFW, New Delhi.
- **Conference Presentations**:
  - AICOG 2015, Chennai: Prescription Event Monitoring study on Oral Natural Micronized Progesterone SR.
  - AOFOG 2015, Malaysia: Safety & outcomes of Oral NMP SR in unexplained infertility.
- **Recognition**: Featured in *Wonder Women* (Hachette India) – dedicated chapter highlighting inspiring gynecologists of India.

The World Health Organization says,

- Endometriosis ***affects roughly 10% (190 million)*** of reproductive age women and girls globally.
- It is a ***chronic disease*** associated with severe, life-impacting pain during periods, sexual intercourse, bowel movements and/or urination, chronic pelvic pain, abdominal bloating, nausea, fatigue, and sometimes depression, anxiety, and infertility.
- ***There is currently no known cure for endometriosis and treatment is usually aimed at controlling symptoms.***
- ***Access to early diagnosis and effective treatment of endometriosis is important***, but is ***limited in many settings***, including in low- and middle-income countries.

https://www.who.int/news-room/fact-sheets/detail/endometriosis

Key considerations in the long-term management of endometriosis



1Park SY, et al. Clin Exp Reprod Med. 2016 Dec;43:215-20. 2Dunselman GA, et al. Human Reproduction. 2014 Mar;29(3):400-12. 3Ouchi N, et al. J Obstet Gynaecol Res. 2014;40:230-6. 4Soliman AM, et al. J Manag Care Spec Pharm. 2016 May;22(5):573–87. 5Sagsveen M, et al. Cochrane Database Syst Rev. 2003;(4):CD001297. 6Angioni S, et al. Gynecol Endocrinol. 2015 May;31(5):406-8. 7. Chapron C, et al. Nat Rev Endocrin 2019;15:666–682

Many gynecological societies have published different guidelines in order to help the clinicians with the diagnosis and treatment of endometriosis.

- A comprehensive review comparing eight widely used endometriosis treatment guidelines summarized the following recommendations.
- **The analysis included six national guidelines:**

  - Collège National des Gynécologues et Obstétriciens Français (CNGOF)
  - German National Guideline
  - Society of Obstetricians and Gynaecologists of Canada (SOGC)
  - American College of Obstetricians and Gynecologists (ACOG)
  - American Society for Reproductive Medicine (ASRM)
  - National Institute for Health and Care Excellence (NICE, UK)

- **And two international guidelines:**
  - World Endometriosis Society (WES)
  - European Society of Human Reproduction and Embryology (ESHRE)

- These ***guidelines provided a consolidated overview of current evidence-based recommendations*** for the management of endometriosis…..

Kalaitzopoulos DR, Samartzis N, Kolovos GN, Mareti E, Samartzis EP, Eberhard M, Dinas K, Daniilidis A. Treatment of endometriosis: a review with comparison of 8 guidelines. BMC Womens Health. 2021 Nov 29;21(1):397. doi: 10.1186/s12905-021-01545-5. PMID: 34844587; PMCID: PMC8628449.

Summary of Guideline Recommendations

- **Surgical Consensus:**
  - ***Laparoscopy*** is unanimously ***preferred over laparotomy***.
  - ***Ovarian endometrioma cystectomy and hysterectomy*** (***for severe/refractory cases***) are widely supported.
  - DIE excision and vaginal approaches are inconsistently recommended; more selective based on symptoms and expertise.

- **Medical Management:**
  - **First-line:** ***Progestins (including dienogest), COCs, NSAIDs*** – broadly endorsed across all guidelines.
  - **LNG-IUS**: ***Strong consensus*** as an effective long-term option.
  - **GnRH analogs (agonists/antagonists)**: ***Mixed recommendations*** due to tolerability concerns and need for add-back therapy.

- **Limited/Not Recommended Options:**
  - Danazol, pentoxifylline, and SERMs/SPRMs are consistently not recommended.
  - Aromatase inhibitors and gestrinone receive selective support (mostly for refractory cases).

Kalaitzopoulos DR, Samartzis N, Kolovos GN, Mareti E, Samartzis EP, Eberhard M, Dinas K, Daniilidis A. Treatment of endometriosis: a review with comparison of 8 guidelines. BMC Womens Health. 2021 Nov 29;21(1):397. doi: 10.1186/s12905-021-01545-5. PMID: 34844587; PMCID: PMC8628449.

Rethinking management of endometriosis

While hormonal treatments offer similar pain relief, they vary in safety, tolerability, and cost. For patients not planning pregnancy, a stepwise approach is advised:

- **First-line:** Low-cost options like COCs or progestins.
- **Limitations:** 25–33% may not respond, have intolerances, or contraindications.
- **Second-line:** Higher-cost GnRHa, reserved for non-responders.

Note: Long-term GnRHa use (>6 months) requires add-back therapy to prevent bone mineral density loss.

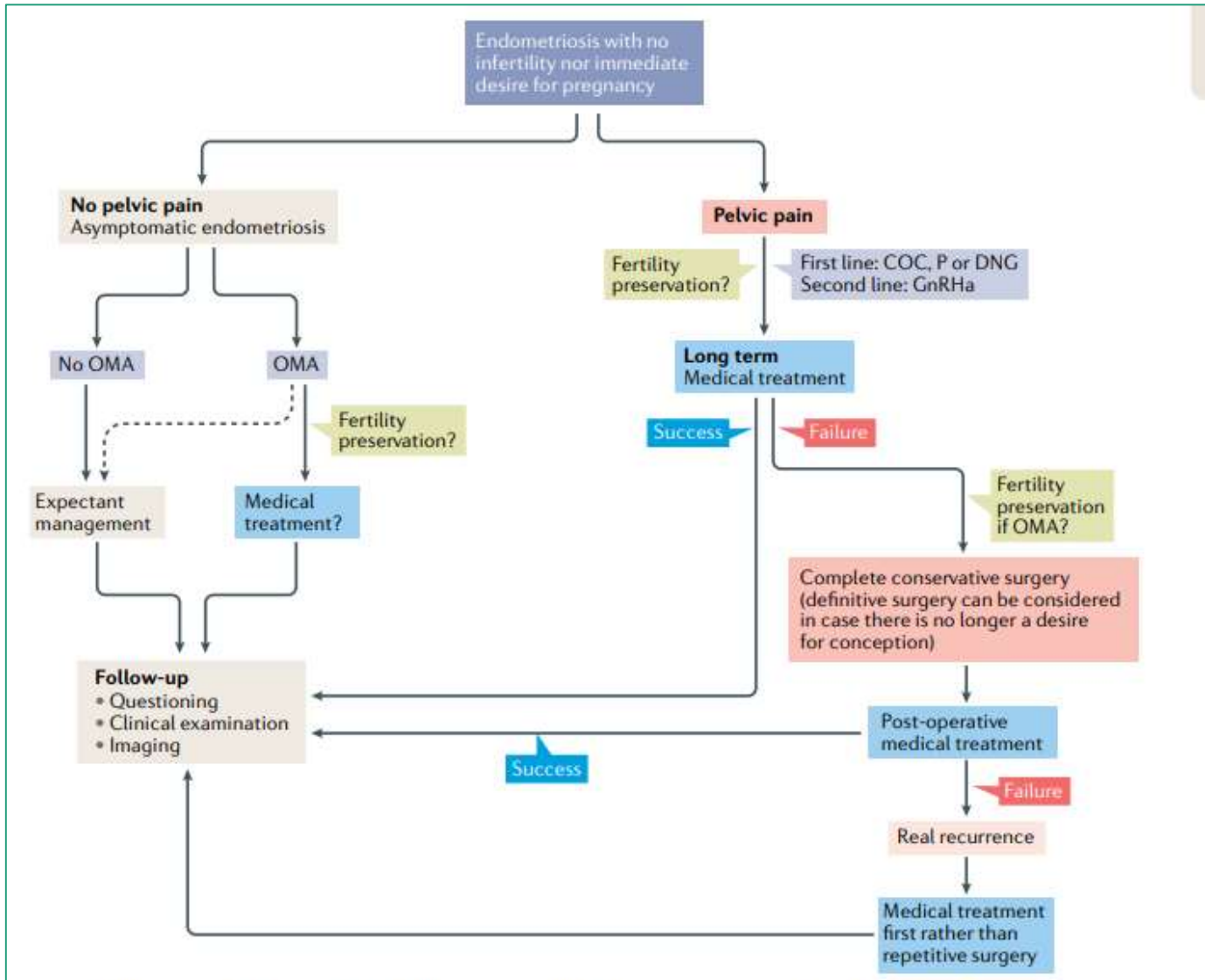


Fig. 5 | **Endometriosis management algorithm for patients without an immediate desire for pregnancy.** This novel algorithm can be used by health-care professionals for the management of patients with endometriosis who have no immediate desire for pregnancy. COC, combined oral contraceptive; DNG, dienogest; GnRHa, gonadotropin-releasing hormone analoques; OMA, ovarian endometriomas; P, progestins.

Chapron C, Marcellin L, Borghese B, Santulli P. Rethinking mechanisms, diagnosis and management of endometriosis. *Nat Rev Endocrinol*. 2019;15(11):666-682. doi:10.1038/s41574-019-0245-z

Rethinking First-Line Surgery in Endometriosis

A. Conventional Approach

Most clinical centers still follow a **surgery-first** strategy.

ART is considered **only after** multiple surgeries or failed conception.

B. Proposed Lifelong Management Strategy ("Endometriosis Life")

For patients desiring pregnancy but unable to conceive naturally:

ART offered early, after just **one surgery**, to improve pregnancy chances.

Post-childbirth: Resume **medical therapy** until the next pregnancy attempt.

C. Non-Surgical Pathway

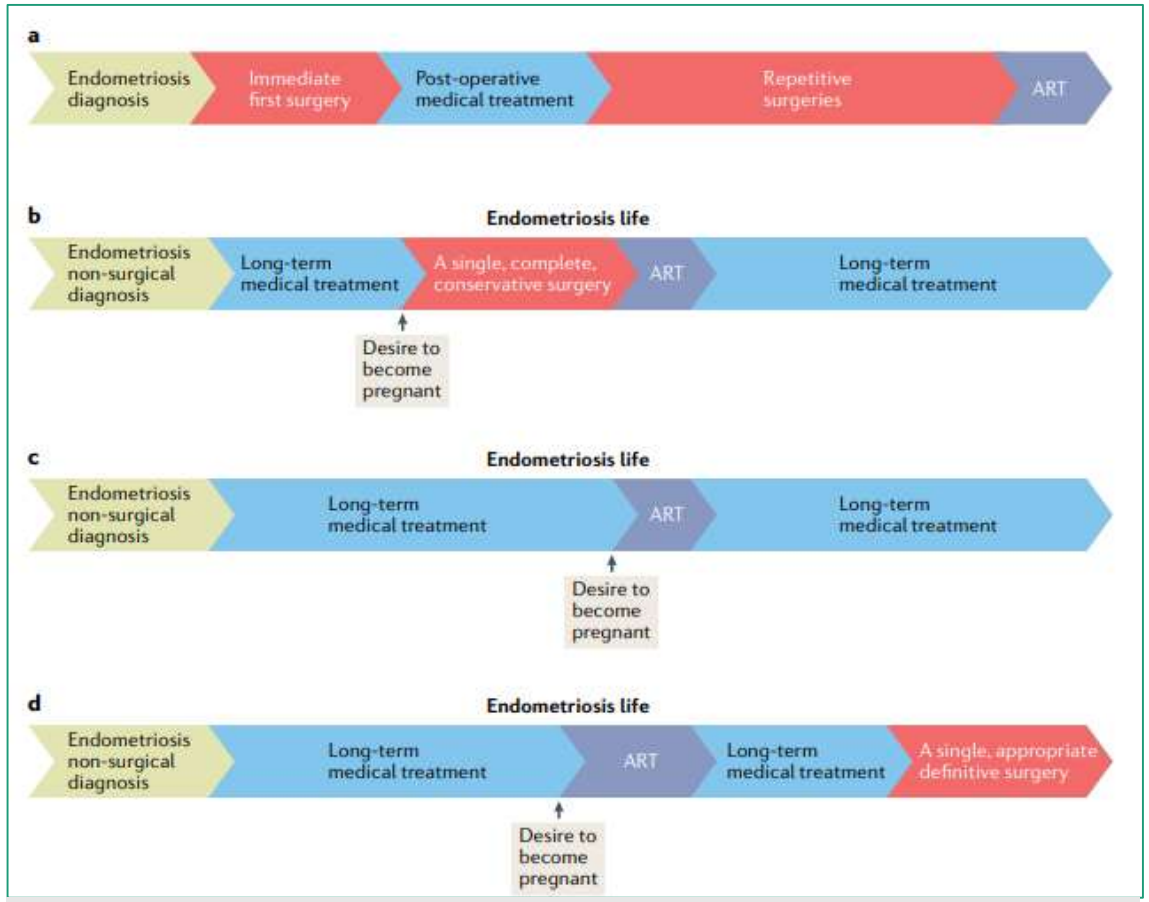
For patients who **refuse or are unsuitable for surgery**:

ART can be initiated without prior surgery.

If medical therapy is effective and tolerated, **surgery may be avoided** altogether.

D. ART-First with Deferred Surgery

ART is prioritized before surgery if: Hormonal treatment is ineffective or poorly tolerated, Or the patient no longer wishes to continue medical therapy.



Approaches for management of endometriosis

Chapron C, Marcellin L, Borghese B, Santulli P. Rethinking mechanisms, diagnosis and management of endometriosis. *Nat Rev Endocrinol*. 2019;15(11):666-682. doi:10.1038/s41574-019-0245-z

The recommendations by NICE for medical management of Endometriosis

1. Initial Pharmacological Treatment

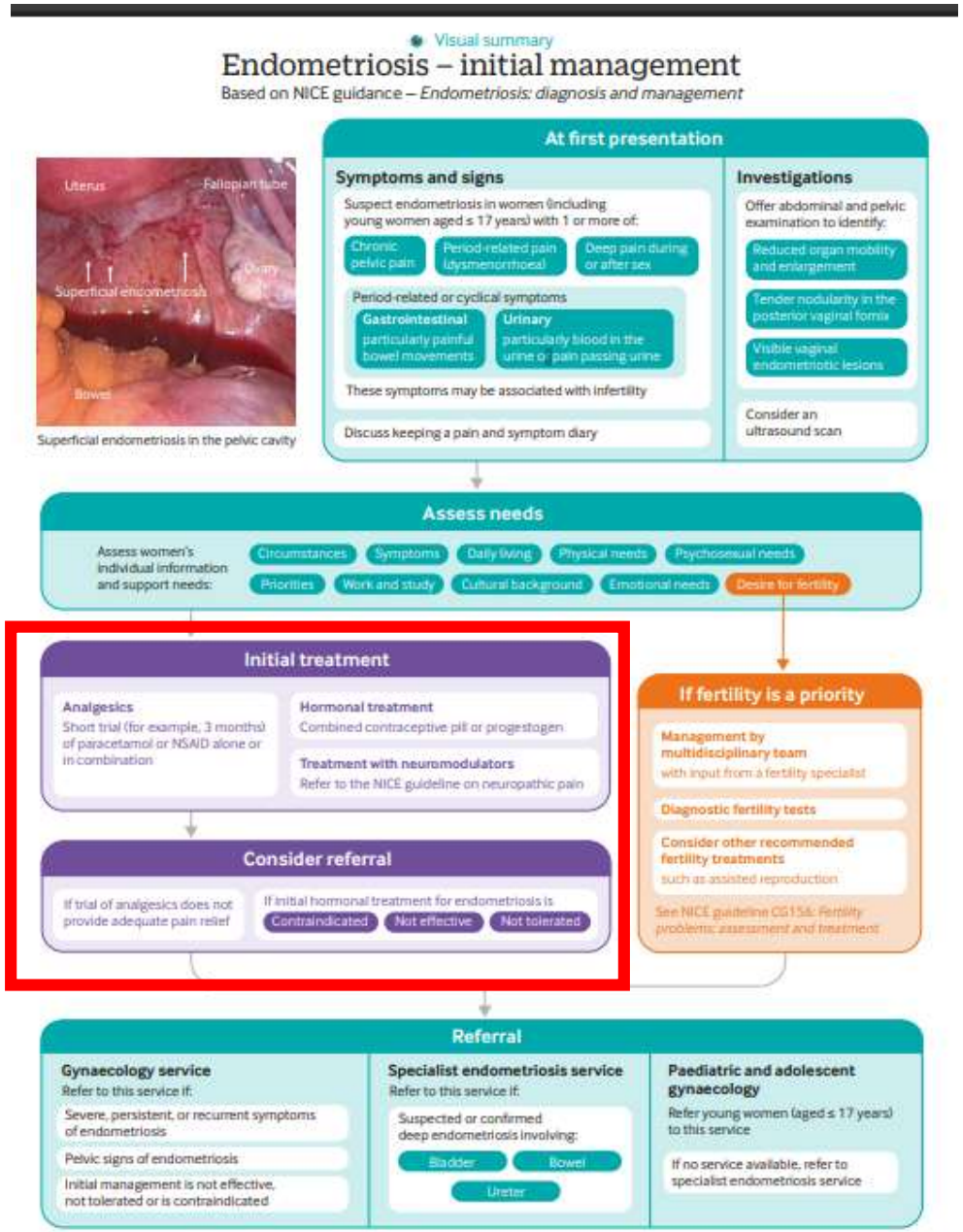
- Begin with a **short trial (≈3 months)** of **analgesics** (paracetamol or NSAIDs) for pelvic pain management

- If pain persists, **offer hormonal therapy** (combined oral contraceptives or progestogens), ensuring patients understand that this does **not impair future fertility**

2. Hormonal Therapy Details

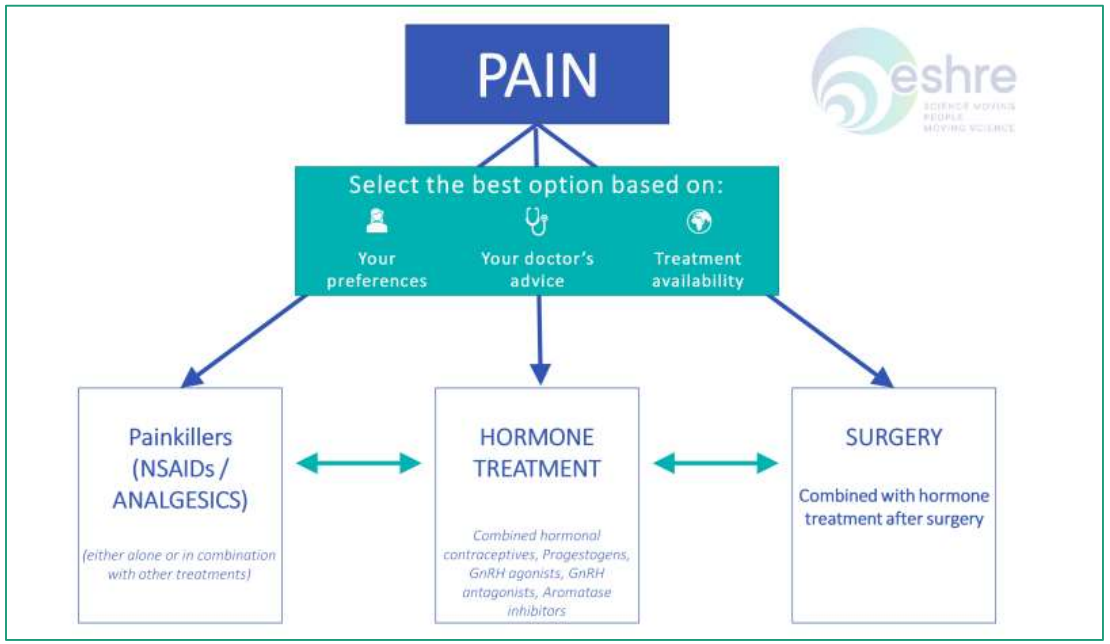
- Use COCs or progestogens **continuously or cyclically**, tailored to patient needs.

- **Escalate to GnRH agonists if first-line hormonal treatments are ineffective or contraindicated**, preferably after specialist referral in severe cases .



BMJ 2017;358:j3935

The recommendations by ESHRE for medical management of Endometriosis



Pain Management

- **First-line hormonal therapy**: Combined hormonal contraceptives or progestogens are recommended to alleviate dysmenorrhea, non-menstrual pain, and dyspareunia
- **Second-line**: Use GnRH agonists (with add-back to prevent bone loss) or GnRH antagonists when combined treatments fail
- **No longer recommended**: Danazol, antiprogestogens, and pre-surgery hormonal suppression are dropped due to limited benefit and side effects

https://www.eshre.eu/guideline/endometriosi s

What does the Indian guidelines say regarding endometriosis medical management?

Medical management of endometriosis

Drug	Type	Special remarks	Side-effects
NSAID	Non hormonal	Symptomatic Does not stop disease progression	Gastric ulcer, renal disease, bronchospasm
COC	First line	Oral, vaginal, trnasdermal Continuous use preferre	VTE, nausea, vomiting
Progesterones	First line	Oral LNG IUS - ease of use, beneficail in dysmenorrhoea	Wt gain, breast tenderness, increase IDL levels
Dienogest	First line	Formulated for endometriosis Can be used for 52 weeks	Irregular bleeding, acne, nausea
GnRH agonist	Second line	Injectable Short term use Add back therapy recommended	BMD loss, VTE, Hot flushes
GnRH antagonist	Second line	Oral	Hot flushes, BMD loss
Aromatase inhibitor	Third line	Add back therapy recommended Can be used in drug resistant recto vaginal endometriosis Can be used in post menopausal patients	Arthralgia, myalgia, decreased BMD

FOGSI considers,

- **Progestogens** are considered as the First Line of treatment and,
- **Oral GnRH antagonist** is considered as Second line of treatment of Endometriosis

Federation of Obstetric and Gynaecological Societies of India (FOGSI). Updates in Endometriosis Management. Published August 2024. Available at: https://www.fogsi.org/wp-content/uploads/2024/08/Binder_Updates-in-Endometriosis-Management.pdf. Accessed February 27, 2025.

COCs in Endometriosis

Review of Literature

COCs are prescribed off-label for the management of endometriosis-associated pain[1–3]

Key reasons COCs are prescribed for the management of endometriosis:

- COCs thin the endometrium, reducing the amount of bleeding[1]
- If taken continuously, COCs can be used to stop periods[1]
- COCs **effectively relieve cramping and pain** through inhibition of the metabolism of arachidonic acid to prostaglandins[1]
- **Generally well-tolerated**, with fewer metabolic and hormonal side effects **than danazol or GnRH agonists**[1,3]
- **Inexpensive**[1]
- **High comfort level for prescribing doctors and patients**[1]

COC, combined oral contraceptive; GnRH, gonadotropin-releasing hormone.

1. Casper et al. Fertil Steril 2017;107:533–536; 2. European Society of Human Reproduction and Embryology. 2013. *Guideline on the management of women with endometriosis*. [ONLINE] Available at: https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Endometriosis-guideline.aspx. [Accessed May 2020];
3. Harada et al. Fertil Steril 2008;90:1583–1588.

But, why COC may not be the best treatment option?

Chronic pelvic pain in suspected or proven endometriosis - OCPs may not be the best treatment option and could potentially lead to progression of the disease. Let us look into "Molecular Basis of Progesterone Resistance in Endometriosis"

In a Normal Endometrium:

- Estrogen (via ER) ↑ PR-B expression in follicular phase.
- Progesterone (via PR-B) in luteal phase:
  - ↓ ER expression
  - ↑ HSD17B2 → converts estradiol (E2) to weaker estrone (E1)
  - Net effect: **Estrogen inactivation & hormonal balance**

VS.

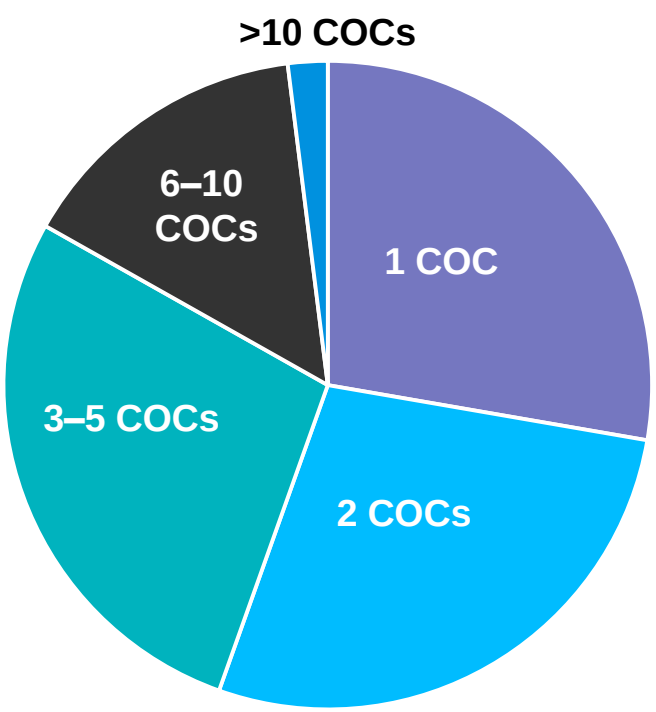
While in Endometriosis Implants:

- ER-α ↓ and ER-β ↑ → disrupted signaling
- PR-B lost → no HSD17B2 induction
- Estradiol remains active → **persistent estrogenic stimulation**
- Net effect: **Progesterone resistance & enhanced estrogen action**

Conclusion: Due to loss of PR-B and failure to inactivate estradiol, endometriotic tissue becomes progesterone-resistant and remains under constant estrogenic stimulation—driving lesion persistence and inflammation.

1. Casper RF. Progestin-only pills may be a better first-line treatment for endometriosis than combined estrogen-progestin contraceptive pills. Fertil Steril.2017;107:533–6.

The majority of women have used multiple COCs in an attempt to relieve their endometriosis-associated pain



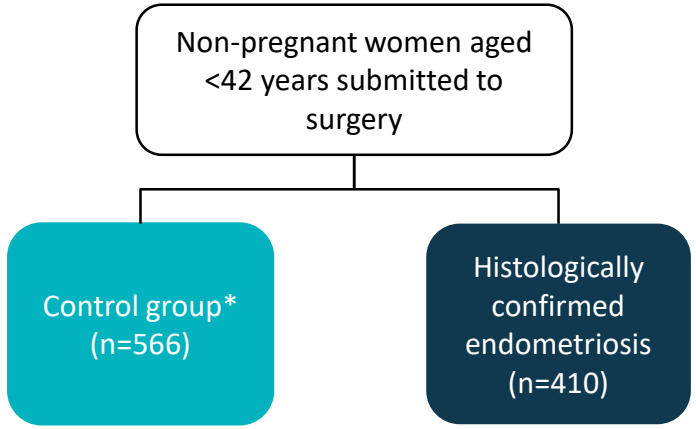
Number of different COCs used for relief of endometriosis symptoms (n=441, global cohort)

- ~70% of women had used multiple COCs
- >40% of women had been prescribed between 3–10 different COCs
- Numerous switches of COCs suggests:
  - Recurrence of pelvic pain while taking a COC
  - COCs are not completely effective in treating endometriosis

COC, combined oral contraceptive

Casper et al. Fertil Steril 2017;107:533–536.

Cross-sectional study to determine if past COC use is associated with an increased risk of endometriosis

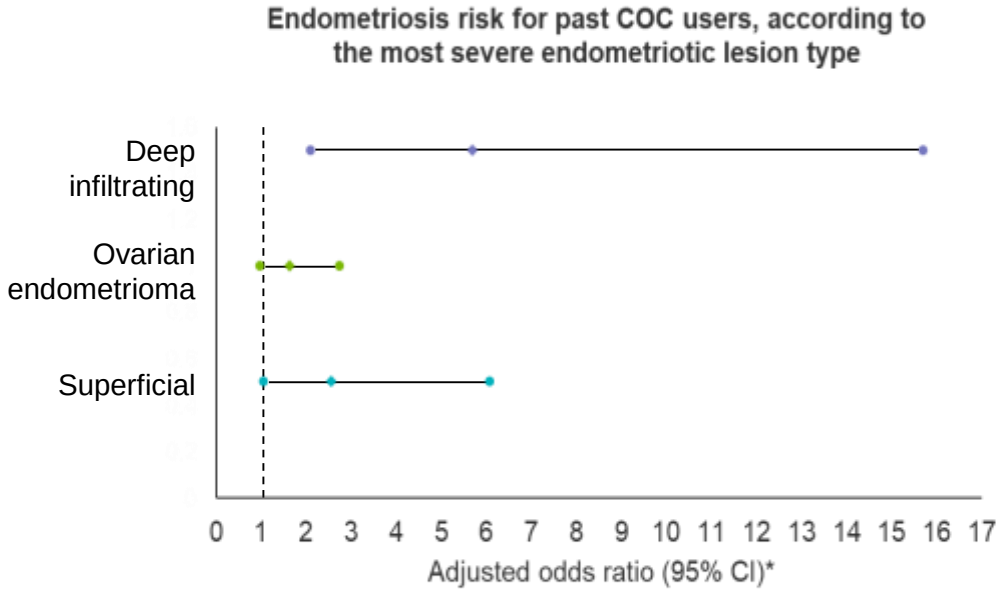


Inclusion criteria:

- Histologically proven endometriosis

Exclusion criteria:

- Women with cancer and/or not providing study consent
- Visually but not histologically confirmed endometriosis



Results showed that the past COC users had a significantly increased risk of superficial and DIE

- COC, combined oral contraceptive; DIE, deep infiltrating endometriosis
- *No visual lesions of endometriosis
- Chapron et al. Hum Reprod 2011;26:2028–2035.

Past OC exposure is associated with endometriosis

Past OC use is most strongly associated with DIE, particularly if prescribed for the treatment of severe primary dysmenorrhaea[1]

Results support previous conclusions that the incidence of endometriosis is decreased in current OC users but increased in past users[2]

- Observed associations between OC exposure and endometriosis do not prove OC use increases the risk of endometriosis[1]
- Careful interpretation of data is necessary, with consideration of confounding factors[1]

Future prospective studies are required to determine the role of OC use in endometriosis, either as a potential marker for women at risk of developing DIE or as causative in the development of endometriosis[1]

DIE, deep infiltrating endometriosis; OC, oral contraceptive

1. Chapron et al. Hum Reprod 2011;26:2028–2035; 2. Vercellini et al. Hum Reprod Update 2011;17:159–170.

Oestrogen in COCs may stimulate disease progression

Human Reproduction Update, Vol.17, No.2 pp. 159–170, 2011
Advanced Access publication on September 10, 2010 doi:10.1093/humupd/dmq042

human reproduction update

Oral contraceptives and risk of endometriosis: a systematic review and meta-analysis

Paolo Vercellini [1,2,*], Brenda Eskenazi [3], Dario Consonni [4], Edgardo Somigliana [1,2], Fabio Parazzini [1], Annalisa Abbiati [1,2], and Luigi Fedele [1]

[1]Clinica Ostetrica e Ginecologica I, Istituto 'Luigi Mangiagalli', Università Statale di Milano, Fondazione IRCCS 'Ca' Granda' - Ospedale Maggiore Policlinico, Via Commenda 12, Milan 20122, Italy [2]Centre for Research in Obstetrics and Gynaecology (C.R.O.G.), Milan, Italy [3]School of Public Health, Division of Epidemiology, University of California, Berkeley CA, USA [4]Unit of Epidemiology, Fondazione IRCCS 'Ca' Granda' - Ospedale Maggiore Policlinico, Milan, Italy

"…the pill could be viewed as a rescue factor for regurgitated endometrial glands that would otherwise undergo necrosis and resorption during the physiologically hypo-estrogenic menstrual milieu"

- Vercellini et al. Hum Reprod Update 2011;17:159–170.

Conclusion for the use of COCs in endometriosis

- Given the widespread and recommended use of the COCP in this setting, clinicians need to make decisions based on other available evidence.
- This statement is line with a Cochrane review conducted in 2018

Brown J, Crawford TJ, Datta S, Prentice A. Oral contraceptives for pain associated with endometriosis. Cochrane Database Syst Rev. 2018 May 22;5(5):CD001019. doi: 10.1002/14651858.CD001019.pub3. PMID: 29786828; PMCID: PMC6494634.

Progestins in Endometriosis

Review of Literature

Compared with COCs, progestin-only treatment may be a more suitable first-line treatment for endometriosis[1]

- **Progestin-only treatments:**
  - Inhibit ovulation and induce a relatively hypoestrogenic state that could help suppress endometriosis and prevent disease progression
  - Induce amenorrhoea (prevent dysmenorrhoea) with relatively few side effects
  - Can be prescribed at any age
  - Are likely to maintain bone density
  - Show no increase in thrombosis risk

COC, combined oral contraceptive.

1. Casper et al. Fertil Steril 2017;107:533–536.

When considering dienogest as medical treatment for ovarian endometriomas in comparison to EE+DNG combination the results showed endometriotic cysts volume to reduce significantly

- Prospective, multicentre, case-control study
- 81 patients with endometrioma
  - 40 treated with 2 mg **DNG**
  - 41 treated with **cyclic oral oestro-progestins** (30 µg EE + DNG 2 mg)
- **The size of endometrioma cysts were significantly reduced in the DNG group**

	DNG	DNG + EE	p
Cyst volume (mL)			
Time, mean (SD)			
0	65 (10)	76 (20)	ns
3	45 (15)	65 (18)	<0.05
6	16 (5)	65 (25)	<0.001
p	<0.001	ns	
VAS			
Time, mean (SD)			
0	65 (14)	70 (18)	ns
3	25 (10)	28 (12)	ns
6	19 (15)	18 (12)	ns
p	<0.001	<0.001	

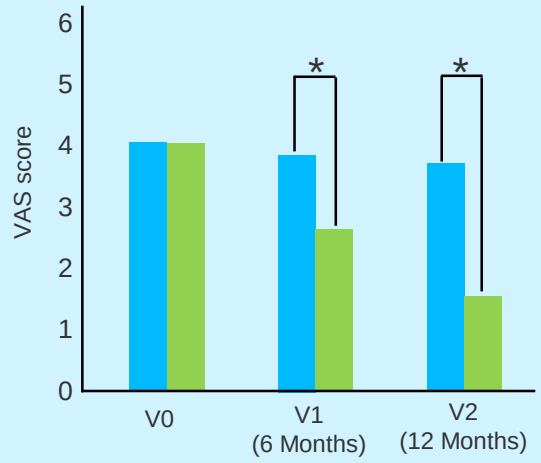
DNG, dienogest; EE, ethinyl estradiol; ns, not significant; SD, standard deviation; VAS, visual analgoue scale.

.

Angioni et al. Gynecol Endocrinol 2020;36:84–86.

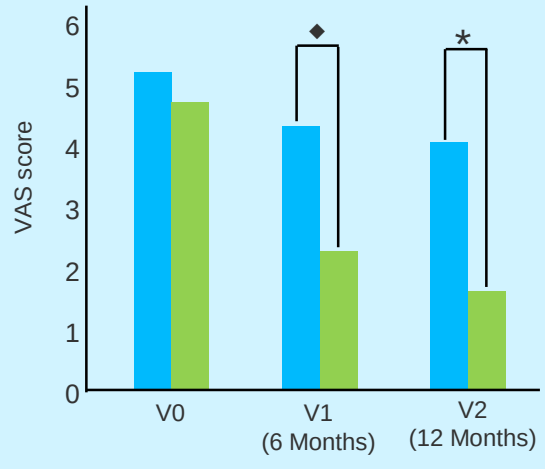
In comparison to NETA, Dienogest resulted in greater improvements in dyspareunia, dysmenorrhoea and chronic pelvic pain

Dyspareunia



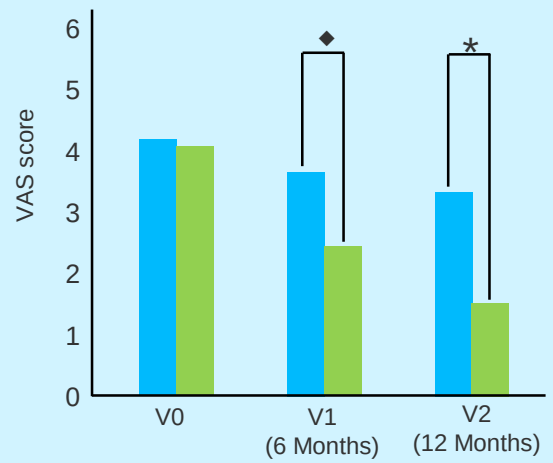
* $p<0.001$

Dysmenorrhoea



◆ $p=0.001$ * $p<0.001$

Chronic pelvic pain



◆ $p=0.002$ * $p<0.001$

NETA Dienogest

At both 6 and 12 months of treatment, significantly greater improvements in dyspareunia, dysmenorrhoea and chronic pelvic pain were observed with dienogest vs NETA
($p<0.001$, $p=0.001$ and $p=0.002$, respectively, at 6 months; $p<0.001$ for all at 12 months)

NETA, norethisterone acetate; V0, baseline visit; V1, after 6 months; V2, after 12 months of treatment; VAS, visual analogue scale.
Figures from Del Forno et al. Eur J Obstet Gynecol Reprod Biol 2019;238:120–124.

Long-term efficacy, safety and tolerability and efficacy of dienogest

Review of Literature

Use of dienogest has been investigated in 4 observational post-authorisation studies

Study type	Study duration	Sample size (n)	Location	Main end-point	Results Conclusion
Daily practice treatment and Influence of Visanne® on the patient Assessment of quality of life parameters (DIVA)	**6 months, optional 12 months**	~3000	11 countries: Belarus, Egypt, Jordan, Kazakhstan, Kuwait, Lebanon, Qatar, Russia, Saudi Arabia, Ukraine, UAE	QoL under real-life conditions	Confirmed **significant reduction in dysmenorrhea, dyspareunia, and pelvic pain** with DNG 2 mg, alongside **improved quality of life**.
VIsanne® Post-approval Observational Study (VIPOS)	**3–7 years**	~28,000	6 European counties: Germany, Poland, Hungary, Switzerland, Russia, Ukraine	Long-term safety (anaemia, depression, treatment failure)	Confirmed DNG's safety profile, especially for **long-term use**, with **low VTE risk** and **high continuation rates**.
EffectiveNess of VISanne® in improving quality of life in AsIan wOmen with ENdometriosis (ENVISION)	**2 years**	~900	6 Asian countries: Korea, Indonesia, Malaysia, Philippines, Thailand, Singapore	QoL Long-term safety	Highlighted **sustained pain relief** over 15 months with **stable bone density** and good tolerability in a large, **diverse population**.
Regulatory Post Marketing Surveillance Study in Korea (KOREA PASS)	**6 months, optional 12 months**	~3000	Korea	Safety and efficacy	Showed DNG is effective and well-tolerated in **Asian populations**, reinforcing its **global applicability**. **DIVA**

Collectively, these studies support dienogest 2 mg as a globally validated, first-line option for long-term endometriosis management—combining efficacy, safety, and patient satisfaction

1. Bayer. Available at: https://clinicaltrials.bayer.com/study/1311. Accessed November 2019; 2.. Bayer. Available at: https://clinicaltrials.bayer.com/study/20018. Accessed November 2019; 3. Bayer. Available at: https://clinicaltrials.bayer.com/study/2084. Accessed November 2019; 4. Techatraisak et al. BMC Womens Health 2019;19:68; 5. Bayer. Available at: https://clinicaltrials.bayer.com/study/2004. Accessed November 2019.

Is there any risk for breast cancer with long-term use of dienogest?

Safety of medical treatments for endometriosis

Nicola Berlanda[†], Edgardo Somigliana, Paola Viganò & Paolo Vercellini
[†]*Obstet-Gynecol Department, Fondazione Ca'Granda, Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*

Areas covered: Formulations of estro-progestins that contain less than 50 µg of estrogen are associated with a low risk of venous thrombosis, myocardial infarction and stroke. When considering the neoplastic effects, data suggest that the overall risk of invasive cancer by age 60 is not increased in previous users of hormonal contraceptives. The use of progestins for contraception has never been associated with an increased risk of breast cancer, venous thromboembolism or bone fractures. Although more data on long-term therapy with progestins are needed, treatment of endometriosis with progestins may be feasible in women with metabolic or cardiovascular contraindications to estroprogestin. The other medications for the treatment of pain associated with endometriosis are less appropriate for long term administration because of side effects (danazol and GnRH analogues), costs (aromatase inhibitors and GnRH agonists) or necessity of complex regimens of associations (GnRH agonists and add back therapy or aromatase inhibitors plus progestins).

Expert Opin Drug Saf 2016;15:21–30.

Progestin and Breast Cancer Risk: A Systematic Review

Marsha Samson, MSPH, MHSA[1,2,3], Nancy Porter, MS[1,2,3], Olubunmi Orekoya, MD, MPH[1,3], James R. Hebert, ScD[1,2,3], Swann Arp Adams, PhD[1,2,3], Charles L. Bennett, MD, PhD[4], and Susan E. Steck, PhD[1,2]

Methods—ProQuest (Ann Arbor, MI) and PubMed-Medline (US National Library of Medicine, Bethesda MD, USA) databases were used to search for epidemiologic studies from 2000–2015 that examined the association between progestin and breast cancer. Search terms included epidemiologic studies + progesterone or progestin or progestogen or contraceptive or contraceptive agents + breast cancer or breast neoplasms. A total of six studies were included in the review.

Results—Five of the six studies reported no association between progestin-only formulations (including norethindrone oral contraceptives, depot medroxyprogesterone acetate, injectable, levonorgestrel system users, implantable and intrauterine devices) and breast cancer risk. Duration of use was examined in a few studies with heterogeneous results.

Conclusion—Unlike studies of other oral contraceptives, studies indicate that progestin-only formulations do not increase the risk of breast cancer, although the literature is hampered by small sample sizes. Future research is needed to corroborate these findings, as further understanding of synthetic progesterone may initiate new prescription practices or guidelines for women's health.

Breast Cancer Res Treat 2016;155:3–12.

In summary, no direct evidence exists of breast cancer risk with dienogest treatment

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Article ST-0633.R1/1744120

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REVIEW ARTICLE

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Use of dienogest in endometriosis: a narrative literature review and expert commentary

Ally Murji[a], Kutay Biberoğlu[b], Jinhua Leng[c], Michael D. Mueller[d], Thomas Römer[e], Michele Vignali[f] and Maria Yarmolinskaya[g]

Breast health

Women with endometriosis may be concerned about a potential increased cancer risk with hormonal treatments[57]. Although evidence for the clinical effects of dienogest on breast tissue is limited, no serious adverse events related to breast disorders were reported in the clinical development program[41]. Breast discomfort was the most frequently reported breast-related adverse event considered to be possibly treatment related in clinical trials[17,41]. A pilot study investigating the impact of high-dose dienogest (20 mg daily for 24 weeks) on breast tissue in women with endometriosis, identified no adverse effects on the breast gland, fat layer thickness at the areola edge, or duct diameter[58].

The relationship between COCs and progestins with breast cancer has been controversial and mainly based on population-based epidemiologic studies[59–62]. The risk of breast cancer was shown to be similar between different COCs, and findings for different progestin-only formulations were inconsistent[57]. Furthermore, in a mouse model, dienogest demonstrated potent anticancer activity against hormone-dependent cancers in two cell lines derived from human endometrial carcinoma, and one cell line derived from human breast carcinoma, where other progestins showed either no response or were only effective at a higher dose than that of dienogest[63]. It has also been demonstrated that dienogest exhibits antiangiogenic activity, which suggests that, in animal models, it may have antitumor effects on human hormone-dependent cancer xenografts, such as endometrial and breast cancers[64]. In summary, there is no direct evidence indicating an additional risk of breast cancer with dienogest treatment in humans, but the risk is likely to be similar to that of other progestins.

Murji et al. Curr Med Res Opin 2020;36:895–907.

Comparing other medical therapies in endometriosis management

(LNG-IUS, GnRH Agonists and Antagonist)

LNG-IUS in Endometriosis: Clinical and Mechanistic Insights

Clinical Benefits:

- ↓ Dysmenorrhea, dyspareunia, pelvic pain
- ↑ Quality of life (QOL), functional improvement
- ↓ Serum **CA-125** and **DIE nodule volume**
- Effective in **postoperative recurrence prevention**

Safety & Tolerability:

- Minimal systemic LNG exposure → no impact on **lipid metabolism** or **bone mineral density (BMD)**
- Excellent long-term compliance due to **non-daily dosing**
- Most common AE: **Irregular bleeding** (esp. first 6–12 months)

Clinical Considerations:

- Option in women unfit for systemic hormonal therapy
- May be used adjunctively with surgical therapy
- ~20% achieve amenorrhea within 12 months

Elbasueny B, Geerts M, Yang EC, Allaire C, Yong PJ, Bedaiwy MA. Medical treatments of endometriosis: a review. Reproductive and Developmental Medicine. 2023 Sep 1;7(3):166-79.

Medroxyprogesterone Acetate (MPA) in Endometriosis Management

- **Efficacy**
  - Oral MPA is effective vs. placebo in reducing endometriosis-related pain for up to 12 months.
  - DMPA formulations show good pain control and dual contraceptive benefit.
  - Clinical benefit includes control of dysmenorrhea, non-cyclic pelvic pain, and dyspareunia.

- **Limitations & Safety Concerns**
  - **Breakthrough bleeding** is common and may lead to discontinuation.
  - **Prolonged anovulation** and **delay in return of menses** post-treatment.
  - **Black box warning (FDA, 2004):** associated with decreased BMD, particularly with long-term use and in adolescents.
  - Risk of weight gain and mood changes may affect adherence.

- **Clinical Use**
  - Considered cost-effective and convenient, especially in settings prioritizing long-acting contraception.
  - Requires bone health monitoring if used >6 months.

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Cyproterone Acetate (CPA) in Endometriosis Management

- **Formulations & Indications**
  - Used orally (2 mg/day) in combination with ethinylestradiol as a COC.
  - Off-label use in **endometriosis-associated pelvic pain**, especially in recurrence post-surgery.

- **Efficacy**
  - Shown to alleviate **dysmenorrhea** and **pelvic pain** in patients post-laparoscopy.
  - May reduce **hirsutism and acne**, offering dual benefit in patients with comorbid hyperandrogenism.
  - In preliminary trials, second-look laparoscopy showed **regression of endometriotic lesions** after CPA use.

- **Safety Profile**
  - Generally well-tolerated with favorable compliance.
  - Lacks extensive long-term safety data in endometriosis specifically.
  - Use is restricted or not approved in some regions due to androgen suppression concerns.

- **Clinical Use**
  - An affordable and accessible option, especially in women with **coexisting androgen excess** (e.g., acne, hirsutism).
  - Consider in recurrence management after conservative surgical treatment.

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GnRH Agonists vs. Elagolix in Endometriosis Management

Parameter	GnRH Agonists	Elagolix
Formulation	Injections (short/long-acting), nasal sprays	Oral (150 mg OD, 200 mg BID)
Onset of Action	Delayed (initial flare-up effect due to transient FSH/LH surge)	Rapid (no flare-up)
Efficacy	Superior to placebo and comparable to DNG/LNG-IUS for dysmenorrhea and CPP	Effective in dysmenorrhea, NMPP, dyspareunia (Elaris EM-I/II/III/IV trials)
Safety Concerns	Hypoestrogenic effects: ↓ BMD, vasomotor symptoms, mood changes, libido loss	Dose-dependent ↓ BMD, hot flushes, lipid changes; less severe than agonists
Add-Back Therapy	Essential beyond 6 months to mitigate estrogen deficiency side effects	Used with higher dose or prolonged use
Treatment Duration	Limited to 6 months due to bone loss risk (± 6 months with add-back)	6–24 months depending on dose and patient risk profile
Fertility Impact	Ovulation suppression reversible after withdrawal	Reversible suppression; incomplete ovulation inhibition—contraception needed
Limitations	Initial flare-up, parenteral admin, high cost, adherence issues, long BMD recovery	Daily oral dosing, teratogenic risk, incomplete ovulation block, BMD Loss

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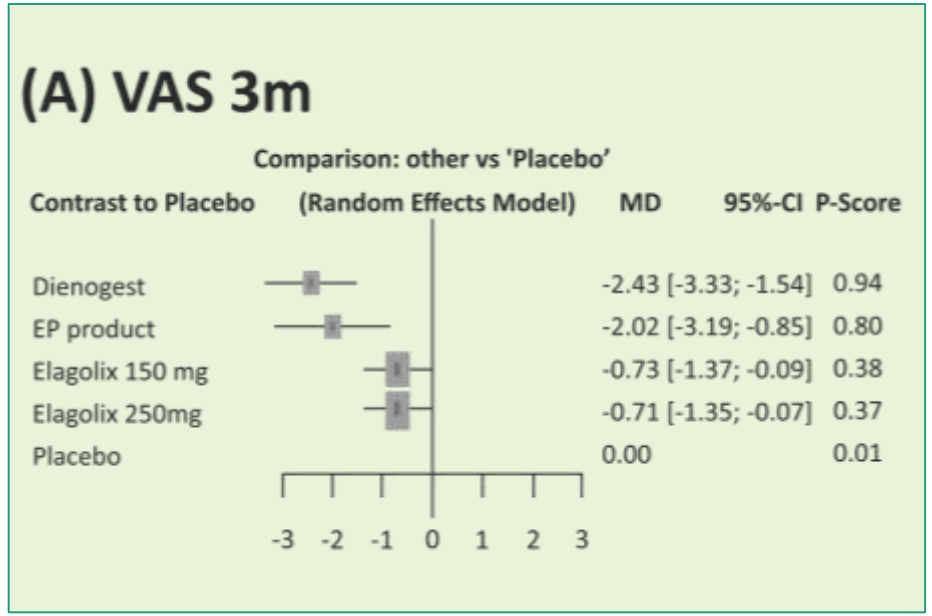
J Gynecol Obstet Hum Reprod. 2021 Jan;50(1):101798. doi: 10.1016/j.jogoh.2020.101798. Epub 2020 May 29.

Medical therapy options for endometriosis related pain, which is better? A systematic review and network meta-analysis of randomized controlled trials

- This 2021, meta-analysis of 36 RCTs (n=7,942) ranked pharmacologic treatments for endometriosis-related pain.
- At 3 months, **DNG**, **CHCs**, and **elagolix** showed the highest efficacy for pelvic pain
- AT 6 months, **GnRH-a**, **LNG-IUS**, and **DNG** ranked highest.
- **Moreover, Greater reduction in VAS pain scores at 3 months with Dienogest vs Elagolix**
- Overall, **CHCs, GnRH-a, progestins (DNG, Desogestral), and elagolix** were the most effective options.



Visual naligue scale: VAS

Samy A, Taher A, Sileem SA, et al. Medical therapy options for endometriosis related pain, which is better? A systematic review and network meta-analysis of randomized controlled trials. *J Gynecol Obstet Hum Reprod*. 2021;50(1):101798. doi:10.1016/j.jogoh.2020.101798

Long-Term Medical Management of Endometriosis

Evidence-Based Conclusions

Endometriosis is a chronic, recurrent inflammatory disease requiring prolonged suppression of ovulation and menstruation for sustained symptom relief and recurrence prevention (ACOG 2023; ESHRE 2022).

Hormonal therapies—progestins (DNG, MPA, LNG-IUS), CHCs, and GnRH analogues (agonists/antagonists)—are first-line and long-term options. They reduce dysmenorrhea, dyspareunia, and chronic pelvic pain by inducing decidualization, atrophy, and estrogen suppression (Brown et al., *Cochrane* 2012; Becker et al., *ESHRE* 2022).

Dienogest (2 mg daily) has demonstrated sustained pain reduction and lesion suppression for up to 108 months, with favorable safety profile and minimal BMD loss (Strowitzki et al., *Arch Gynecol Obstet* 2010; Techatraisak et al., *Int J Womens Health* 2019).

LNG-IUS provides effective long-term control of endometriosis-related pain and reduces recurrence post-surgery, with minimal systemic side effects and high continuation rates (Vercellini et al., *Hum Reprod Update* 2013; Cho et al., *Obstet Gynecol Sci* 2018).

GnRH agonists and antagonists (e.g., elagolix) are effective for moderate-to-severe pain, but their use is limited by hypoestrogenic side effects including BMD loss, requiring **add-back therapy** or dose adjustments for safe long-term use (Taylor et al., *NEJM* 2017; Surrey et al., *Fertil Steril* 2018).

Long-term management must be individualized, balancing efficacy, safety, reproductive goals, and patient preferences.