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Extended GnRH Agonist and NETA Add-Back: An Effective and Safe Option for Refractory Endometriosis/Adenomyosis Pain

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This prospective, open-label, two-arm clinical study evaluated the efficacy and safety of prolonged gonadotropin-releasing hormone agonist (GnRH-a) therapy exceeding 24 months, combined with norethisterone acetate (NETA) add-back, in women experiencing endometriosis-associated pain refractory to standard treatments. Eighty-one premenopausal women with confirmed endometriosis and/or adenomyosis received either Triptorelin SR 11.25 mg or Goserelin acetate 10.8 mg every three months, together with daily NETA 5 mg for 24 months. Significant reductions in dysmenorrhea and deep dyspareunia were observed, with mean visual analogue scale scores decreasing from 7.9 to 2.3 and 6.1 to 0.6, respectively ($P < 0.0001$), along with improvements in dyschezia, dysuria, bloating, alternating bowel habits, and cold intolerance. Mild osteopenia occurred in only 2.4% of participants, and no major adverse events were reported, confirming safety through laboratory and imaging follow-up. These findings suggest that long-term GnRH-a therapy with NETA add-back is highly effective and well-tolerated in women with severe, treatment-resistant endometriosis-related pain, and may serve as a viable second-line medical treatment when surgery is not feasible.

Keywords: Add-Back Therapy; Adenomyosis; Chronic Pelvic Pain; Endometriosis; GnRH Agonist; Long-Term Safety.

Endometriosis is a chronic, estrogen-dependent disorder characterized by the presence of endometrial-like epithelium and stroma outside the uterus, most commonly within the pelvic cavity. It is often associated with chronic inflammation, neuroangiogenesis, and sensitization of both the central and peripheral nervous systems.[1] Although it predominantly affects women of reproductive age, endometriosis may persist well beyond menopause.[2]

Clinically, endometriosis presents with a wide spectrum of symptoms, including dysmenorrhea, deep dyspareunia, chronic pelvic pain, dyschezia, dysuria, and subfertility.[3] More than 60% of women with chronic pelvic pain are found to have endometriosis.[4] Ectopic endometrial tissue remains hormonally responsive, and its cyclic activation contributes to pain, local invasion, and recurrence. Despite substantial research into its pathophysiology, including immune dysregulation, hormonal imbalance, and genetic susceptibility, optimal long-term management remains elusive.

Gonadotropin-releasing hormone agonists (GnRH-a) represent an effective second-line option for pain relief in women with moderate-to-severe disease. Since the early 1980s, their therapeutic

role has been established through suppression of ovarian hormone production and a subsequent hypoestrogenic state.[5] According to the European Society of Human Reproduction and Embryology (ESHRE), GnRH-a is recommended for reducing endometriosis-associated pain, although its use is constrained by adverse effects, particularly loss of bone mineral density.[6]

The mechanism of GnRH-a involves receptor desensitization, with a resulting decline in pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion and reduced estradiol levels.[7] The therapeutic goal is to maintain estradiol within the 30–60 pg/mL threshold to balance efficacy and safety.[8] Beyond endocrine suppression, GnRH-a may exert direct antiproliferative and antiangiogenic effects on ectopic endometrial tissue.[9,10] In vitro studies demonstrate their ability to inhibit endometrial cell growth.[11] and induce apoptosis via GRP78 downregulation.[12] The proposed KNDy neuron pathway consisting of kisspeptin, neurokinin B, and dynorphin may also modulate GnRH release, further explaining central hypothalamic effects.[13,14]

While short-term use (d"6 months) is effective, questions remain regarding the optimal duration and safety of prolonged therapy. Add-back regimens typically progestin-only (e.g., norethisterone acetate, NETA) or combined estrogen-progestin are widely endorsed to mitigate hypoestrogenic adverse effects.[15-17] NETA is commonly selected due to its favorable efficacy, affordability, and partial estrogenic activity after hepatic metabolism.[18-20]

Although guidelines recommend a treatment duration of up to six months,[1] emerging evidence suggests that extended use of GnRH agonists, particularly with appropriate add-back therapy, may be safe and effective in well-selected patients.[21,29] Studies have described consistent symptom suppression with longer durations of treatment while maintaining bone health through add-back regimens.[30] Norethisterone acetate (NETA), in particular, has demonstrated a favorable metabolic and partial estrogenic profile, supporting its use as add-back therapy.[31]

In addition, chronic pelvic pain syndromes associated with endometriosis have been linked to a broader symptom complex, including cold intolerance, as documented in regional studies.[32] This observation may reflect a neuro-inflammatory pathophysiology not limited to gynecologic structures alone.

Given the high recurrence rates following surgery and the limitations of first-line hormonal therapy, prolonged medical suppression is often necessary. However, data on extended (>24 months) use of GnRH-a with NETA add-back therapy remain scarce. In this study, we aimed to evaluate the long-term efficacy and safety of this regimen in a cohort of Jordanian women with refractory endometriosis or adenomyosis.

MATERIALS AND METHODS

Study design and participants

This was a double-armed, open-label, prospective clinical trial conducted between August 2011 and May 2018 in various gynecology clinics across Jordan. A total of 110 premenopausal women aged 22–45 years with severe endometriosis and/or adenomyosis-associated pain were initially enrolled. Of these, 81 participants completed the full 24-month treatment protocol. Twenty-nine patients were lost to follow-up and excluded from the final analysis.

All patients had a confirmed diagnosis of endometriosis based either on laparoscopy with histological confirmation or through solid imaging evidence. Of the 81 participants, 46 (51.7%) had coexisting adenomyosis. Inclusion required a history of severe chronic pelvic pain for at least six months that was refractory to standard medical or surgical treatments.

Inclusion and exclusion criteria

Women were eligible if they were aged 22 to 45 years, had regular menstrual cycles (24–38 days), and had a clinical diagnosis of endometriosis with or without adenomyosis within the past three years. Participants had to be willing to comply with the 24-month treatment protocol and have no intention to conceive during this period. All had previously failed other hormonal or surgical options for managing their symptoms.

Exclusion criteria included a known bone mineral density (BMD) T-score d" "2, unexplained vaginal bleeding, personal or family history of breast cancer, or any contraindication to GnRH agonist therapy. Patients with abnormal liver or renal function tests within six months, persistent

pelvic pain not attributed to endometriosis, or known hypersensitivity to study drugs were also excluded.

Treatment protocol

Participants received one of two GnRH agonists: Triptorelin SR 11.25 mg (30 women) administered intramuscularly every three months (Decapeptyl® SR, Ipsen Ltd) or Goserelin acetate 10.8 mg subcutaneous implant every three months (Zoladex®, AstraZeneca) (51 women). Both were combined with norethisterone acetate (NETA) 5 mg orally daily (PRIMOLUT-N®, Bayer plc) as add-back therapy, initiated from the first day of GnRH-a administration. The patients were carefully instructed to take at the same time and in case of skipping one or two tablets, to take two and continue. The choice of GnRH-a agent depended on drug availability and insurance coverage. As this was a within-patient comparison study, no control group was included.

Clinical and imaging evaluation

At baseline, all patients underwent detailed medical history-taking and physical examination, including documentation of BMI and pain assessment using a visual analogue scale (VAS, 1–10) for dysmenorrhea and deep dyspareunia. Other symptoms recorded included dysuria, dyschezia, bloating, alternating constipation and diarrhea, and cold intolerance, defined by a positive response to validated screening questions.

All participants underwent transvaginal or transabdominal pelvic ultrasound before initiating treatment. For those with adenomyosis, uterine volume was measured before and after therapy using the ellipsoid formula: length × width × depth × 0.52.

Follow-up and outcome assessment

Follow-up evaluations were scheduled for 3, 6, 12, 18, and 24 months from the baseline visit. A final evaluation was performed at 30 months, six months after completing treatment. At each visit, patients completed a menstrual calendar, and data on pain symptoms, bleeding pattern, analgesic use, and side effects were collected. Bone mineral density was assessed using dual-energy X-ray absorptiometry (DEXA) at the lumbar spine and proximal femur at the end of 24 months. Laboratory assessments, including full blood count, liver enzymes, and renal function, were repeated at 12 and 24 months and in selected patients at 30 months.

Ethical considerations

Written informed consent was obtained from all participants. The study was approved by the Mutah University Ethics Committee (Reference No. 652010) and conducted according to the Declaration of Helsinki.

Statistical analysis

Data was analyzed using SPSS version 20 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to summarize demographic data. Paired t-tests were used to compare continuous variables, the Shapiro-Wilk test was applied to the data, and it was determined that the data were normally distributed and categorical data were analyzed using Chi-square or Fisher's exact tests. A p-value of <0.05 was considered statistically significant.

RESULTS

Demographic features

The main demographic features of the study participants are summarized in Table 1. The mean age was 33.35 ± 7.3 years. Among them, 18 were single and 63 were married. Most had a normal BMI. The mean duration of pain symptoms was 10.5 years, with an average diagnostic delay of 11.2 years from symptom onset. Forty-three participants (53%) had a history of heavy menstrual bleeding. Seventy-two women (89%) had previously undergone one or more surgical interventions for endometriosis.

Pain and associated symptoms

Main findings of clinical symptoms before and after 24 months of treatment are listed in Table 2. At baseline, 93.8% of participants reported severe dysmenorrhea (VAS score >7), and 46 women (56.8%) had deep dyspareunia. Additional symptoms included dysuria (6.2%), dyschezia (54.3%), bloating (54.3%), alternating constipation and diarrhea (63%), and cold intolerance (76.5%).

Following 24 months of treatment, there was a statistically significant reduction in pain scores. The mean VAS for dysmenorrhea decreased from 7.86 ± 0.15 to 2.35 ± 0.14 ($P < 0.0001$), and for deep dyspareunia from 6.09 ± 0.30 to 0.60 ± 0.12 ($P < 0.0001$) (Table 3). Other symptoms also improved significantly: dysuria decreased to 2.5% (n = 2), dyschezia to 11.1% (n = 9), bloating to

11.1% (n = 9), alternating bowel habits to 12.3% (n = 10), and cold intolerance to 19.8% (n = 10) (Table 4).

Among the 18 participants who discontinued therapy to pursue pregnancy, 78% (14 women) experienced recurrence of symptoms within six months after cessation, supporting the observation that symptom control is drug-dependent and not curative.

Uterine volume

In the subgroup with confirmed adenomyosis (n = 46), there was a significant reduction in uterine volume from 294.5 ± 270.1 cm^3 to 183.7 ± 136.5 cm^3 ($P < 0.001$). Both GnRH agonist regimens showed comparable effects (Table 5).

Laboratory results

Table 1. Main demographic features of our patients (N: 81)

Domain	Result
Age (mean (± SD))	33.35 (± 7.3) years
The mean (± SD) BMI	24.52 (± 5.8) kg/m2
Mean age at Menarche	13.1 years
Mean age at first diagnosis from the start of symptoms	11.2 years
Marital status	singles-18, married-63
The mean duration of pain symptoms	10.5 years (3-12 years)
Diagnosis of endometriosis	100%
Diagnosis of endometriosis and adenomyosis	46 patients (56.8%)
History of surgery for endometriosis	72 (89%)
History of another medical treatment	100%
History of heavy menstrual flow	43 (53%)

Table 2. Main results of clinical symptoms before and after 24 months of treatment

	Clinical symptom	Number (%)
Dysmenorrhea	Before treatment (VAS >7)	76 patients (93%)
	After treatment (24 months) (VAS<7)	81 (100%) patients
Deep dyspareunia	Before treatment (VAS >7)	46 patients (56.8 %)
	After treatment (24 months) (VAS<7)	81 (100%) patients
Dysuria	Before treatment	Yes: 5 (6.2 %)
		No: 76 (93.8 %)
	After treatment (24 months)	Yes: 2 (2.5 %)
		No: 79 (97.5 %)
Dyschezia	Before treatment	Yes: 44 (54.3 %)
		No: 7 (45.7%)
	After treatment (24 months)	Yes: 7 (8.6%)
		No: 74 (91.4 %)
Bloating	Before treatment	Yes: 44 (54.3%)
		No: 37 (45.7%)
	After treatment (24 months)	Yes: 9 (11.1%)
		No: 74 (91.4%)
Alternating constipation/ diarrhea	Before treatment	Yes: 51 (63%)
		No: 30 (37%)
	After treatment (24 months)	Yes: 7 (8.6%)
		No: 74 (91.4%)
Cold intolerance	Before treatment	Yes: 62 (76.5%)
		No: 19 (23.5%)
	After treatment (24 months)	Yes: 16 (19.8%)
		No: 65 (80.2%)

Table 3. Mean comparison of VAS scores of dysmenorrhea and deep dyspareunia before and after treatment

	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)
Dysmenorrhea VAS score before treatment and after 24 months	7.25926	1.78730	.19859	6.86405	7.65446	36.554	80	.000
Deep dyspareunia VAS score before treatment and after 24 months	5.48148	2.66510	.29612	4.89218	6.07078	18.511	80	.000

No significant abnormalities were observed in liver or renal function tests during the treatment course. Serum ALT showed a transient elevation at 12 months (from 23 ± 7.5 to 27 ± 21.7 U/L; P = 0.05) but remained within normal physiological limits. AST levels remained stable. Similarly, urea and creatinine concentrations did not significantly change during the 24 months.

Hematological profile

At baseline, 50 participants (61%) had anemia (Hb < 11 g/dL), particularly among those with adenomyosis. By the end of the 24 months, the mean hemoglobin had increased from 10.73 ± 0.09 g/dL to 12.60 ± 0.81 g/dL (P < 0.0001), likely due to the induction of amenorrhea and subsequent reduction in menstrual blood loss (Table 5).

Safety outcomes

At the 24-month assessment, dual-energy X-ray absorptiometry (DEXA) confirmed normal bone mineral density (BMD) values in 79 patients (97.5%). Only two women (2.5%) developed mild osteopenia (T-scores of -1.2 and -1.4, respectively), with no cases of osteoporosis. These findings indicate that concurrent use of NETA add-back therapy effectively protects against significant bone loss during prolonged GnRH-a treatment.

Reported side effects were generally mild and manageable with counseling. All participants experienced amenorrhea, as expected. Mood swings were reported in 25 patients (30.9%), vaginal spotting in 27 (33.3%), decreased libido in 16 (19.8%), hot flushes in 34 (42%), and night sweats in 32 (40%), predominantly during the first three months. Eight women (9.8%) had injection or implant site pain, and nine (11.1%) reported weight gain of 2–4 kg (Table 6). No serious adverse events were reported during the study.

DISCUSSION

Our findings demonstrate that prolonged use of GnRH agonists, in combination with norethisterone acetate (NETA) as add-back therapy, is both effective and well-tolerated for the long-term management of endometriosis- and adenomyosis-associated pelvic pain. Significant reductions were observed in key symptom domains, most notably dysmenorrhea and deep dyspareunia, with sustained clinical improvement over the 24-month treatment period. These outcomes are

Table 4. Results of comparisons of the presence of other clinical symptoms before and after treatment (Chi-square)

Domain	Chi-square	df	Sig.
Cold intolerance before and after treatment	4.573	1	.032
Dysuria before and after treatment	31.170.	1	0.000
Dyschezia before and after treatment	4.876	1	0.027
Bloating before and after treatment	4.876	1	0.027
Alternating constipation/diarrhea before and after treatment	3.576	1	0.05

Table 5. Results of investigations between the first visit assessment and at 24 months

Domain	First Visit	Last visit	Sig. (2-tailed) P value
Hemoglobin (g/dL)	10.7336 g/dL	12.6000 g/dL	0.000
Uterine volume (n=46)	285.5 ± 220.1 cm3	180.7 ± 131.5 cm3	P < 0.001
ALT	23 U/L (± 7.53)	27 U/L (± 21.74)	P = 0.05
AST	25.64 U/L (± 4.75)	23 U/L (± 7.33)	P = 0.32
Urea mean (± SD)	3.73 mmol/L (± 0.89)	3.18 mmol/L (± 1.06)	P =0.67
Creatinine	64.31 mmol/L (± 11.9)	63.15 mmol/L (± .84).	P = 0.22

Table 6. Main side effects during and after treatment.

Treatment Adverse Effects	Number of patients affected
Amenorrhea	81 (100%)
Mood swings	25 (30.9%)
Vaginal spotting	27 (33.3%)
Loss/decrease of libido	16 (19.8%)
Hot flushes (first 3 months)	34 (42%)
Night sweats (first 3 months)	32 (first 3 months)
Pain at the injection or implant site	8 (9.8 %)
Weight gain (2-4kg)	9 (11.1%)

consistent with previous reports confirming the efficacy of long-term GnRH-a use when paired with appropriate add-back strategies [21].

The reduction in uterine volume among women with adenomyosis corroborates the antiproliferative effects of GnRH agonists, supported by earlier data on long-term medical management for these conditions.[2]y Improvements in hemoglobin levels in patients with heavy menstrual bleeding further underline the value of sustained medical amenorrhea.[3]p

Furthermore, the metabolic characteristics of norethisterone acetate, including partial estrogenic conversion, are advantageous for bone health during prolonged hypoestrogenic states.[31] An interesting observation in our cohort was the significant decrease in cold intolerance, consistent with regional data highlighting this symptom in women with chronic endometriosis-related pain.[32] This supports the concept that endometriosis may involve systemic neurogenic pathways beyond the pelvis.

The extended suppression of estrogen through GnRH-a therapy led to symptomatic relief in multiple endometriosis-related complaints beyond pelvic pain, including dyschezia, bloating, and alternating bowel habits. Notably, the reduction in cold intolerance from 76.5% at baseline to 19.8% adds support to emerging literature associating this symptom with the neuro-inflammatory phenotype of endometriosis.[32-3]t While not commonly addressed in mainstream clinical guidelines, cold

intolerance may represent a marker of systemic neuroimmune dysregulation.[3]u [-3]w

Importantly, the benefit of medical suppression appeared to be symptom-contingent, as 78% of patients who stopped therapy for fertility purposes experienced rapid symptom recurrence within six months. This pattern underscores the symptomatic nature of current medical approaches to endometriosis, in which therapeutic efficacy is largely lost upon discontinuation.[1Ò1]x

Regarding safety, the concurrent use of NETA provided effective protection against hypoestrogenic complications. Only two patients (2.5%) developed mild osteopenia, and no cases of osteoporosis were reported. These results are consistent with the findings of Wu et al., who concluded that progestin-based add-back does not compromise treatment efficacy while offering bone-protective benefits.[1]w Furthermore, NETA is cost-effective, widely available, and has partial estrogenic activity through its hepatic metabolism, making it a practical choice for long-term use.[19,31]

Our study also confirmed a significant reduction in uterine volume in patients with adenomyosis, aligning with other studies demonstrating that GnRH agonists reduce myometrial proliferation and estradiol-driven hypertrophy.[22,2]x Improvements in hemoglobin levels among participants with baseline anemia are likely attributable to treatment-induced amenorrhea, which reduced menstrual blood loss.

The treatment was generally well tolerated. Common side effects such as mood swings, vasomotor symptoms, and vaginal spotting were transient and managed through patient education. No serious adverse events were encountered. Our safety data are in line with previous long-term studies using GnRH-a with hormonal add-back.[21,23,3]p

Limitations of this study include its open-label design and the absence of a placebo or active comparator group. However, ethical considerations and the chronic nature of refractory pelvic pain precluded a non-treatment control arm. The relatively large sample size, prolonged follow-up, and inclusion of both endometriosis and adenomyosis cases provide strength to the generalizability of these findings.

CONCLUSION

This prospective study demonstrates that prolonged (24-month) administration of GnRH agonists with norethisterone acetate add-back therapy is a safe and effective approach for managing chronic pelvic pain in women with severe, treatment-resistant endometriosis and adenomyosis. The regimen significantly reduces pain scores, improves associated clinical symptoms, and is associated with minimal risk of bone loss when add-back is initiated at treatment onset. Both Triptorelin SR and Goserelin acetate showed comparable efficacy and safety. This strategy may be considered a valuable second-line option in patients who are not candidates for surgery or have experienced recurrence following other therapies.

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Conflict of Interest

The author(s) do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

The study was approved by the Mutah University Ethics Committee (Reference No. 652010) and conducted according to the Declaration of Helsinki.

Informed Consent Statement

Written informed consent was obtained from all participants

Clinical Trial Registration

This research does not involve any clinical trials.

Permission to reproduce material from other sources

Not applicable.

Authors' Contributions

Moamar Al-Jefout conceptualized the study, managed patient recruitment and follow-

up, and drafted the manuscript; Shamsa Al Awar contributed to critical manuscript revision, editing, and coordination of institutional collaboration and corresponding publication; Samer Yaghi participated in patient referrals, clinical evaluation, manuscript revision, and follow-up assessments; Omar Dabas contributed to patient referral, clinical evaluation, manuscript revision, and follow-up assessments.

REFERENCES

1. Becker CM, Bokor A, Heikinheimo O, et al. ESHRE guideline: endometriosis. *Hum Reprod Open.* 2022;2022(2):hoac009.
2. Smolarz B, Szy³³o K, Romanowicz H. Endometriosis: epidemiology, classification, pathogenesis, treatment and genetics (review of literature). *Int J Mol Sci.* 2021;22(19):10554.
3. Zondervan K, Becker C, Koga K, et al. Endometriosis. *Nat Rev Dis Primers.* 2018;4(1):9.
4. Guo SW, Wang Y. The prevalence of endometriosis in women with chronic pelvic pain. *Gynecol Obstet Invest.* 2006;62(3):121-130.
5. Meldrum DR, Chang RJ, Lu J, Vale W, Rivier J, Judd HL. "Medical oophorectomy" using a long-acting GnRH agonist: a possible new approach to the treatment of endometriosis. *J Clin Endocrinol Metab.* 1982;54(5):1081-1083.
6. Vestergaard P. Drugs causing bone loss. *Bone Regulators Osteoporos Ther.* 2020:475-497.
7. Ferrero S, Evangelisti G, Barra F. Current and emerging treatment options for endometriosis. *Expert Opin Pharmacother.* 2018;19(10):1109-1125.
8. Barbieri RL. Hormone treatment of endometriosis: the estrogen-threshold hypothesis. *Am J Obstet Gynecol.* 1992;166(2):740-745.
9. Surrey ES. GnRH agonists in the treatment of symptomatic endometriosis: a review. *F S Rep.* 2023;4(2):40-45.
10. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. *Fertil Steril.* 2012;98(3):511-519.
11. Levine D, Kaufman L, Cuenca VG, Badawy S. Cell growth effects of leuprolide on cultured endometrioma cells. *J Reprod Med.* 2007;52(7):581-584.
12. Weng H, Liu F, Hu S, Li L, Wang Y. GnRH agonists induce endometrial epithelial cell apoptosis via GRP78 down-regulation. *J Transl Med.* 2014;12:1-10.
13. Navarro VM, Gottsch ML, Chavkin C, et al. Regulation of gonadotropin-releasing hormone secretion by kisspeptin/dynorphin/neurokinin B neurons in the arcuate nucleus of the mouse. *J Neurosci.* 2009;29(38):11859-11866.
14. Cheng G, Coolen LM, Padmanabhan V, Goodman RL, Lehman MN. The kisspeptin/neurokinin B/dynorphin (KNDy) cell population of the arcuate nucleus: sex differences and effects of prenatal testosterone in sheep. *Endocrinology.* 2010;151(1):301-311.
15. Samy A, Taher A, Sileem SA, Abdelhakim AM, Fathi M, Haggag H, 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.
16. Brown J, Pan A, Hart R. Gonadotropin releasing hormone analogues for pain associated with endometriosis. *Obstet Gynecol.* 2011;117(3):727-728.
17. Wu D, Hu M, Hong L, et al. Clinical efficacy of add-back therapy in treatment of endometriosis: a meta-analysis. *Arch Gynecol Obstet.* 2014;290:513-523.
18. Buggio L, Somigliana E, Barbara G, Frattaruolo MP, Vercellini P. Oral and depot progestin therapy for endometriosis: towards a personalized medicine. *Expert Opin Pharmacother.* 2017;18(15):1569-1581.
19. Vercellini P, Bracco B, Mosconi P, et al. Norethindrone acetate or dienogest for the treatment of symptomatic endometriosis: a before and after study. *Fertil Steril.* 2016;105(3):734-743.e3.
20. Hornstein MD, Surrey ES, Weisberg GW, Casino LA, Group LA-BS. Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. *Obstet Gynecol.* 1998;91(1):16-24.
21. Surrey ES, Hornstein MD. Prolonged GnRH agonist and add-back therapy for symptomatic endometriosis: long-term follow-up. *Obstet Gynecol.* 2002;99(5 Pt 1):709-719.
22. Cedars MI, Lu JK, Meldrum DR, Judd HL. Treatment of endometriosis with a long-acting gonadotropin-releasing hormone agonist plus medroxyprogesterone acetate. *Obstet Gynecol.* 1990;75(4):641-645.
23. Pierce SJ, Gazvani MR, Farquharson RG. Long-term use of gonadotropin-releasing hormone analogs and hormone replacement therapy in the management of endometriosis: a randomized trial with a 6-year follow-up. *Fertil Steril.* 2000;74(5):964-968.
24. Tahara M, Matsuoka T, Yokoi T, et al. Treatment of endometriosis with a decreasing dosage of a gonadotropin-releasing hormone agonist (nafarelin): a pilot study with low-dose agonist therapy. *Fertil Steril.* 2000;73(4):799-804.

25. Tsai HW, Wang PH, Huang BS, et al. Low-dose add-back therapy during postoperative GnRH agonist treatment. *Taiwan J Obstet Gynecol.* 2016;55(1):55-59.
26. Stjernbrandt A, Carlsson D, Pettersson H, et al. Cold sensitivity and associated factors: a nested case–control study performed in Northern Sweden. *Int Arch Occup Environ Health*. 2018;91:785-797.
27. Sheth SS, Hajari AR, Lulla CP, Kshirsagar D. Sonographic evaluation of uterine volume and its clinical importance. *J Obstet Gynaecol Res.* 2017;43(1):185-189.
28. Crosignani P, Olive D, Bergqvist A, Luciano A. Advances in the management of endometriosis: an update for clinicians. *Hum Reprod Update.* 2006;12(2):179-189.
29. Sauerbrun-Cutler MT, Alvero R. Short- and long-term impact of gonadotropin-releasing hormone analogue treatment on bone loss and fracture. *Fertil Steril.* 2019;112(5):799-803.
30. Sitruk-Ware R, Nath A. Characteristics and metabolic effects of estrogen and progestins contained in oral contraceptive pills. *Best Pract Res Clin Endocrinol Metab.* 2013;27(1):13-24.
31. Al-Jefout M, Alnawaiseh N, Yaghi S, Alqaisi A. Prevalence of endometriosis and its symptoms among young Jordanian women with chronic pelvic pain refractory to conventional therapy. *J Obstet Gynaecol Can.* 2018;40(2):165-170.
32. Khabbazi A, Farzaneh R, Mahmoudi M, et al. Cold intolerance and associated factors: a population study. *Sci Rep.* 2022;12(1):18029.
33. Soeda M, Ohka S, Nishizawa D, et al. Cold pain sensitivity is associated with single-nucleotide polymorphisms of PAR2/F2RL1 and TRPM8. *Mol Pain.* 2021;17:17448069211002009.
34. Moore C, Gupta R, Jordt SE, Chen Y, Liedtke WB. Regulation of pain and itch by TRP channels. *Neurosci Bull.* 2018;34:120-142.
35. Mrozkova P, Palecek J, Spicarov D. The role of protease-activated receptor type 2 in nociceptive signaling and pain. *Physiol Res.* 2016;65(3).
36. Zhang M, Gao CX, Wang YP, et al. The association between the expression of PAR2 and TMEM16A and neuropathic pain. *Mol Med Rep.* 2018;17(3):3744-3750.