Efficacy of drugs in treating endometriosis-associated pain: A systematic review and network meta-analysis

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This certifies that the master's thesis

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List of Abbreviations

AE	Adverse Event
BMD	Bone Mineral Density
CI	Confidence Interval
CNGOF	The French College of Gynecologists and Obstetricians
CrI	Credible Interval
DNG	Dienogest
DMPA	Depot Medroxyprogesterone Acetate
DSG	Desogestrel
E2	17 ß-estradiol
ENG Implanon	Etonogestrel Implanon
EM	Endometriosis
ESHRE	European Society of Human Reproduction and Embryology
FDA	Food and Drug Administration of the United States
GnRH	Gonadotropin Releasing Hormone
HAS	The French National Authority for Health
ICER	Incremental Cost Effectiveness Ratio
LA	Leuprolide Acetate
LNG-IUS	Levonorgestrel-releasing Intrauterine System
MA	Meta Analysis
MCMC	Markov Chain Monte Carlo
MD	Mean Difference
MPA	Medroxyprogesterone Acetate
NETA	Norethindrone Acetate

NMPP	Non-Menstrual Pelvic Pain
NMA	Network Meta Analysis
NOMAC	Nomegestrol Acetate
NRS	Numeric Rating Scale
OCP	Oral Contraceptives Pills
QALY	Quality Adjusted Life Year
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale
WHO	World Health Organization

ABSTRACT

Efficacy of Drugs in Treating Endometriosis-associated pain: A Systematic Review and Network Meta-Analysis

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Introduction

Endometriosis affects about 10% of reproductive age women and exert negative impact on quality of life such as endometriosis-associated pains. There are published literatures that explored the efficacy and safety of the endometriosis treatments using traditional pairwise meta-analysis. However, this approach has limitations on comparing treatment classes or a wide range of individual treatment, if there is no direct comparison in the trial. In addition, there are only few well-designed studies to compare the efficacy and results are controversial.

The aim of the study is to perform a network meta-analysis on the efficacy of both treatment classes and individual treatments and to provide optimal options to select treatments for improving endometriosis-associated pains: non-menstrual pelvic pain (NMPP), dysmenorrhea, and dyspareunia.

Method

PubMed, Embase, and Cochrane library databases were searched for published studies reporting pain scores of NMPP, dysmenorrhea, and dyspareunia assessed by Visual Analog Scale (VAS) until 13 Aug 2023. The primary outcome was mean difference of pain scores

between the baseline and 24 weeks of treatment period measures and 95% credible intervals (CrI) were used to describe efficacy. A Bayesian network meta-analysis was performed on the efficacy outcomes. Pair-wise meta-analysis was conducted to assess for sensitivity analysis.

Results

Our NMA included thirteen RCTs for the evaluation of improving NMPP, dysmenorrhea, and dyspareunia. GnRH agonist was associated with statistically significant reduction in dysmenorrhea when compared with OCP. There was no significant improvement observed in treatment classes and individual treatment for both NMPP and dyspareunia. GnRH-addback was the first ranking treatment class for NMPP reduction while goserelin was the highest-raking individual treatment. GnRH agonist associated with dysmenorrhea reduction was the first ranking treatment class while leuprorelin was the highest-ranking individual treatment. For improving dyspareunia, anti-estroprogestin and gestrinone were the best ranking treatment class and individual treatment, respectively. Heterogeneity calculated in NMA and the evidence that no publication bias existed were verified by sensitivity analyses.

Conclusion

The efficacy outcomes showed that GnRH agonist significantly improved dysmenorrhea at 24 weeks of treatment period.

KEYWORDS: Endometriosis, Endometriosis-associated pain, Efficacy, Network Meta-Analysis, Systemic review, Non-Menstrual Pelvic Pain, Dysmenorrhea, Dyspareunia

1. Introduction

Endometriosis (EM) is a chronic disease, in which endometrial tissues grow outside the uterine cavity. It is one of the gynecological disorders that affects 10% of reproductive-age women (WHO 2023). Classic symptoms of EM include non-menstrual pelvic pain, dysmenorrhea, dyspareunia, and dysuria. Infertility is also associated with the disorder. The pain associated with EM causes a distressing condition that can lead to hospitalization and impaired quality of life. A prospective cohort study conducted every 3 years from 1996 to 2018 showed that women with endometriosis were more likely to have poorer HRQoL than those without endometriosis, including physical, mental, social functioning, well-being, and bodily pain (Gete et al. 2023). There is no known way to prevent the endometriosis. Therefore, it is important to choose the most effective treatment to manage the EM associated pain. European Society of Human Reproduction and Embryology (ESHRE) Guideline Endometriosis, issued in 2022 offers more than 100 practice recommendations on caring of women with endometriosis, including diagnostic approaches and treatments for symptom management in female adolescents and young adults. According to this guideline, there are several medical treatment options: Nonsteroidal anti-inflammatory drugs (NSAIDs), Gonadotropin-releasing hormone (GnRH) agonist, GnRH antagonist, intrauterine system/subdermal implant (LNG-IUS or ENG-Implanon), combined oral contraceptives (OCP), and anti-progestogens, etc. (Becker et al. 2022). However, there are limitations on comparing the efficacy of various treatments if there is no direct comparison.

Therefore, the purpose of this study is to perform a network meta-analysis (NMA) on the efficacy of different treatments for EM associated pain. Direct and indirect evidence derived from this NMA will help clinicians to choose the most effective treatment class for reducing the EM associated pain.

2. Method

Systematic review, meta-analysis (MA), and network meta-analysis (NMA) were performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. This study was registered on PROSPERO (CRD42023401724).

2.1. Search strategy

PubMed, Embase, and Cochrane library databases were searched for studies published until 13 Aug 2023. The search keywords for each database are presented in Appendix 1. The PICO framework (Table 1 PICOS) was used as a quantitative systematic review tool to identify literature search strategy and develop a research question. First, literatures were screened by title and abstract followed by full text screening. Two reviewers (SYP and MJC) independently assessed included studies for the final eligibility and discrepancies were resolved through discussion and consensus.

Table 1 PICOS

Elements	Contents
P: Population	Endometriosis-associated pain
I: Intervention	GnRH receptor agonist/antagonist, Estrogen-progestin hormone therapy, Progestin only, Anti-estrogenic and anti-progestogenic
C: Comparator	Not applicable
O: Outcome	Efficacy
S: Study design	Randomized Controlled Trial

2.2. Inclusion and Exclusion Criteria

For the network meta-analysis, studies were included if (i) randomized controlled trial with 24 weeks treatment period, (ii) premenopausal women with a histologically

and surgically confirmed diagnosis of endometriosis, (iii) studies with at least one reported efficacy outcome (NMPP, dysmenorrhea, or dyspareunia). The exclusion criteria included (i) studies without any efficacy outcome, (ii) non-relevant publication type (e.g., review, letters, or meta-analysis), (iii) inappropriate population (e.g. case report, not endometriosis patient), (iv) inappropriate study design (e.g., single arm trial, patch, or spray medication type, retrospective or observational cohort trials).

2.3. Outcome Measures

The primary efficacy outcomes were endometriosis-associated pelvic pain. Co-primary efficacy outcomes were dysmenorrhea and dyspareunia. These outcomes were defined as mean differences in pain scores between the baseline and the 24 weeks of treatment period measures.

2.4. Data extraction and Risk of Bias Assessment

The data from included trials were extracted into spreadsheets. The collected study information was study characteristics (author, publication year, number of subjects, treatment period, placebo-arm availability), participants (diagnosis, age), interventions (name of drug, drug class, route of administration, duration, and dosage of intervention), efficacy outcomes (assessment tool for pain score).

Risk level of bias in each eligible randomized trial was appraised using version 2 of the Cochrane Risk-of-Bias, Rob 2 (Sterne et al. 2019). The RoB includes five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. A risk of bias for each domain and overall was scored as low, some concerns, or high risk of bias. If there was any disagree with proposed risk of bias result, both domain level and overall bias were overridden by the two independent reviewers after discussion.

2.5. Statistical Analysis

A Bayesian random effect network meta-analysis was performed using 'gemtc' statistical package version 4.3.1 in R software for Windows (van Valdenhoef et al. 2023). Continuous data were pooled as mean difference (MD) with 95% credible intervals (95% CrI) to describe endometriosis-associated pains. Significant differences were considered when 95% CrI did not include 0 for MD Markov Chain Monte Carlo (MCMC) simulations were run for 10,000 iterations following a burn-in of 5,000 with 1 thinning interval.

Gelman-Rubin plot, density and trace plots were used to monitor MCMC convergence. Consistency test was conducted by node-splitting function in the 'gemtc' package. *P*-value > 0.05 indicates no significant inconsistency observed between direct and indirect estimates. Then, it is concluded that the model is properly fitted for the NMA. Heterogeneity can also be estimated by the statistic, I^2 value. The Cochrane Handbook for Systematic Reviews of Intervention presents thresholds for the interpretation. It states that I^2= 0% to 40%: no heterogeneity; 30% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; 75% to 100%: considerable heterogeneity (Higgins JPT 2023).

Relative effect estimates (mean differences in pain scores) of treatments are presented in a league table which provides information about effectiveness and uncertainty for pairs of treatments. Moreover, our NMA can generate ranking probabilities to indicate the probabilities for each treatment to be best, second best, etc. Network plot describes connectivity between pair of treatments. Each node represents each treatment while the edge connecting two nodes means a direct comparison has been done in the trial. The line thickness is proportional to number of studies in the comparison.

In addition, 'meta' package version 6.5-0 in R software for Window was used to

perform sensitivity analysis (Balduzzi et al. 2019). It aimed to investigate potential publication bias by Egger's linear regression method test and to assess the heterogeneity by Higgins and Cochran's Q statistics for providing concrete evidence of the NMA results.

2.6. Sensitivity analysis for publication bias and heterogeneity

I^2 statistics suggested that no significant heterogeneity was observed across studies included in the NMA of NMPP, dysmenorrhea, and dyspareunia. As the NMA was performed with a relatively small number of studies, there may have been concerns on small-study effects such as potential inconsistency and publication bias in our data.

To check the robustness of our NMA results, we carried out sensitivity analysis for Higgins I^2, Cochrane Q statistics, and publication bias through pairwise meta-analysis.

3. Results

3.1. Literature Search and Study Characteristics

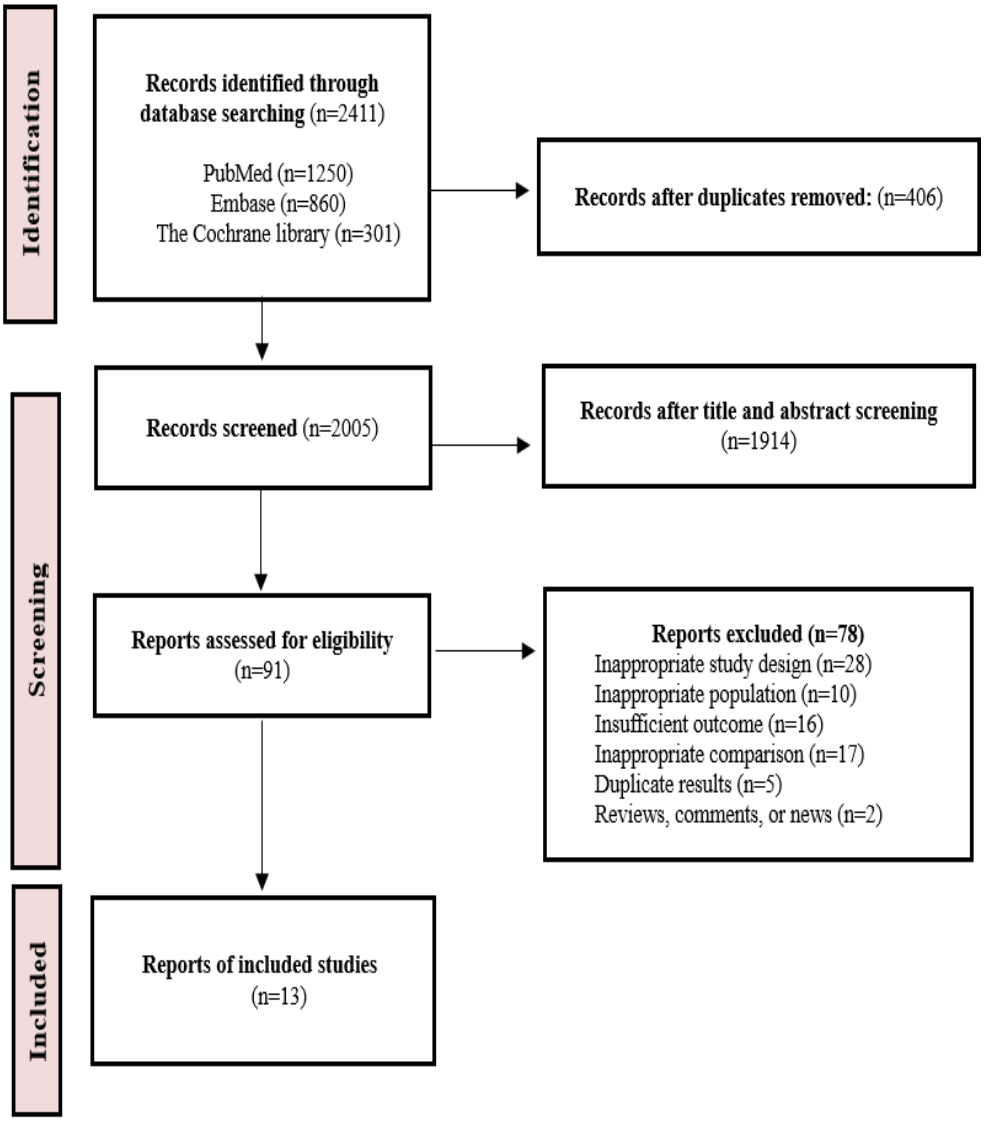


Figure 1 PRISMA flow chart of study selection

Table 2 Characteristics of studies included in the network meta-analysis

Study	Treatment class	Individual treatment	No. of patients+	Mean age (SD)
Vahid-Dastjerdi 2023	Progestin (10 mg BID)	MPA	53	35.12±5.81
	Progestin (2 mg QD)	Dienogest	48	35.49±4.68
Tang 2023	GnRH-agonist (3.75 mg Q28D)	NR	40	40.15±7.68
	Progestin (2 mg BID)	Dienogest	41	41.98±7.24
Harada 2022	GnRH antagonist (40 mg QD)	Relugolix	171	37.1±7.3
	GnRH-agonist (3.75 mg Q4W)	Leuprorelin	164	35.0±7.2
Caruso 2022	OCP (1.5 mg / 2.5 mg QD)	E2/NOMAC	99	26.4±6.8
	Progestin (2 mg QD)	Dienogest	98	27.4±8.3
Carvalho 2018	Progestin Releasing Device	LNG-IUS	51	34.7±6.67
	Progestin Releasing Device	ENG Implanon	52	33.4±6.37
Tanmahasamut 2017	Progestin (0.075 mg QD)	Desogestrel	20	29.1±4.9
	Placebo	Placebo	20	32.7±6.7
Carr 2014	GnRH antagonist (150 mg QD)	Elagolix	56	32.4±5.99
	Progestin (104 mg in Week 1 and Week 12)	DMPA	51	31.6±2.86
Cheewadhanaraks 2012	OCP (0.03 mg / 0.075 mg QD)	E2/Gestodene	42	30.5±5.4
	Progestin (150 mg Q12W)	DMPA	42	31.9±5.5
Bayoglu 2011	Progestin Releasing Device	LNG-IUS	20	36.5±4.5
	GnRH-agonist (NR Q4W)	Goserelin	20	38.7±4.8
Gomes 2007	Progestin Releasing Device	LNG-IUS	11	29.2±5.5
	GnRH-agonist (3.75 mg Q28D)	Leuprorelin	11	32.6±5.3

Study	Treatment class	Individual treatment	No. of patients+	Mean age (SD)
Petta 2005	Progestin Releasing Device	LNG-IUS	39	29.4±4.8
	GnRH-agonist (3.75 mg Q28D)	Leuprorelin	43	30.5±6.4
Zupi 2004	GnRH Addback (11.25 mg/ 25 μg/ 5 mg Q3M)	Leuprorelin/E2/NETA	46	35.8±5.0
	GnRH-agonist (11.25 mg Q3M)	Leuprorelin	44	35.1±4.8
	OCP (30 μg/0.75 mg QD)	E2/Gestodene	43	36.1±5.3
Vercellini 1996	GnRH-agonist (3.75 mg Q4W)	Leuprorelin	28	28.6±6.2
	Anti-estroprogestin (2.5 mg BIW)	Gestrinone	27	31.9±5.4

Abbreviations: MPA, medroxyprogesterone acetate; E2, 17ß-estradiol; NETA, norethindrone acetate; NOMAC, nomegestrol acetate; LNG-IUS, levonorgestrel-releasing intrauterine system; ENG Implanon, etonogestrel implanon; OCP, oral contraceptive pill; NMPP, non-menstrual pelvic pain; QD, once a day; BID, twice a day; d, day; BIW, twice a week; Q28D, every 28days; Q4W, every 4 weeks; Q12W, every 12 weeks; Q3M, every 3 months; NR, not reported; d, day; w, week.

+Number of participants randomized to study arm

Table 3 Mean pain score measured by VAS at baseline and 24 weeks

Study	Intervention Class	NMPP			Dysmenorrhea			Dyspareunia		
		Baseline	24weeks	MD	Baseline	24weeks	MD	Baseline	24weeks	MD
Vahid-Dastjerdi 2023	Progestin (MPA)	70.8	53	-17.8	88.4	55.4	-33	NR	47.1	
	Progestin (Dienogest)	67.2	46	-21.2	85.8	52.2	-33.6	66.7	48	
Tang 2023	GnRH-agonist				56.5	7.8	-48.7			
	Progestin				42.9	7.3	-35.6			
Harada 2022	GnRH antagonist	11.8	NR	-6.67	33.1	NR	-32.6	30.2	NR	-13.2
	GnRH-agonist	11.3	NR	-8.02	34.2	NR	-33.6	27.4	NR	-15.4
Caruso 2022	OCP	80	33	-47						
	Progestin	75	26	-49						
Carvalho 2018	Progestin Releasing Device (LNG-IUS)	74	19	-55	73	19	-54			
	Progestin Releasing Device (ENG Implanon)	76	20	-56	75	22	-53			
Tanmahasamut 2017	Progestin	84	24.2	-59.7	92	NR	-62.2	46	NR	-46.7
	Placebo	86	44.2	-41.7	87	NR	-54.5	48	NR	-43.2
Carr 2014	GnRH antagonist	NR	NR	-1.1	NR	NR	-1.5	NR	NR	-1.1
	Progestin	NR	NR	-1.1	NR	NR	-1.7	NR	NR	-1.1
Cheewadhanaraks 2012	OCP	20	0	-20	82	0	-82	45	0	-45
	Progestin	25	0	-25	90	0	-90	30	0	-30
Bayoglu 2011	Progestin Releasing Device (LNG-IUS)	42.5	35.7	-6.8						
	GnRH-agonist	64.1	37.4	-26.7						
Gomes 2007	Progestin Releasing Device (LNG-IUS)	79	21	-58						
	GnRH-agonist	65	4	-61						

Study	Intervention Class	NMPP			Dysmenorrhea			Dyspareunia		
		Baseline	24weeks	MD	Baseline	24weeks	MD	Baseline	24weeks	MD
Petta 2005	LNG-IUS	73	13	-60						
	GnRH-agonist	73	13	-60						
Zupi 2004	GnRH Addback	69	15	-54	58	0	-58	58	24	-34
	GnRH-agonist	67	13	-54	61	0	-61	59	26	-33
	OCP	63	19	-44	60	19	-41	56	27	-29
Vercellini 1996	GnRH-agonist	46.7	16.4	-30.3	67.1	0.5	-66.6	45.3	16.1	-29.2
	Anti-estroprogestin	40.7	12.3	-28.4	62.3	8.7	-53.6	40.1	4.4	-35.7

Abbreviations: NR, not reported

3.2. Efficacy Outcomes

In the selected trials, various efficacy outcomes were evaluated: pain symptoms (pelvic pain, dysmenorrhea, dyspareunia), pelvic tenderness, serum sex hormone levels, pregnancy rate, bone mineral density, and induration severity. This study aims to investigate the efficacy of different classes of endometriosis-associated pain treatment in a large-scaled network meta-analysis. Only pain symptoms measured by VAS were assessed for efficacy outcomes in this study. The details of all included studies are listed in Table 3.

3.2.1. Non-Menstrual Pelvic Pain (NMPP)

The NMA for the non-menstrual pelvic pain included ten RCTs (N= 1095 participants) comparing eight treatment classes. Two studies (Carvalho et al. 2018, Vahid-Dastjerdi et al. 2023) that did not connect the network were excluded. All studies used the Visual Analogic Scale (VAS) to evaluate NMPP scores at pretreatment, and after 24 weeks of treatment.

According to Table 5, there was no significant difference regarding the efficacy among Placebo, GnRH agonist, GnRH antagonist, GnRH-addback, OCP, Progetin releasing device, Anti-estroprogestin, and Progestin. Similar results were observed in Table 6 for network meta-analysis of NMPP treatment. No statistically significant NMPP reduction was found among gestrinone, goserelin, leuprorelin, leuprorelin/E2/NETA, LNG-IUS, relugolix, E2/gestrinone, and ENG-Implanon.

Node splitting analysis result suggested that there was no significant inconsistency in terms of NMPP comparison between direct and indirect results (p-value > 0.05) (Figure 5). No significant heterogeneity was observed across the studies (I2= 7%). As demonstrated in Figure 5, GnRH-addback has the highest probability to be the first ranking for NMPP reduction, followed by GnRH agonist, and GnRH antagonist. In addition, goserelin has the highest probability to be the first ranking among individual treatment, followed by ENG-Implanon, and leuprorelin.

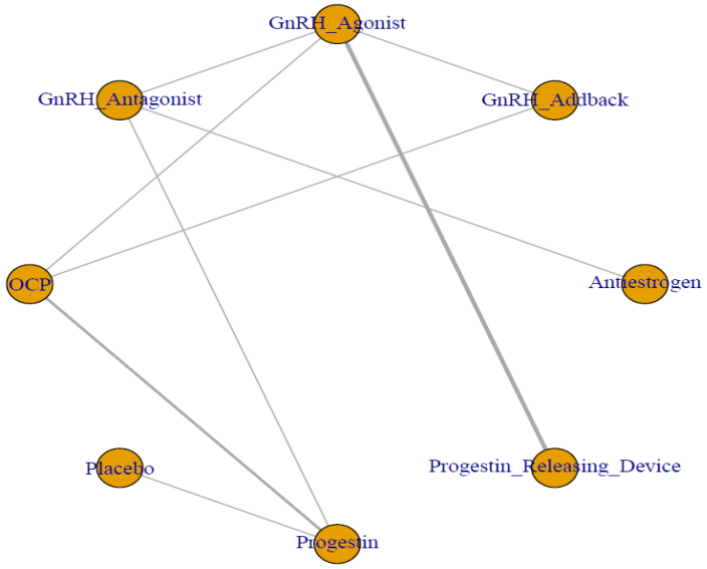


Figure 2 Network plot of treatment classes for NMPP. The line thickness is proportional to the number of trials.

Table 4 Summary estimates for NMPP derived from network meta-analysis of ten studies by treatment class

Placebo							
-24 (-56, 6.7)	GnRH Agonist						
-21 (-52, 9.5)	3.6 (-12, 20)	GnRH Antagonist					
-26 (-60, 7.2)	-1.4 (-20, 17)	-5.1 (-28, 17)	GnRH_Add back				
-18 (-47, 11)	6.8 (-9.2, 23)	3.2 (-15, 20)	8.3 (-9.9, 27)	OCP			
-19 (-53, 16)	5.3 (-6.1, 19)	1.5 (-18, 23)	6.6 (-14, 31)	-1.7 (-21, 20)	Progestin Releasing Device		
-19 (-57, 20)	5.8 (-22, 35)	2.0 (-21, 25)	7.3 (-25, 40)	-1.0 (-30, 28)	0.40 (-30, 30)	Anti-estroprogestin	
-18 (-45, 8.5)	6.1 (-11, 25)	2.5 (-13, 19)	7.6 (-13, 30)	-0.75 (-13, 12)	0.94 (-21, 22)	0.43 (-28, 29)	Progestin

The values are expressed as mean difference (95% Bayesian credible intervals). Treatments are expected to reduce NMPP; mean difference greater than 0 favors the column-defined treatment, and mean difference less than 0 favors the row-defined treatment. The bold values mean statistically significant results.

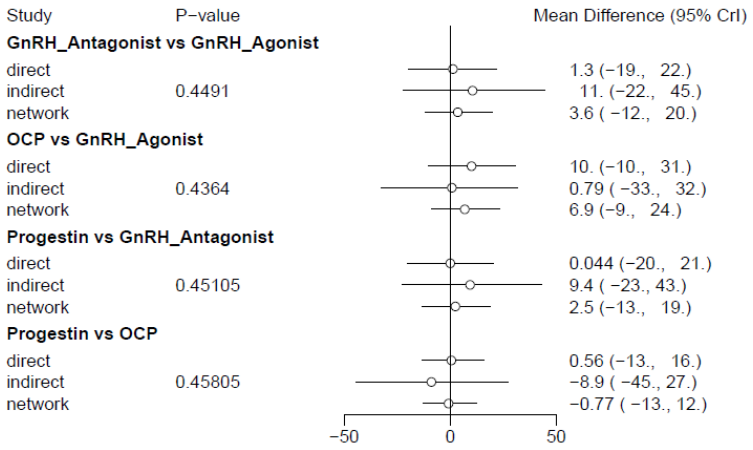


Figure 3 Node splitting analysis for NMPP treatment by treatment class

p-value < 0.05 indicates significant inconsistency between direct and indirect estimates.

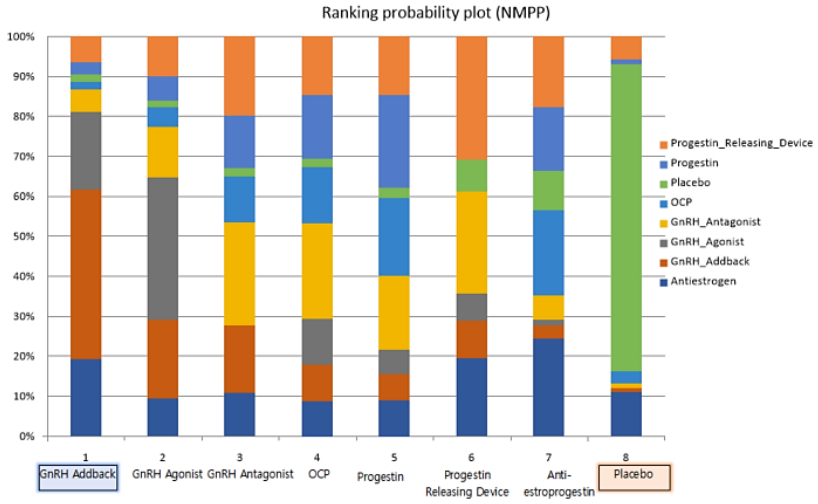
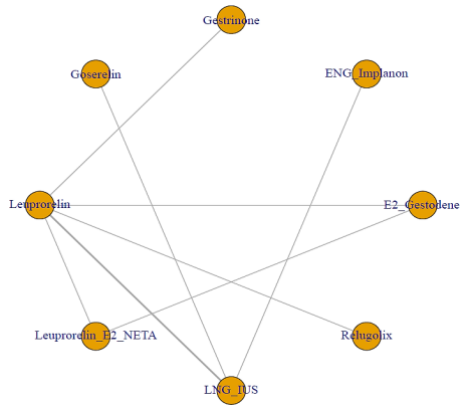


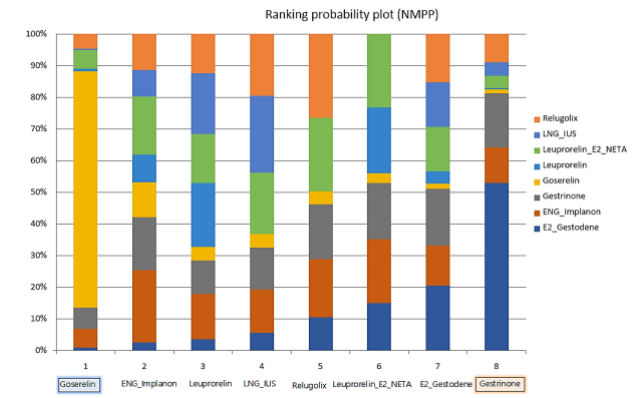
Figure 4 Network meta-analysis ranking probability bar graph of eight treatment classes for NMPP

Table 5 Network meta-analysis of NMPP treatment by individual treatment

Network plot



Ranking probability plot



League table

Gestrinone							
-21 (-60, 19)	Goserelin						
-2.1 (-27, 22)	18 (-12, 48)	Leuprorelin					
-2.1 (-34, 30)	18 (-19, 55)	0.025 (-22, 22)	Leuprorelin_E2_ NETA				
-1.0 (-30, 29)	19 (-6.1, 45)	1.2 (-15, 18)	1.1 (-26, 29)	LNG_IUS			
-2.1 (-38, 35)	18 (-15, 53)	0.071 (-27, 27)	0.089 (-34, 34)	-1.1 (-23, 20)	ENG_Implanone		
7.9 (-25, 41)	28 (-8.4, 65)	10 (-12, 32)	10 (-12, 32)	8.9 (-19, 36)	9.8 (-24, 44)	E2_Gestodene	
-0.76 (-33, 31)	20 (-17, 56)	1.4 (-20, 22)	1.4 (-29, 32)	0.24 (-27, 27)	1.3 (-33, 36)	-8.6 (-39, 21)	Relugolix

In the NMA of NMPP treatments, five studies (Carr et al. 2014, Caruso et al. 2022, Cheewadhanaraks et al. 2012, Tanmahasamut et al. 2017, Vahid-Dastjerdi et al. 2023) were excluded as network was not connected.

3.2.2. Dysmenorrhea

The NMA for dysmenorrhea (seven studies, participants= 835) was performed to compare seven treatment classes (Figure 6). Two studies (Carvalho et al. 2018, Vahid-Dastjerdi et al. 2023) that did not connect the network were excluded. All studies used the VAS to evaluate dysmenorrhea scores at pretreatment, and after 24 weeks of treatment. It showed that GnRH agonist was associated with the statistically significant reduction in dysmenorrhea, compared to OCP (MD: -18, CrI: 1.3, 36). Yet there was no significant dysmenorrhea improvement among gestrinone, leuprorelin, relugolix, leuprorelin/E2/NETA, and E2/gestodene as illustrated in Table 8.

Node splitting analysis result suggested that there was no significant inconsistency in terms of dysmenorrhea comparison between direct and indirect results (p-value > 0.05) (Figure 6). No significant heterogeneity was observed across the studies (I^2= 7%).

Figure 7 suggests that GnRH agonist has the highest probability to be the first ranking for dysmenorrhea reduction, followed by GnRH addback, and GnRH antagonist. In addition, leuprorelin has the highest probability to be the first ranking among individual treatment, followed by relugolix, and leuprorelin/E2/NETA.

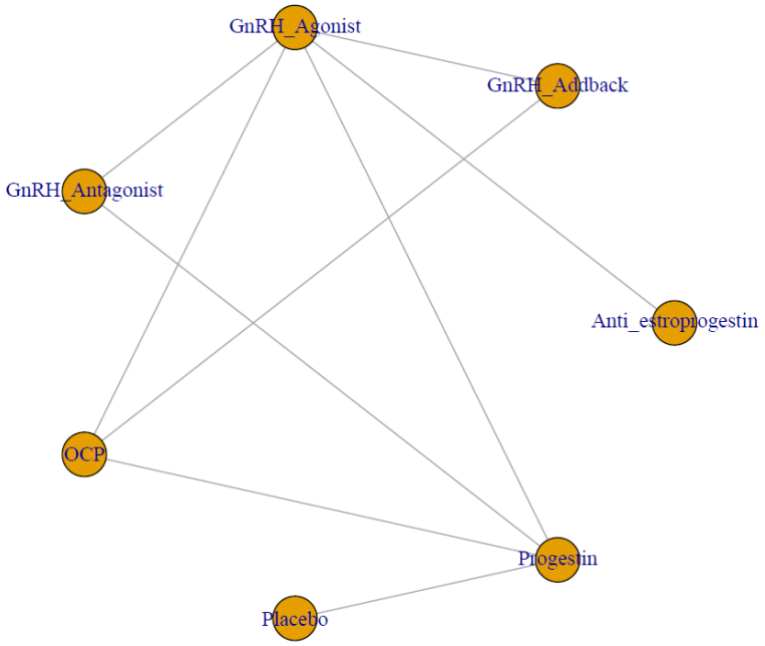


Figure 5 Network plot of seven treatment classes for dysmenorrhea. The line thickness is proportional to the number of trials.

Table 6 Summary estimates for dysmenorrhea derived from network meta-analysis by treatment class

Placebo						
-16 (-47, 13)	GnRH Agonist					
-12 (-42, 19)	4.5 (-11, 22)	GnRH Antagonist				
-14 (-49, 20)	2.1 (-18, 23)	-2.5 (-28, 23)	GnRH_Add back			
1.8 (-29, 32)	**18** **(1.3, 36)**	13 (-7.4, 35)	16 (-4.4, 37)	OCP		
-3.5 (-43, 35)	13 (-11, 38)	8.2 (-22, 38)	11 (-21, 43)	-5.3 (-35, 25)	Anti-estroprogestin	
-7.5 (-34, 18)	8.7 (-6.0, 25)	4.1 (-12, 21)	6.5 (-16, 30)	-9.4 (-26, 7.5)	-4.1 (-33, 25)	Progestin

The values are expressed as mean difference (95% Bayesian credible intervals). Treatments are expected to reduce NMPP; mean difference greater than 0 favors the column-defined treatment, and mean difference less than 0 favors the row-defined treatment. The bold values mean statistically significant results.

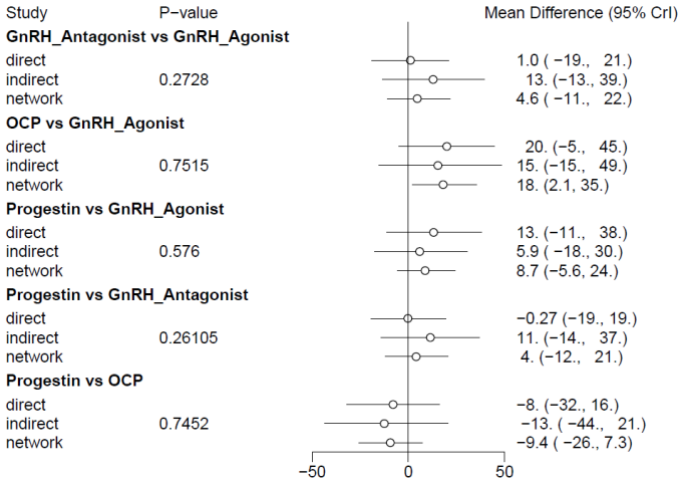


Figure 6 Node splitting analysis for dysmenorrhea treatment by treatment class

p-value < 0.05 indicates significant inconsistency between direct and indirect estimates.

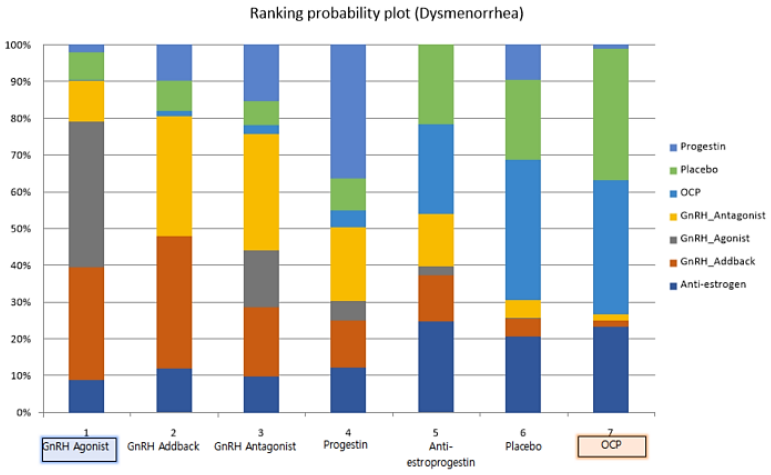
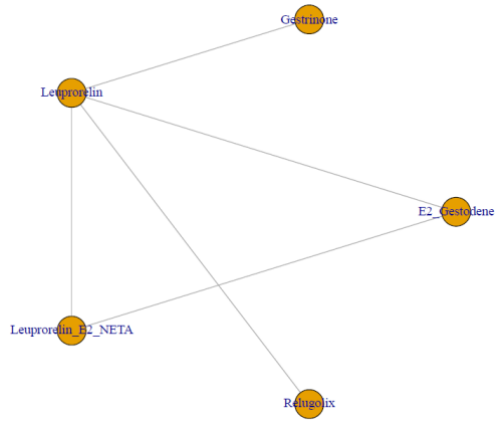


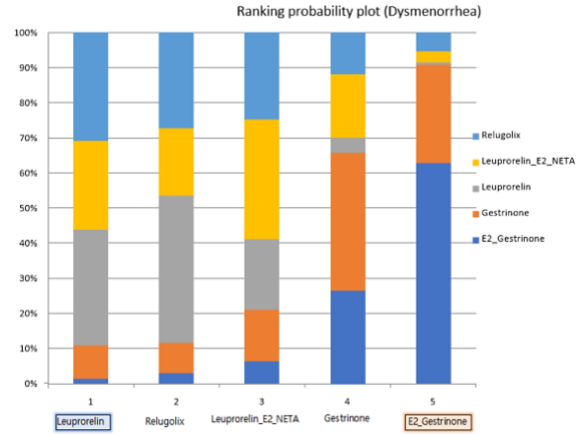
Figure 7 Network meta-analysis ranking probability bar graph of seven treatment classes for dysmenorrhea

Table 7 Network meta-analysis of dysmenorrhea treatments by individual treatment

Network plot



Ranking probability plot



League table

Gestrinone				
-13 (-41, 16)	Leuprorelin			
-12 (-49, 26)	1.1 (-24, 27)	Relugolix		
-9.9 (-48, 29)	2.9 (-22, 29)	1.8 (-34, 38)	Leuprorelin_E2_ NETA	
7.2 (-30, 46)	20 (-5.3, 46)	19 (-17, 54)	17 (-8.6, 42)	E2_Gestrinone

In the NMA of dysmenorrhea, four studies (Carr et al. 2014, Tanmahasamut et al. 2017, Cheewadhanaraks et al. 2012, Tang et al. 2023) were excluded as network was not connected.

3.2.3. Dyspareunia

For the NMA of dyspareunia, six studies (participants= 472) were included to compare the efficacy of seven treatment classes. One study (Vahid-Dastjerdi et al. 2023) was excluded as it did not connect the network. All studies used the VAS to evaluate dyspareunia scores at pretreatment, and after 24 weeks of treatment.

The result showed that there was no significant dyspareunia reduction observed among placebo, GnRH agonist, GnRH antagonist, GnRH-addback, OCP, anti-estroprogestin, and progestin. Similar results were observed when comparisons among individual treatment were made. No statistically significant improvement was found among gestrinone, leuprorelin, relugolix, leuprorelin/E2/NETA, and E2/gestodene.

Node splitting analysis result suggested that there was no significant inconsistency in terms of dyspareunia comparison between direct and indirect results (p-value > 0.05) (Figure 9).

Furthermore, no significant heterogeneity was observed across the studies (I^2= 10 %). As demonstrated in Figure 10, anti-estroprogestin has the highest probability to be the first ranking for dyspareunia reduction, followed by GnRH-addback, and GnRH agonist. In addition, gestrinone has the highest probability to be the first ranking among individual treatment, followed by leuprorelin/E2/NETA, and leuprorelin.

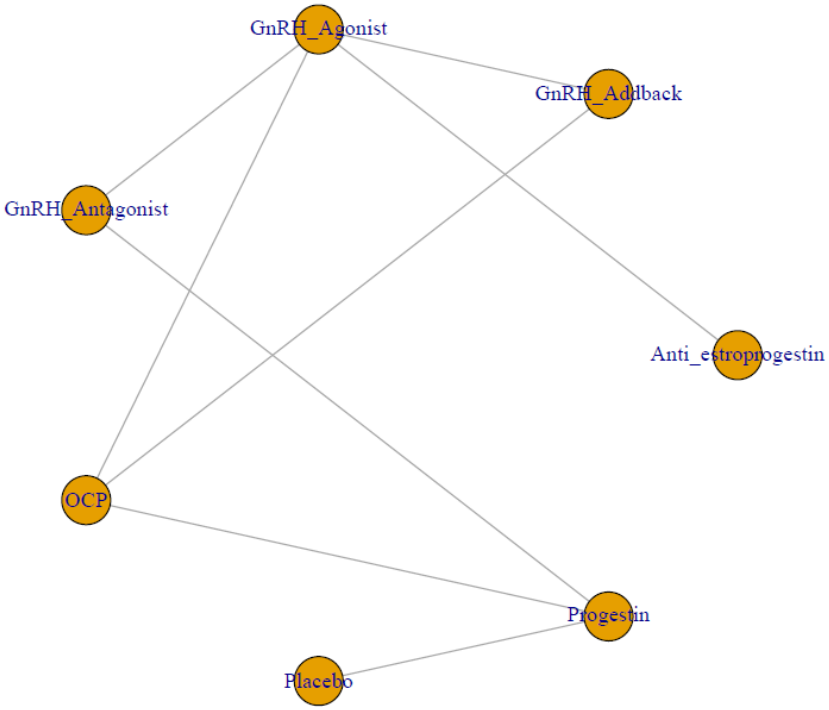


Figure 8 Network plot of seven treatment classes for dyspareunia. The line thickness is proportional to the number of trials.

Table 8 Summary estimates for dyspareunia derived from network meta-analysis of six studies by treatment class

Placebo						
-14 (-46, 19)	GnRH Agonist					
-6.6 (-38, 24)	7.3 (-11, 24)	GnRH Antagonist				
-17 (-51, 19)	-2.8 (-22, 16)	-10 (-33, 15)	GnRH_Add back			
-15 (-46, 16)	-1.3 (-19, 46)	-8.7 (-28, 12)	1.5 (-18, 20)	OCP		
-20 (-60, 21)	-6.5 (-31, 18)	-14 (-43, 17)	-3.7 (-34, 27)	-5.0 (-34, 24)	Anti-estroprogestin	
-3.7 (-30, 23)	10 (-10, 30)	2.5 (-13, 20)	13 (-11, 36)	11 (-5.6, 28)	16 (-14, 48)	Progestin

The values are expressed as mean difference (95% Bayesian credible intervals). Treatments are expected to reduce dyspareunia; mean difference greater than 0 favors the column-defined treatment, and mean difference less than 0 favors the row-defined treatment.

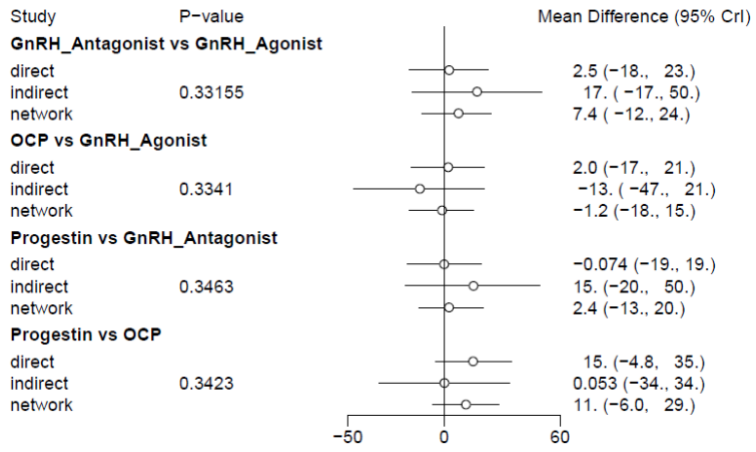


Figure 9 Node splitting analysis for dyspareunia treatment by treatment class
p-value < 0.05 indicates significant inconsistency between direct and indirect estimates.

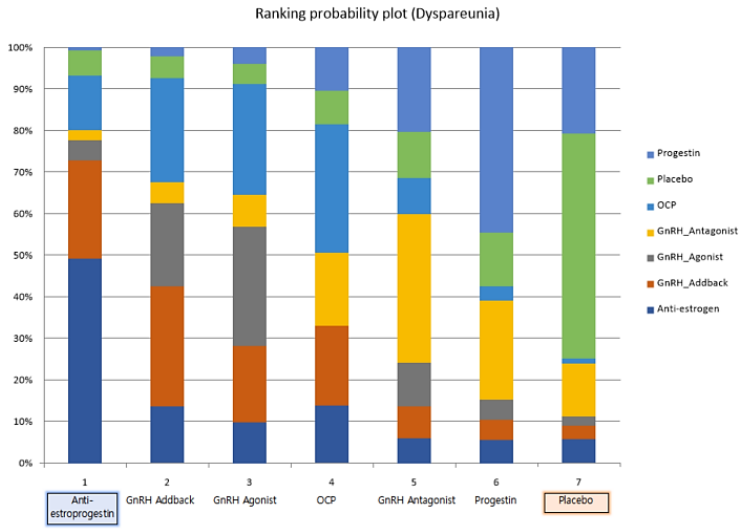
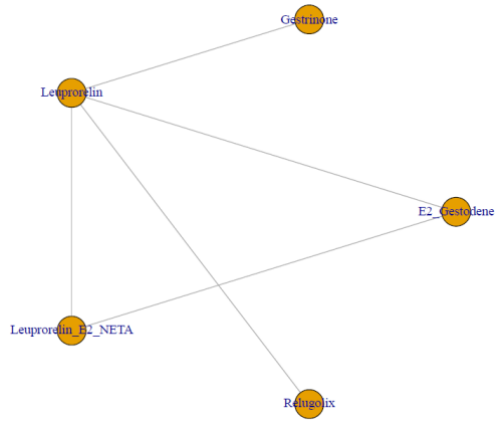


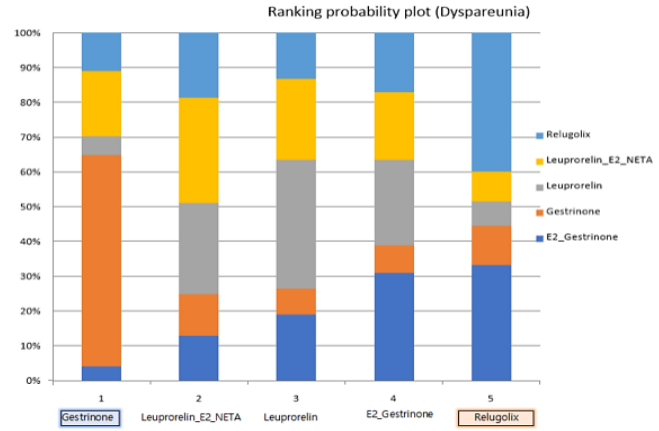
Figure 10 Network meta-analysis ranking probability bar graph of seven treatment classes for dyspareunia

Table 9 Network meta-analysis of dyspareunia treatments by individual treatment

Network plot



Ranking probability plot



League table

Gestrinone				
6.1 (-11, 24)	Leuprorelin			
8.2 (-13, 30)	2.0 (-10, 15)	Relugolix		
5.3 (-15, 25)	-0.89 (-10, 8.6)	-3.0 (-19, 12)	Leuprorelin_E2_ NETA	
8.2 (-12, 28)	2.0 (-7.3, 11)	-0.030 (-16, 15)	3.0 (-6.4, 12)	E2_Gestrinone

In the NMA of dyspareunia treatments, four studies (Carr et al. 2014, Tanmahasamut et al. 2017, Cheewadhanaraks et al. 2012, Vahid-Dastjerdi et al. 2023) were excluded as network was not connected.

3.2.4. Sensitivity analysis for publication bias and heterogeneity

First, heterogeneity in NMPP studies was 59.5% with *p*-value of 0.0044; it may represent substantial heterogeneity. A result of Egger's linear regression method test showed that studies for NMPP were less likely to have publication bias (*p*-value of 0.1960 > 0.05).

Second, heterogeneity was 87.0% with *p*-value < 0.0001 across studies involved in dysmenorrhea. It may represent considerable heterogeneity. Egger's linear regression method test suggested that studies for dysmenorrhea were less likely to have publication bias (*p*-value of 0.7504 > 0.05).

Third, heterogeneity in the NMA of dyspareunia was 70.2% with *p*-value of 0.0026. It may represent substantial heterogeneity. A result of Egger's linear regression method test indicated that the involved studies were less likely to have publication bias (*p*-value of 0.7257 > 0.05).

We were unable to conduct meta-regression due to a small number of studies involved (less than 10 trials). Meta-analysis has revealed that statistically significant heterogeneity was observed among studies involved in the NMA of NMPP, dysmenorrhea, and dyspareunia while no publication bias was present (Appendix 2). Overall, there was no evidence of publication bias; heterogeneity did not affect our data.

3.3. Risk of bias assessment

The visual representation of the risk of bias assessment results is presented in Figure 11. The domain of randomization process was evaluated to have some concerns in three studies (Tang et al. 2023, Caruso et al. 2022, Zupi et al. 2004) due to lack of information on whether the allocation sequence was concealed until subjects were enrolled and assigned to interventions. Two studies (Tang et al. 2023, Caruso et al. 2022) showed some concerns for bias for domains of deviations from intended interventions. Insufficient information given in the studies have resulted in some concerns for risk of bias. The domain of measurement

of the outcome was also evaluated to have high risk (Vahid-Dastjerdi et al. 2023, Tang et al. 2023, Carvalho et al. 2018) and to have some concerns (Caruso et al. 2022, Petta et al. 2005), most commonly because of lack of blinding. Except for these studies, all other studies were evaluated to have low risk of bias.

Study ID	Experimental	Comparator	D1	D2	D3	D4	D5	Overall
M.Vahid 2023	Progestin (MPA)	Progestin (Dienogest)	+	+	+	-	+	-
M.Tang 2023	GnRH-agonist	Progestin	!	!	+	-	+	-
T.O Harada 2022	GnRH antagonist	GnRH-agonist	+	+	+	+	+	+
S.C.Caruso 2022	Progestin	OCP	!	!	+	!	+	!
N.M.Carvalho 2018	Progestin Releasing Device (ENG Implanon)	Progestin Releasing Device (LNG-IUS)	+	+	+	-	+	+
P.S.Tanmahasamut 2017	Progestin	Placebo	+	+	+	+	+	+
B.D.Carr 2014	Progestin	GnRH antagonist	+	+	+	+	+	+
S.C.Cheewadhanaraks 2012	Progestin	OCP	+	+	+	+	+	+
Y.D.Bayoglu 2011	GnRH-agonist	Progestin Releasing Device (LNG-IUS)	+	+	+	+	+	+
M.K.O.F. Gomes 2007	GnRH-agonist	Progestin Releasing Device (LNG-IUS)	+	+	+	+	+	+
C.A.F.Petta 2005	GnRH-agonist	Progestin Releasing Device (LNG-IUS)	+	+	+	!	+	!
E.M.Zupi 2004	GnRH-agonist	OCP	!	+	+	+	+	!
P.S.Vercellini 1996	GnRH-agonist	Anti-estroprogestin	+	+	+	+	+	+

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Figure 11 Risk of bias 2 Assessment Result

4. Discussion

4.1. Key findings

This NMA included studies with 24 weeks treatment duration and VAS tool used for pain assessment to minimize potential variations. The baseline demographic, pain scores, and clinical characteristics were not significantly different between groups. Also, patients were restricted from using medication for pain relief other than allocated interventions during the trial. In addition, heterogeneity and node-splitting analysis result supported that no heterogeneity was observed across the studies and there was no significant inconsistency between direct and indirect results of NMPP, dysmenorrhea, and dyspareunia. Yet, none of treatments had shown significant improvement in NMPP and dyspareunia at 24 weeks of treatment. Inclusion criteria in the most involved studies was surgically and/or histologically diagnosed women. Some studies specified durations after the conservative surgery (e.g., after 3 to 5 days) but other studies requiring post-operative conditions for eligibility did not provide information on the postoperative period. This may have caused variations in the characteristic of study designs, setting, and population, leading to the insignificant results of the NMA. Thus, further sensitivity analysis was performed to reduce concerns potential inconsistency.

The difficulty is found in the evaluation of each type of pain and the validity of the scales as patients' feeling about pain experience is subjective (Puchar et al. 2021). Thus, it is often perplexing to determine which assessment tool can provide a good description of each patient's pain level. There are four FDA-approved drugs for endometriosis pain reduction. First, Lupron depot (monotherapy) and Lupron depot with addback therapy are indicated for endometriosis pain management. Clinical trials to prove the efficacy of these treatments were found to have used scales: 1= none, 2= mild, 3= moderate, 4= severe (AbbVie 2023). Relugolix/E2/NETA and elagolix are also FDA approved drugs for the same indication and the trials were found to use numeric rating scale (NRS) 11 points (0= no pain to 10= severe pain) (SPIRIT Trials | Myfembree® (Relugolix, Estradiol, and Norethindrone Acetate)

Tablets, n.d.-b & Orilissa (Elagolix), n.d.). In addition, in the study of goserelin, the pain measurement used was 4-scales pain assessment (0= absent, 1= mild, 2= moderate, 3= severe) (Rock et al. 1993).

Among different scales, VAS seems to be the strongest pain measurement because it uses a continuous scale (1-100 mm) and the patient probably answer pain-related information other than pain intensity (Bourdel et al. 2015). However, considering limited response categories that pain scales may have, it is recommended that more than one pain measurement methods (VAS, NRS, VRS, and the detailed questionnaire of pains, etc.) are used to evaluate the efficacy of drugs treating endometriosis associated pains. A reason for controversial result may be because of different pain assessment tools (e.g., VAS scale used in Zupi et al. 2004 while B&B scale in Guzick et al. 2011). Thus, the NMA included studies that assessed pain scores with VAS scale and with 24 weeks treatment duration to eliminate factors that may cause heterogeneity. Controversial results may also be found as there are limited number of direct and indirect analysis to assess the efficacy of treatments. According to ESHRE guideline, OCP can be effective for dysmenorrhea when it is used as postoperative treatment for 6 to 24 months (Becker et al. 2022). This means the efficacy of OCP may not be sufficiently substantiated in this NMA. The efficacy seems to be related to the treatment duration.

Until the 1990s, progestins and high-dose OCP were the most prevalent medical therapies (Surrey 2023). However, the continuous regimen is highly associated with a significant increase in adverse effects, particularly bleeding. This occurrence may lead to discontinuation of the treatment (Cheewadhanaraks et al. 2012). Thus, to date, highly potent GnRH agonists have become a new approach as a significant additional option for management of EM associated pain. It is noted that the FDA has approved the use of goserelin and leuprolide acetate (GnRH agonist) for up to six months when administered without any add-back therapy as bone mineral density loss was great due to lowering estradiol level (Surrey 2023). In this NMA for dysmenorrhea, GnRH agonist was more effective than OCP in dysmenorrhea pain reduction at six months (MD: -18; CrI: 1.3, 36).

In accordance with this finding, a RCT conducted by Zupi et al. reported that GnRH agonist and GnRH agonist-addback showed better improvements in dysmenorrhea than OCP at 6 and 12 months of treatment (Zupi et al. 2004). On the other hand, a previous 48-week trial showed that there was statistically significant decline in NMPP, dysmenorrhea, and dyspareunia from baseline in both GnRH agonist and OCP and there was no significant difference in the extent of pain reduction between two groups (Guzick et al. 2011).

Despite several studies and guidelines recommend OCP as the first-line treatment for endometriosis-associated pains, some patients fail to response to OCPs, and GnRH agonist is more frequently prescribed because its effectiveness in reducing further recurrence rate. Wu et al. conducted cost effectiveness analysis in the perspectives of the Chinese health care system (Wu et al. 2018). The results of the analysis indicated that the costs per QALY gained with the GnRH agonist were $6,185 for deep endometriosis higher than that with no medical therapy, and $6,425 higher for peritoneal endometriosis.; it was suggested that GnRH agonist was highly cost-effective according to WHO recommendation (WHO 2023). Monthly cost for OCP therapy is low, but the ICERs were greater than the per capita GDP of China ($7,400 in 2015); it indicated that OCP was not a cost-effective therapy in the Chinese setting (Wu et al. 2018). GnRH agonists, when used for 24 weeks after surgery, can be a first-line therapy to effectively relieve endometriosis-associated symptoms and decrease the recurrence rate.

Though the NMA to compare the efficacy of different treatment classes for NMPP did not show any significant improvement in pain reduction, GnRH-addback, GnRH agonist, and GnRH antagonist were ranked top three treatments that can alleviate NMPP and dysmenorrhea pains. The French National Authority for Health (HAS) and the French College of Gynecologists and Obstetricians (CNGOF) updated a clinical practice guideline in 2018. This guideline stated that GnRH agonist alleviates dysmenorrhea and use of GnRH combined with add-back therapy is highly recommended for improving quality of life (Collinet et al. 2018). It was reported that GnRH-addback therapy did not reduce the efficacy of EM pain management.

The NMA also showed that goserelin (GnRH agonist) had the highest probability to be the first treatment choice for mitigating the severity of NMPP, followed by ENG-Implanon, leuprorelin, and LNG-IUS. Reducing the inflammatory process can consequently lead to relieving NMPP and dysmenorrhea. LNG-IUS and ENG-Implanon have emerged as non-oral progestin treatments with few side effects (Margatho et al. 2020). The cost of LNG-IUS in treatment of endometriosis is currently under insurance coverage in Korea. Thus, if the purpose of treatment is to control endometriosis-associated pain, not necessarily to expect remission of its associated lesions, LNG-IUS and ENG-Implanon can also be used to provide pain control.

There was no significant difference associated with dyspareunia reduction observed in the analysis. Most studies reported that treatments did not show significant improvement. Dlugi et al. suggested that as patients reported less intercourse due to pains during treatment period, it was difficult to assess dyspareunia (Dlugi et al. 1990). In our NMA, gestrinone had the highest probability to be the best treatment option for dyspareunia, followed by leuprorelin/E2/NETA, and leuprorelin. In agreement with this finding, a previous study also showed that dyspareunia score was significantly lower with gestrinone than with the leuprorelin (Vercellini et al. 1996).

ESHRE guideline stated that although NSAIDs are widely used as the first-line treatment, there is limited evidence that supports the efficacy of reducing EM associated pains (Becker et al. 2022). Published trials that investigated the management of endometriosis-related pain were excluded during full-text screening due to inappropriate efficacy endpoints.

Our findings show that there was no significant difference between any pair of treatments analyzed, except for dysmenorrhea. Factors that may have caused the results were investigated. Pain is a subjective and complex domain and no evaluation that perfectly reflects patients' response to the pain is yet available (Bourdel et al. 2015). VAS is the most common tool to evaluate the level of pain; all studies involved in this NMA were also found

to use this VAS scale. When endometriosis pain is scored, pain scales need to be valid, precise, and reliable and expected to provide similar results (Bourdel et al. 2015). Thus, it is important to carefully compare pain scales and choose the optimal method with the least potential bias or to use multiple assessment methods to evaluate the efficacy of the treatments for pain reduction.

In present, there are few head-to-head randomized clinical trials conducted to assess the efficacy of different treatments in treating endometriosis-associated pains. Various factors such as severity of endometriosis, medication compliance could have led to controversial results. Furthermore, it is challenging to confirm that one medication is superior to any other options for pain reduction.

4.2. Limitations

Despite the strength of this study, some limitations are present thus, interpretation of our results must be done with caution. First, a methodological limitation was the open-label design. LNG-IUS and ENG-Implanon cannot be blinded due to the characteristics. A lack of blinding could have caused some bias when patients scored the level of pains during treatment. Second, limited number of studies is involved in the NMA. Although this NMA has established large sample size for trials on the efficacy of endometriosis, the number of involved studies may restrict the confidence in the results. Third, heterogeneity among studies is potentially present. There was no statistically significant difference between treatment arms in terms of baseline demographic characteristics and VAS scores but potential variations in characteristics of study population, designs, and VAS scores across the involved studies may have restricted the reliability of the results.

5. Conclusion

Our findings suggest that GnRH agonist may be a promising strategy if used for 24 weeks after surgery. To reduce the side effect (e.g., BMD decrease), GnRH agonist can be used with addback medication for longer than 24 weeks.

In conclusion, this NMA is the first wide network meta-analysis to compare both class and individual treatments for endometriosis associated pains; this may provide the clinicians guidance to personalize the treatment depending on patient's compliance, costs, and side effects.

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Appendix 1. Search strategies

PubMed	
1	endometriosis"[MeSH Terms]
2	"gnrh antagonist"[Title/Abstract] OR "gnrh agonist"[Title/Abstract] OR "intrauterine device"[Title/Abstract] OR "IUD"[Title/Abstract] OR "Goserelin"[Title/Abstract] OR "relugolix"[Title/Abstract] OR "progestins"[Title/Abstract] OR "estroprogestins"[Title/Abstract] OR "NSAID"[Title/Abstract] OR "Lupron"[Title/Abstract] OR "nafarelin"[Title/Abstract] OR "elagolix"[Title/Abstract] OR "norethindrone acetate"[Title/Abstract] OR "NETA"[Title/Abstract] OR "depot medroxyprogesterone acetate"[Title/Abstract] OR "DMPA"[Title/Abstract] OR (("estrogen progestin"[All Fields] OR "oestrogen progestin"[All Fields]) AND ("contracept"[All Fields] OR "contracepted"[All Fields] OR "contracepting"[All Fields] OR "contraception"[MeSH Terms] OR "contraception"[All Fields] OR "contraceptions"[All Fields] OR "contraceptive agents"[Pharmacological Action] OR "contraceptive agents"[MeSH Terms] OR ("contraceptive"[All Fields] AND "agents"[All Fields]) OR "contraceptive agents"[All Fields] OR "contraceptives"[All Fields] OR "contraceptive devices"[MeSH Terms] OR ("contraceptive"[All Fields] AND "devices"[All Fields]) OR "contraceptive devices"[All Fields] OR "contraceptive"[All Fields] "contraceptive s"[All Fields] OR "contraceptively"[All Fields]))
3	"clinical study" [All Fields] OR "study" [All Fields] OR "clinical trial" [All Fields] OR "trial" [All Fields]
4	#1 AND #2 AND #3
EMBASE	
1	‘endometriosis/exp OR 'adenomyosis externa' OR 'endometriosis' OR 'endometriosis externa'
2	(('gonadorelin antagonist'/exp OR 'LHRH antagonist' OR 'antigonadorelin' OR 'gnrh antagonist' OR 'gonadorelin antagonist' OR 'gonadorelin, anti' OR 'gonadotropin releasing factor antagonist' OR 'gonadotropin releasing hormone antagonist' OR 'gonadotropin releasing hormone antagonists' OR 'gonadotropin-releasing hormone antagonists' OR 'lh rh antagonist' OR 'lrf antagonist' OR 'luliberin antagonist' OR 'luteinising hormone releasing hormone antagonist' OR 'luteinizing hormone releasing hormone antagonist') OR ('gonadorelin agonist'/exp OR 'LHRH agonist' OR 'gnrh agonist' OR 'gonadorelin agonist' OR

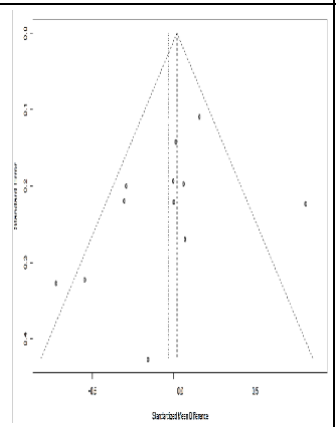
	'gonadotropin releasing hormone agonist' OR 'luteinising hormone releasing hormone agonist' OR 'luteinizing hormone releasing hormone agonist') OR ('intrauterine contraceptive device'/exp OR 'Dalkon shield' OR 'Femilis Cu-T 300' OR 'IUD' OR 'Lippes loop' OR 'Saf T coil' OR 'contraception, intrauterine' OR 'contraceptive coil' OR 'contraceptive device, intrauterine' OR 'contraceptive intrauterine device' OR 'dana device' OR 'i.u.d.' OR 'i.u.d. contraception' OR 'intra uterine device' OR 'intracervical device' OR 'intraperitoneal intrauterine contraceptive device' OR 'intraperitoneal iud' OR 'intrauterine coil' OR 'intrauterine contraception' OR 'intrauterine contraception device' OR 'intrauterine contraceptive' OR 'intrauterine contraceptive agent' OR 'intrauterine contraceptive device' OR 'intrauterine device' OR 'intrauterine devices' OR 'intrauterine devices (IUDs)' OR 'intrauterine devices, medicated' OR 'iucd' OR 'marguilies spiral' OR 'margulie coil' OR 'medicated intrauterine devices' OR 'novagard' OR 'obstructive contraceptive device' OR 'uterus contraceptive') OR (goserelin/exp OR 'buserelin carbazamide' OR 'gonadorelin [1-9] [6 (o tert butyl dextro serine)] carbazamide' OR 'gonadorelin [1-9] carbazamide [6 (o tert butyl dextro serine)]' OR 'gonadorelin [6 dextro o tert butylserine 10 glycine azide]' OR 'goserelin' OR 'goserelin acetate' OR 'ici 118 630' OR 'ici 118630' OR 'ici 118630 depot' OR 'ici118630' OR 'lhrh [6 dextro o tert butylserine 10 glycine azide]' OR 'ly 01005' OR 'ly01005' OR 'novimp' OR 'prozoladex' OR 'pyroglutamylhistidyltryptophylseryltyrosyl (o tert butyl dextro seryl) leucylarginylprolylcarbazamide' OR 'reseligo' OR 'zd 9393' OR 'zd9393' OR 'zoladex' OR 'zoladex depot' OR 'zoladex inj.' OR 'zoladex la' OR 'zoreline') OR (relugolix/exp OR '1 [4 [1 (2, 6 difluorobenzyl) 5 [(dimethylamino) methyl] 1, 2, 3, 4 tetrahydro 3 (6 methoxy 3 pyridazinyl) 2, 4 dioxothieno [2, 3 d] pyrimidin 6 yl] phenyl] 3 methoxyurea' OR '1 [4 [1 [(2, 6 difluorophenyl) methyl] 5 [(dimethylamino) methyl] 1, 2, 3, 4 tetrahydro 3 (6 methoxy 3 pyridazinyl) 2, 4 dioxothieno [2, 3 d] pyrimidin 6 yl] phenyl] 3 methoxyurea' OR '1 [4 [1 [(2, 6 difluorophenyl) methyl] 5 [(dimethylamino) methyl] 3 (6 methoxypyridazin 3 yl) 2, 4 dioxo 1, 2, 3, 4 tetrahydrothieno [2, 3 d] pyrimidin 6 yl] phenyl] 3 methoxyurea' OR 'mvt 601' OR 'mvt601' OR 'n [4 [1 (2, 6 difluorobenzyl) 5 [(dimethylamino) methyl] 1, 2, 3, 4 tetrahydro 3 (6 methoxy 3 pyridazinyl) 2, 4 dioxothieno [2, 3 d] pyrimidin 6 yl] phenyl] n` methoxyurea' OR 'n [4 [1 [(2, 6 difluorophenyl) methyl] 5 [(dimethylamino) methyl] 1, 2, 3, 4 tetrahydro 3 (6 methoxy 3 pyridazinyl) 2, 4 dioxothieno [2, 3 d] pyrimidin 6 yl] phenyl] 3 methoxyurea' OR 'n [4 [1 [(2, 6 difluorophenyl) methyl] 5 [(dimethylamino) methyl] 3 (6 methoxypyridazin 3 yl) 2, 4 dioxo 1, 2, 3, 4 tetrahydrothieno [2, 3

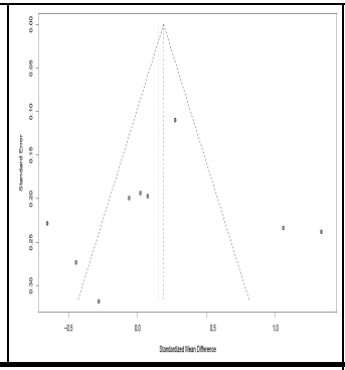
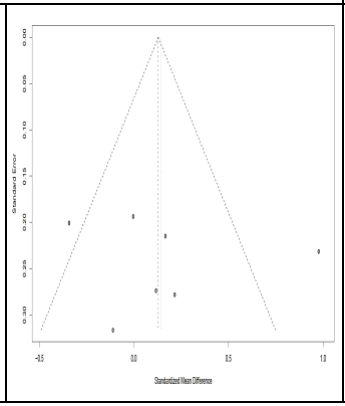
	d] pyrimidin 6 yl] phenyl] n` methoxyurea' OR 'orgovyx' OR 'relugolix' OR 'relumina' OR 'rvt 601' OR 'rvt601' OR 't 1331285' OR 't1331285' OR 'tak 385' OR 'tak385') OR (gestagen/exp OR 'gestagen' OR 'gestogen' OR 'progestagen' OR 'progestational activity' OR 'progestational agent' OR 'progestational drug' OR 'progestational hormones' OR 'progestational hormones, synthetic' OR 'progestative agent' OR 'progestative drug' OR 'progestin' OR 'progestine' OR 'progestins' OR 'progestogen') OR ('nonsteroid antiinflammatory agent'/exp OR 'NSAID' OR 'anti inflammatory agents, non steroidal' OR 'anti-inflammatory agents, non-steroidal' OR 'antiinflammatory agent, nonsteroid' OR 'non steroid antiinflammatory agent' OR 'non steroid antiinflammatory drug' OR 'non steroidal anti inflammatory agent' OR 'non steroidal anti inflammatory drug' OR 'non steroidal antiinflammatory agent' OR 'non steroidal antiinflammatory drug' OR 'nonsteroid antiinflammatory agent' OR 'nonsteroid antiinflammatory drug' OR 'nonsteroid antirheumatic agent' OR 'nonsteroidal anti inflammatory drug' OR 'nonsteroidal anti inflammatory drugs' OR 'nonsteroidal anti-inflammatory drugs' OR 'nonsteroidal antiinflammatory agent' OR 'nonsteroidal antiinflammatory drug') OR (leuprorelin/exp OR '5 oxoprolyl his trp ser tyr dextro leu leu arg n ethylprolinamide' OR '5 oxoprolylhistidyltryptophylseryltyrosyl dextro leucylleucylarginyl n ethylprolinamide' OR 'a 43818' OR 'a43818' OR 'abbott 43818' OR 'cam 2032' OR 'cam2032' OR 'camcevi' OR 'camcevi kit' OR 'carcinil' OR 'ckd 841' OR 'ckd841' OR 'daronda' OR 'depo lupron' OR 'depo-eligard' OR 'eligard' OR 'eligard depot' OR 'eliprogel' OR 'elityran' OR 'elityran depot' OR 'enanton' OR 'enanton depot' OR 'enantone' OR 'enantone depot' OR 'enantone lp' OR 'enantone sr' OR 'enantone-gyn' OR 'fensolvi' OR 'fensolvi kit' OR 'fp 001' OR 'fp001' OR 'ginecrin' OR 'ginecrin depot' OR 'gonadorelin [6 dextro leucine 9 (n ethylprolinamide) 10 deglycinamide]' OR 'gonadorelin ethylamide [6 dextro leucine 10 deglycine]' OR 'gonadorelin ethylamide [6 dextro leucine 10 deglycine]' OR 'klebrocid' OR 'klebrocid depot' OR 'la 2575' OR 'la2575' OR 'leptoprol' OR 'lerin' OR 'leuplin' OR 'leuplin depot' OR 'leupro-sandoz' OR 'leuprogel' OR 'leuprol' OR 'leuprolid' OR 'leuprolide' OR 'leuprolide acetate' OR 'leuprolide mesilate' OR 'leuprolide mesylate' OR 'leuprolide methanesulfonate' OR 'leupron' OR 'leuprone' OR 'leuprorelin' OR 'leuprorelin acetate' OR 'leuprorelin mesilate' OR 'leuprorelin mesylate' OR 'leuprorelin methanesulfonate' OR 'leuprorelina' OR 'leuprostin' OR 'lorelin depot' OR 'lucrin' OR 'lucrin depot' OR 'lucrin depot inj' OR 'lupride' OR 'lupride depot' OR 'luprolex' OR 'luprolex depot' OR 'lupron' OR 'lupron depo' OR 'lupron depot'

	OR 'lupron depot ped' OR 'lupron depot-3' OR 'lupron depot-4' OR 'lupron depot-gyn' OR 'lupron depot-ped' OR 'lutrate' OR 'lutrate depot' OR 'nh 901' OR 'nh901' OR 'ovarest (leuprorelin)' OR 'politrate' OR 'politrate depot' OR 'procren depot' OR 'procrin' OR 'procrin mensual' OR 'procrin semestral' OR 'procrin trimestral' OR 'prostap' OR 'prostap 3' OR 'prostap 3 dcs' OR 'prostap pd dcs' OR 'prostap sr' OR 'prostap sr dcs' OR 'prostaplant' OR 'reliser' OR 'sixantone' OR 'sot 375' OR 'sot375' OR 'staladex' OR 'tap 144' OR 'tap 144 sr' OR 'tap144' OR 'tap144 sr' OR 'tapros (leuprorelin)' OR 'tol 2506' OR 'tol2506' OR 'trenantone' OR 'trenantone-gyn' OR 'viadur' OR 'vp 4896' OR 'vp4896' OR 'zeulide' OR 'zeulide depot' OR 'zeulidedepot') OR (nafarelin/exp OR '5 oxoprolylhistidyltryptophylseryltyrosyl [3 (2 naphthyl) dextro alanyl] leucylarginylprolylglycinamide' OR 'gonadorelin [6 [3 (2 naphthyl) dextro alanine]]' OR 'gonadorelin [6 dextro [3 (2 naphthyl) alanine]]' OR 'nafarelin' OR 'pyroglutamylhistidyltryptophylseryltyrosyl [3 (2 naphthyl) dextro alanyl] leucylarginylprolylglycinamide' OR 'rs 94991' OR 'rs94991') OR (elagolix/exp OR '4 [[2 [5 (2 fluoro 3 methoxyphenyl) 3 [[2 fluoro 6 (trifluoromethyl) phenyl] methyl] 4 methyl 2, 6 dioxo 3, 6 dihydropyrimidin 1 (2h) yl] 1 phenylethyl] amino] butanoic acid' OR '4 [[2 [5 (2 fluoro 3 methoxyphenyl) 3 [2 fluoro 6 (trifluoromethyl) benzyl] 4 methyl 2, 6 dioxo 3, 6 dihydropyrimidin 1 (2h) yl] 1 phenylethyl] amino] butanoic acid' OR 'abt 620' OR 'abt620' OR 'elagolix' OR 'elagolix sodium' OR 'nbi 56418' OR 'nbi56418' OR 'orilissa') OR ('norethisterone acetate'/exp OR '10 norethindrone acetate' OR '17 ethinyl 19 nortestosterone acetate' OR '17 ethinyl nortestosterone acetate' OR '17 ethynyl 19 nortestosterone acetate' OR '17alpha ethynyl 19 nortesterone acetate' OR '19 nor 17alpha ethynyltestosterone acetate' OR '19 norethindrone acetate' OR '19 norethinyltestosterone acetate' OR '19 norethisterone acetate' OR 'aminor' OR 'anhydrohydroxynorprogesterone acetate' OR 'aygestin' OR 'errin' OR 'ethinyl nortestosterone acetate' OR 'ethinylnortestosterone acetate' OR 'milligynon' OR 'noresthisterone acetate' OR 'norethidrone acetate' OR 'norethindron acetate' OR 'norethindronacetate' OR 'norethindrone 17 acetate' OR 'norethindrone acetate' OR 'norethisteron acetate' OR 'norethisteronacetate' OR 'norethisterone acetate' OR 'norethisteroneacetate' OR 'norethistone acetate' OR 'norethistosterone acetate' OR 'noretindrone acetate' OR 'norlutane' OR 'norlutate' OR 'norlutin a' OR 'primolut nor' OR 'primolutnor' OR 'primosistan' OR 'sh 420' OR 'sh 420c' OR 'sh420' OR 'sh420c') OR 'depot medroxyprogesterone acetate'/exp OR (dienogest/exp OR '17alpha cyanomethyl 17beta hydroxy 13beta methylgona 4, 9 dien 3 one' OR '17alpha cyanomethyl 17beta hydroxy 4, 9 estradien 3 one' OR

	'17alpha cyanomethyl 17beta hydroxyestra 4, 9 (10) dien 3 one' OR '17alpha cyanomethyl 17beta hydroxyestra 4, 9 dien 3 one' OR '17alpha cyanomethylestra 4, 9 (10) dien 17 ol 3 one' OR 'bay 86 5258' OR 'bay 865258' OR 'bay86 5258' OR 'bay865258' OR 'dienogest' OR 'dimetrum' OR 'dinagest' OR 'endometrion' OR 'estra 4, 9 dien 17beta ol 3 one, 17alpha cyanomethyl' OR 'gona 4, 9 dien 17beta ol 3 one, 17alpha cyanomethyl 13beta methyl' OR 'm 18575' OR 'm18575' OR 'mjr 35' OR 'mjr35' OR 'sh t 00660aa' OR 'sht00660aa' OR 'sts 557' OR 'sts557' OR 'visanne' OR 'visannette' OR 'zk 37659' OR 'zk37659'))
3	'randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'trial, randomized controlled'
4	#1 AND #2 AND #3
Cochrane	
1	"endometriosis"[MeSH Terms]
2	(gnrh antagonist) OR (gnrh agonist) OR (intrauterine device) OR (IUD) OR (Goserelin) OR (relugolix) OR (progestins) OR (estroprogestins) OR (NSAID) OR (lupron) OR (nafarelin) OR (elagolix) OR (norethindrone acetate) OR (NETA) OR (depot medroxyprogesterone acetate) OR (DMPA) OR (dienogest) OR (contraceptive)
3	(clinical study) OR (randomized clinical study) OR (randomised trial) OR (study) OR (clinical trial) OR (trial)
4	#1 AND #2 AND #3

Appendix 2. Sensitivity analysis for publication bias and heterogeneity by meta-analysis.

	Analysis	Outcome	Interpretation
NMPP	Heterogeneity	Quantifying heterogeneity Tau ^{2} = 0.0726 [0.0122; 0.3605]; Tau = 0.2694 [0.1103; 0.6005] I^2 = 59.5% [23.5%; 78.5%]; H = 1.57 [1.14; 2.16] Test of heterogeneity Cochran's Q = 27.15, df =11, *p*-value = 0.0044	*p*-value < 0.05 ***Substantial heterogeneity was observed.**
	Funnel plot & Egger's regression test (Publication bias)	Linear regression test of funnel plot asymmetry Tau = -1.39, df = 10, *p*-value = 0.1960 Sample estimates bias: -1.7372, se.bias: 1.2537 intercept: 0.3401, se.intercept: 0.2469 	*p*-value > 0.05 ***No publication bias was detected.**
	Heterogeneity	Quantifying heterogeneity Tau ^{2} = 0.3701 [0.1408; 1.5430]; Tau = 0.6083 [0.3752; 1.2422] I^2 = 87.0% [77.3%; 92.5%]; H = 2.77 [2.10; 3.65] Test of heterogeneity Cochran's Q: 61.38, df = 8, *p*-value < 0.0001	*p*-value < 0.05 ***Considerable heterogeneity was observed.**

Dysmenorrhea	Funnel plot & Egger's regression test (Publication bias)	Linear regression test of funnel plot asymmetry Tau = -0.33, df = 7, *p*-value = 0.7504 Sample estimates bias: -1.0317, se.bias: 3.1182 intercept: 0.3790, se.intercept: 0.6052		*p*-value > 0.05 ***No publication bias was detected.**
Dyspareunia	Heterogeneity	Quantifying heterogeneity Tau ^{2} = 0.1260 [0.0195; 0.7748]; Tau = 0.3549 [0.1398; 0.8802] I^2 = 70.2% [34.7%; 86.4%]; H = 1.83 [1.24; 2.71] Test of heterogeneity Cochran's Q: 20.13, df = 6, *p*-value = 0.0026		*p*-value < 0.05 ***Substantial heterogeneity was observed.**
	Funnel plot & Egger's regression test (Publication bias)	Linear regression test of funnel plot asymmetry Tau = 0.37, df = 5, *p*-value = 0.7257 Sample estimates: bias: 1.6764, se.bias: 4.5168 intercept: -0.2577, se.intercept: 1.0560		*p*-value > 0.05 ***No publication bias was detected.**

ABSTRACT (Korean)

Endometriosis-associated pain치료약물의 유효성에 대한 체계적 문헌고찰과 네트워크 메타 분석

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박소영

연구 배경

자궁내막증은 가임기 여성 중 약 10%에서 나타나며, 자궁내막증의 주요 증상인 통증은 삶의 질을 저하시키는 만성 질환이다. 자궁내막증 치료에 사용되는 약물의 효과와 안전성을 입증하기 위해 임상시험이 수행되었다. 그러나 직접적인 비교가 없는 경우 약물 계열별 또는 약물별로 다양하게 비교하는 데 제한이 있으며, 임상시험 디자인의 적절성과 일관성이 없는 연구 결과에 대한 의문점이 있었다.

본 연구의 목적은 네트워크 메타분석을 수행하여 자궁내막증 증상인 비월경 골반 통증, 월경통, 성교통을 개선하는 치료 효과를 약물 계열별 및 약물별 비교하여, 최적의 치료 방법을 선택할 수 있도록 임상적 근거를 제시하고자 한다.

연구 방법

PubMed, Embase, 및 Cochrane library 데이터베이스에서 자궁내막증 진단을 받은 여성을 대상으로 진행한 무작위 배정 임상시험으로 비월경 골반 통증, 월경통, 성교통이 VAS로 측정되어 2023년 8월 13일까지 보고된 연구를

검색하였다. 유효성 평가변수는 기저치 대비 24주 치료 기간 시점의 비월경 골반 통증, 월경통, 성교통 통증 점수의 평균 차이이며, 95% 신용구간 (CrI)도 포함되었다. 본 연구의 분석 방법으로 유효성 평가를 위한 베이지안 네트워크 메타분석 및 민감도 분석을 위한 pair-wise 메타분석을 포함하였다.

연구결과

본 네트워크 메타분석에 총 13개의 무작위배정 임상시험이 포함되었다. 그 결과, GnRH agonist가 OCP보다 통계적으로 유의미한 월경통 개선을 보였다. 비월경 골반 통증 및 성교통 완화를 위한 약물들은 유의미한 변화를 확인할 수 없었다. 비월경 골반 통증 감소와 관련하여 GnRH agonist가 약물 계열 1위, goserelin이 약물별 비교에서 1위로 확인되었다. 월경통 감소 치료제로 GnRH agonist가 약물 계열 1위, leuprorelin이 약물별 비교에서 1위였다. 또한, 성교통 개선에는 anti-estroprogestin과 gestrinone이 약물 계열별, 약물별 비교에서 각각 1위로 선정되었다. 네트워크 메타분석에 적은 수의 연구가 포함되어 이질성 수치에 통계적으로 유의하게 영향을 주었는지 검정하기 위해 민감도 분석을 수행하였다. 그 결과, 출판편향의 증거는 없었으며, 본 연구의 결과가 과대 또는 과소 추정되었을 가능성은 낮음을 확인하였다.

결론

GnRH agonist는 OCP보다 기저치 대비 24주 시점 월경통 감소에 통계적으로 유의미한 효과를 보였다.

핵심 용어: 자궁내막증, Endometriosis-associated pains, 비월경 골반 통증, 월경통, 성교통, 유효성, 네트워크 메타분석, 체계적 문헌고찰