doi.org/10.36721/PJPS.2026.39.3.REG.14471.1

Comparative analysis of combined oral contraceptives and non-steroidal anti-inflammatory drugs (NSAIDS) in treating dysmenorrhea: A multi-center study

Meiyi Ren[1#], Yi Yang[2#] and Huifen Xu[3]*

[1]Department of Medical, People's Hospital of Xiaodian District, Taiyuan, Shanxi, China
[2]Department of Traditional Chinese Medicine, Tongxiang Maternal and Child Health-Care Center, Tongxiang, Zhejiang, China
[3]Department of Pharmacy, The Second Hospital of Jinhua, Jinhua, Zhejiang, China

Abstract: **Background**: The incidence of dysmenorrhoea is high and mainly concentrated in young women, which seriously affects their quality of life. **Objective**: To compare and analyze the clinical efficacy of compounded oral contraceptives and non-steroidal anti-inflammatory drugs in the treatment of dysmenorrhoea. **Methods**: In a multicenter study, 120 cases of dysmenorrhea patients from People's Hospital of Xiaodian district between October 2020 and December 2023 were divided into CC group (treatment with ethinyl estradiol cyproterone tablets) and ND group (treatment with celecoxib capsules). The pain scores, sex hormone levels and clinical efficacy were mainly compared. The secondary indexes included cancer antigen 125 (CA125), osteocalcin (BGP) level, immune indexes and adverse reaction rates and recurrence rate. **Results**: After treatment, significant changes in the indicators of both groups was (P<0.05). The pain score, sex hormone levels, CA125 level and immune indexes in CC group were below ND group and the clinical efficacy was above ND group (P<0.05). No obvious differences were found in the BGP levels, adverse reaction rates and recurrence rates of both groups was (P>0.05). **Conclusion**: Both have some efficacy in the treatment of dysmenorrhoea and compound oral contraceptives were found to be more effective, which is worth promoting their use in the clinic.

Keywords: Compound oral contraceptives; Clinical efficacy; Dysmenorrhea; Immunization; Non-steroidal anti-inflammatory drugs

Submitted on 16-04-2025 – Revised on 03-07-2025 – Accepted on 20-11-2025

INTRODUCTION

Dysmenorrhea is categorized into primary dysmenorrhea and secondary dysmenorrhea (Ferries Rowe *et al.*, 2020). According to a survey, close to 80% of women worldwide suffer from different degrees of dysmenorrhea and the incidence of primary dysmenorrhea in adolescent girls continues to grow to 69%-84%, which has a great impact on the quality of life and work (Gutman *et al.*, 2022). Primary is dysmenorrhea without organic lesions of the reproductive organs, 1-2 years after menarche in the pre-menstrual or menstrual dysmenorrhea appeared in the lower abdomen pain, swelling, accompanied by lumbago or other discomfort, the symptoms of severe cases or even vomiting, fainting and so on. In clinical practice, primary dysmenorrhea refers to menstrual pain not accompanied by pelvic diseases, which is mainly concentrated in the lower abdomen, mostly in unmarried women, with a high incidence and a certain impact on daily work and life (Fitrianingsih and Santanu, 2021). Primary dysmenorrhea is mainly due to abnormal contraction of uterine smooth muscle caused by excessive increase in endometrial synthesis and secretion of prostaglandins during menstruation, resulting in elevated uterine pressure and ischemia and hypoxia and partly due to uterine dysplasia or uterine cavity stenosis. Patients usually have the most intense pain on the first day of menstruation, which is mostly cramping pain, often accompanied by nausea, vomiting and fatigue and usually lasts for 2 - 3 days before gradually relieving (Karout *et al.*, 2021).

Secondary dysmenorrhea refers to dysmenorrhea that occurs gradually after the first few years of menstruation. Unlike primary dysmenorrhea, it is caused by organic pelvic diseases (uterine fibroids, endometriosis and chronic pelvic inflammatory disease, etc.) and is often accompanied by abdominal distension, lower abdominal cramps and traction pains (Barbosa-Silva *et al.*, 2024). In endometriosis, for example, the endometrial cells, which are supposed to grow inside the uterine cavity, are ectopic outside the uterine cavity and they also bleed during the menstrual cycle, irritating the surrounding tissues and triggering pain, which tends to worsen with the progression of the disease (Martire *et al.*, 2023). In patients with adenomyosis, the ectopic endometrial glands within the myometrium are congested and bleed, resulting in increased pressure within the uterus and progressively worsening dysmenorrhea, which is often accompanied by increased menstrual flow and prolonged menstrual periods (Krzemińska *et al.*, 2024). Dysmenorrhea caused by pelvic inflammatory diseases is mostly characterized by lower abdominal swelling and pain, which is aggravated before

**Corresponding author:* e-mail: XuHF188@163.com
#Co-first authors

and after menstruation, after exertion or sexual intercourse and may be accompanied by leukorrhea abnormalities and menstrual disorders. Secondary dysmenorrhea tends to be more severe and prolonged, with progressive worsening of symptoms. Some patients may have menstrual abnormalities, such as increased menstrual flow and prolonged menstrual periods (McKenna and Fogleman, 2021).

Common medications used to treat dysmenorrhea include oral contraceptives, nonsteroidal anti-inflammatory drugs (NSAIDs) and other medications (Itani *et al.*, 2022). Oral contraceptives such as drospirenone ethinyl estradiol tablets and ethinyl estradiol cyproterone tablets are effective in inhibiting ovulation and endometrial growth by suppressing the hypothalamo-pituitary-ovarian axis and lowering the levels of prostaglandins and pressor hormones, so as to minimize the painful and uncomfortable menstrual reactions. However, this class of drugs is taken for a long time in the treatment of dysmenorrhea and adverse reactions such as early pregnancy-like reactions, decreased menstrual flow or even menopause and weight gain have been observed after taking the drugs (Schroll *et al.*, 2023). NSAIDs refer to non-steroidal drugs with anti-inflammatory, analgesic and antipyretic effects, which are commonly used in gynecology or surgery to reduce or control dysmenorrhea caused by inflammation, postoperative pain, joint or soft tissue pain, etc. NSAIDs reduce prostaglandin synthesis by inhibiting the enzyme cyclooxygenase (COX), which relieves spasmodic uterine contractions induced by prostaglandins and results in a reduction of painful symptoms (Nie *et al.*, 2020). NSAIDs include ibuprofen, celecoxib capsules and diclofenac, etc. The mechanism of action is to inhibit the activity of prostaglandin synthase in the endometrial cells and reduce prostaglandin synthesis, which in turn prevents the uterine smooth muscle from over-contracting and spasming and achieves the effect of reducing or eliminating dysmenorrhea. However, such drugs cannot prevent the progression of the disease and may cause side effects such as gastrointestinal discomfort and dizziness (Lin *et al.*, 2021). In addition, non-pharmacological treatments used to alleviate the symptoms of dysmenorrhea include acupuncture, acupressure and transcutaneous electrical stimulation of acupoints, etc. Acupuncture and moxibustion can regulate the operation of qi and blood, stimulate the function of meridian qi and blood and relieve pain. The shortcoming of Chinese medicine in treating dysmenorrhea is that the taste of Chinese herbal soup is poor and many patients find it difficult to insist on taking it on time, which affects the therapeutic effect. Moreover, the treatment cycle of Traditional Chinese Medicine is relatively long, unlike some western medicines that can relieve pain quickly. For example, for acute attacks of dysmenorrhea, the slow onset of action of Chinese medicines does not provide timely relief of patients' pain (Cortes *et al.*, 2023).

Therefore, although the use of NSAIDs and combined oral contraceptives in the treatment of dysmenorrhoea has been widely investigated, most of the existing studies focus on single efficacy comparisons or monitoring of single biochemical indexes and lack a systematic analysis of the "sex hormone-immunity-inflammation" network. In this study, we innovatively monitored the dynamic changes of CA125, osteocalcin (BGP) and immune indicators ($CD4^+/CD8^+$) simultaneously with multicentre clinical data to reveal the differences in the effects of the two classes of drugs at the level of multiple biomarkers. The long-term efficacy and bone safety of ethinyl estradiol cyproterone tablets and celecoxib capsules in young women were compared and the comprehensive evaluation of pain scores, recurrence rates and multi-system indexes provided a certain basis for the clinical differentiation of the treatment of 'short-term analgesia-long-term regulation of menstruation'.

MATERIALS AND METHODS

Study design and participants

The present study is a systematic evaluation and integration aimed at comparatively analyzing the clinical efficacy of combined oral contraceptives and NSAIDs in the treatment of patients with dysmenorrhea and further evaluating their effects on patients' pain profiles and sex hormone profiles. This study was a retrospective study and 120 patients with dysmenorrhea admitted from October 2020 to December 2023 were selected and divided into two groups, the CC group and the ND group, according to the different interventions. The flow chart of this study is shown in Fig. 1.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients who met the diagnostic criteria for dysmenorrhea and were admitted to the hospital after pathological examination to determine the absence of complications (Wang *et al.*, 2023); (2) Patients had not taken hormone-containing drugs within six months of treatment; (3) Age 21-50 years; (4) Patients without other gynecological diseases; (5) Patients with good compliance and willingness to cooperate with the treatment program developed by the study; (6) Patients with good overall mental status and basic physical health, who can truthfully express their complaints about symptoms and answer relevant questions from healthcare professionals; (7) Those who can tolerate the drugs involved in this study; (8) The patients and their families are informed and agreeable and sign an informed consent form.

Exclusion criteria: (1) Any site or type of malignant tumor, such as gynecological malignant tumors; (2) Patients with combined hemorrhagic and coagulation disorders, or severe liver or renal function defects, severe cardiovascular disease, or other more serious gynecological endocrine diseases; (3) Combined chronic infectious diseases.

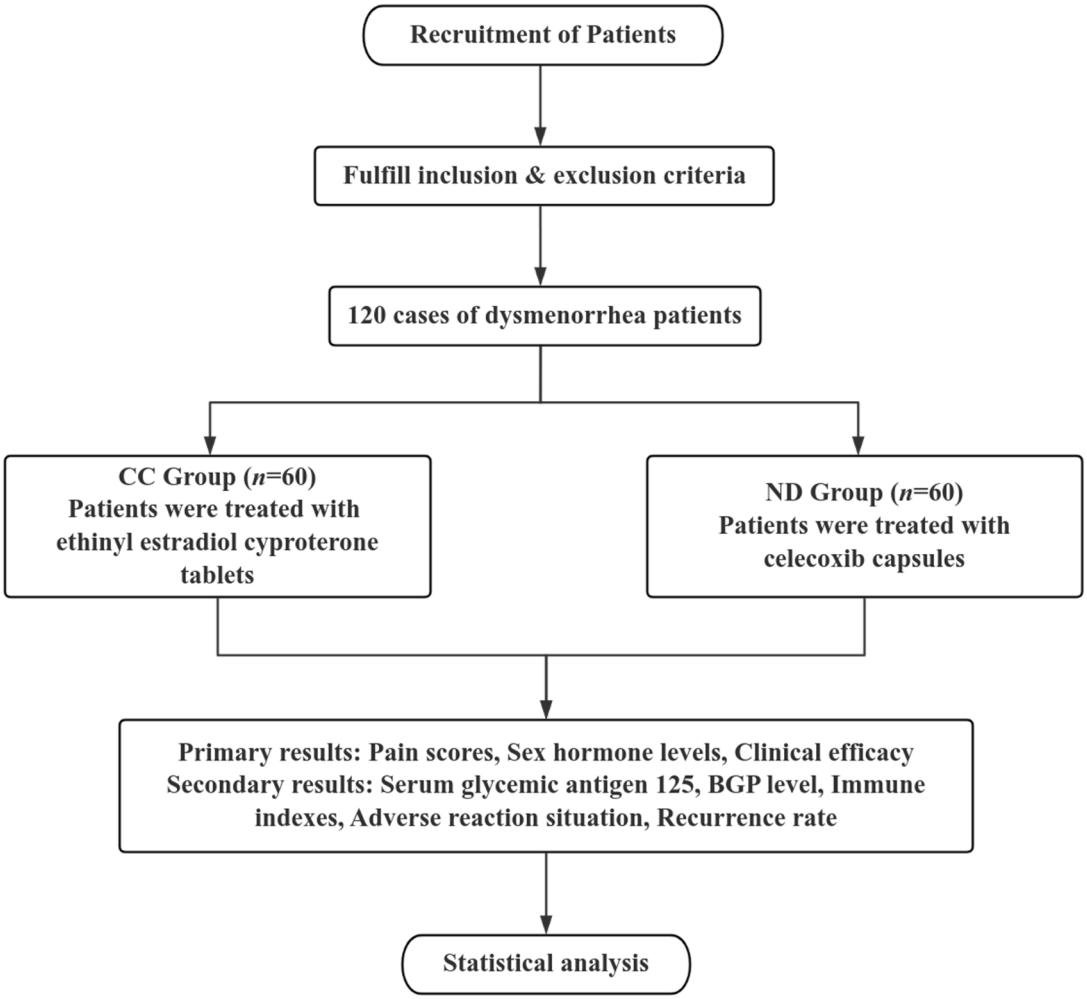

Fig. 1: Flow chart

(4) Patients with abnormal lipid metabolism, venous or arterial thrombosis, or hypertension; (5) Patients who have participated in clinical drug trials or clinical studies; (6) Patients with comorbid neurological or psychiatric disorders that make it difficult to communicate normally; (7) Requesting to stop treatment or automatic discharge for personal reasons; (8) Patients with a combination of other medical conditions; (9) Mental illness; (10) Those who are allergic to the drugs used in this study; (11) Other conditions that, in the opinion of the study physician, should not be included; (12) Other conditions affecting the indicators of follow-up observation.

Interventions

The CC group was given ethinyl estradiol cyproterone tablets. Ethinylestradiol cyproterone tablets (Dayin-35, manufactured by Bayer Weimar GmbH und Co. KG, batch no. 160 B, cyproterone acetate 2 mg & ethinylestradiol 0. 035 mg/tablet) were taken as 1 tablet per day starting from the first day of menstruation for 21 consecutive days, followed by 7 day of discontinuation, which constituted a complete cycle of treatment. The next cycle begins on day 8 of withdrawal and continues with 1 tablet daily for 21 day and so on. A total of 3 cycles. The ND group was given celecoxib capsules. Celecoxib capsule (Qingdao Baiyang Pharmaceutical Co., Ltd., State Pharmaceutical License H20203325), 0.2 g was taken orally at the onset of menstruation and at the beginning of dysmenorrhea and if the symptoms were not relieved, an additional 0.2 g could be taken after 12 h. The maximum daily dose should not exceed 0.4 g. The maximum daily dose should not exceed 0.4 g. It should be taken as needed on the days when dysmenorrhea occurs and should not be taken for more than 3-5 consecutive days, which is one cycle, for a total of 3 cycles.

Observational indicators

Primary indicators

Pain scoring

Pain visual analog score (VAS) was used to evaluate dysmenorrhea as well as painful intercourse and pelvic pain at the first menstrual period before medication and after stopping medication (Bielewicz *et al.*, 2022). It was counted as 0 ~ 10 scores, 1 ~ 3 as mild pain, 4 ~ 7 as moderate pain and >7 ~ 10 as severe pain.

Sex hormone measurement
The levels of follicular estrogen (FSH), luteinizing hormone (LH) and estradiol (E2) were measured by radioimmunoassay (Targonskaya and Maslowski, 2023).

Clinical efficacy
The evaluation of efficacy at the end of the treatment program was based on the VAS scores of dysmenorrhea, sexual intercourse and pelvic pain. Obvious effect: >65% decrease; effective: 33% ~ 65% decrease; ineffective: <33% decrease. Overall effective rate = significant rate + improvement rate.

Secondary indicators
Determination of cancer antigen 125 (CA125)
Before and after treatment, 3 mL of fasting venous blood was drawn from the patients, centrifuged and kept refrigerated for testing. Serum CA125 levels were determined by chemiluminescence immunoassay in each group of patients before and after drug administration (Charkhchi *et al.*, 2020).

Serum osteocalcin (BGP) level
Serum BGP levels were determined by enzyme-linked immunosorbent assay (ELISA) before and after treatment in each group of patients (Zhou *et al.*, 2020). The kit used was a human BGP ELISA kit (ml058528, Shanghai Enzyme-linked Biotechnology Co., Ltd.).

Immunity indexes
Immunity indexes were observed in the two groups of patients and the levels of immunity indexes in peripheral blood samples were measured using enzyme-linked immunosorbent assay (Aljabr *et al.*, 2022). Human $CD4^+$ T cells ELISA kit (JKbio 14552, Shanghai Jingkang Bioengineering Co., Ltd.), Human $CD8^+$ T cells ELISA kit (JKbio 14553, Shanghai Jingkang Bioengineering Co., Ltd.) were used to detect the percentage of $CD4^+$ and $CD8^+$ T cells respectively.

Adverse reaction
The occurrence of adverse reactions, including nausea/vomiting, hot flashes/sweating, headache and vaginal discomfort during treatment was recorded for both groups.

Recurrence rate
Record the recurrence rate at 12-month follow-up after the end of treatment.

Follow-up visits
This study was primarily scheduled for a 12-month post-treatment follow-up to assess the durability of the effect and to address any potential adverse reactions or problems.

Sample size calculation
Sample size was based on power analysis using G*Power 3.1.9.7 computer software to determine the sample size required to detect a statistically significant difference. The sample size was calculated based on the VAS score as the primary outcome. Considering an α level of 0.05 and 85% efficacy, we calculated that a sample size of 49 patients was required for each group. Considering the potential uncertainties, a sample size of 60 cases per group was chosen for this study and we believe that the sample size of this study is able to draw reliable conclusions.

Statistical methods
SPSS27.0 statistics software was applied for analysis of the data. Measurements that conform to normally distributed value are represented as ($\bar{x}$±s) and comparisons among groups adopts act independently pattern t examination and counting data is expressed as rate (%) using x^2 test. All statistical tests were two-sided, with P<0.05 indicating a statistical significance of the difference.

RESULTS

Basic information
In this study, 120 patients with dysmenorrhea admitted from People's Hospital of Xiaodian district between October 2020 to December 2023 were randomized to CC (n=60) and ND (n=60) groups based on different interventions. The baseline demographic and baseline characteristics of the patients in the both groups are presented in table 1 and these characteristics showed no remarkable differences among the both groups (P>0.05). Thus, the randomization process achieved the important goal of randomly assigning participants to the both groups, the both groups were comparable at the pre-treatment level and the confounding of demographic/clinical factors did not affect the analysis of the results.

Primary results
VAS score
VAS score is an important indicator to assess the degree of dysmenorrhea. The results of the VAS scores of the both groups of patients are presented in table 2. Before treatment, no obvious discrepancy was found among the scores of dysmenorrhea, sexual intercourse and pelvic pain in the both groups of patients (P>0.05). After treatment, the scores of patients in both groups were decreased remarkably (P<0.05). The scores of dysmenorrhea, sexual intercourse and pelvic pain of patients in CC group were 0.63±0.30, 0.53±0.21 and 0.54±0.29, respectively, which were obviously below the scores of 0.83±0.38, 0.98±0.30 and 0.81±0.27 in ND group (P<0.05). It indicated that both treatments could relieve pain and the CC group had a better relief effect.

Sex hormone measurement
The results of the comparison of sex hormone levels of the both groups of patients are illustrated in table 3. Before treatment, no obvious discrepancy was found in the comparison of sex hormone levels of both groups of patients (P>0.05). After treatment, the sex hormone levels of patients in both groups were obviously reduced (P<0.05).

Table 1: Patient demographics and baseline disease characteristics

Parameter	CC group (n=60)	ND group (n=60)	t/x^2	P
Age (year)	32.57±6.24	32.45±5.60	-0.111	0.912
Height (cm)	158.93±5.59	158.43±4.36	-0.546	0.586
Weight (kg)	50.24±4.75	49.95±4.43	-0.346	0.730
Body mass index (kg/m^2)	23.05±2.56	23.41±2.36	0.801	0.425
Dysmenorrhea lasting 3 d (yes/no)	50/10	49/11	0.035	0.852
Sexual history (yes/no)	19/41	20/40	0.023	0.880
Fertility (yes/no)	16/44	17/43	0.025	0.874
Family history (yes/no)	35/25	33/27	0.183	0.669
Smoking (yes/no)	26/34	25/35	0.020	0.886
Alcohol consumption (yes/no)	37/23	35/25	0.333	0.564
Temperature (°C)	36.25±0.29	36.31±0.29	1.133	0.259
Breathing (breaths/min)	17.50±2.13	17.16±2.07	-0.887	0.377
Heart rate (beat/min)	74.38±7.44	74.18±6.22	-0.160	0.873
Systolic blood pressure (mmHg)	118.37±5.82	118.61±5.25	0.237	0.813
Diastolic blood pressure (mmHg)	75.76±5.65	75.89±5.20	0.131	0.896

Table 2: VAS score ($\bar{x}$±s, score)

Norm	Time	CC group	ND group	t	P
Dysmenorrhea	Pre-treatment	5.62±1.16	5.43±1.31	-0.841	0.402
	Post-treatment	0.63±0.30*	0.83±0.38*	3.200	<0.05
Sexual intercourse pain	Pre-treatment	2.01±0.84	2.02±1.08	0.057	0.955
	Post-treatment	0.53±0.21*	0.98±0.30*	9.519	<0.001
Pelvic pain	Pre-treatment	2.52±1.56	2.46±1.56	-0.211	0.834
	Post-treatment	0.54±0.29*	0.81±0.27*	5.278	<0.001

Note: "*" represents marked discrepancy compared with pre-treatment, P<0.05.

Table 3: Measurement of sex hormones ($\bar{x}$±s)

Norm	Time	CC group	ND group	t	P
FSH/	Pre-treatment	4.93±0.31	4.97±0.29	0.730	0.467
(U/L)	Post-treatment	2.17±0.31*	3.51±0.33*	22.925	<0.001
LH/	Pre-treatment	6.52±1.19	6.56±1.12	0.190	0.850
(U/L)	Post-treatment	2.41±0.76*	3.94±1.11*	8.810	<0.001
E2/	Pre-treatment	192.23±12.49	191.89±14.27	-0.139	0.890
(pmol/L)	Post-treatment	94.59±7.80*	141.03±7.60*	33.031	<0.001

Note: "*" represents marked discrepancy compared with pre-treatment, P<0.05.

Table 4: Clinical efficacy analysis

Group	Obvious effect (n)	Effective (n)	Ineffective (n)	Total effective rate (n, %)
CC group	25	30	5	55 (91.67)
ND group	20	24	16	44 (73.33)
x^2		12.502		
P		<0.001		

Table 5: CA125 and BGP levels ($\bar{x}$±s)

Norm	Time	CC group	ND group	t	P
CA125/	Pre-treatment	61.41±16.70	61.94±20.62	0.155	0.877
(IU/L)	Post-treatment	23.12±5.49*	26.44±5.86*	3.203	<0.05
BGP/	Pre-treatment	3700.33±1506.15	3720.07±1618.25	0.069	0.945
(ng/L)	Post-treatment	3654.60±1801.57	3620.73±1906.51	-0.099	0.921

Note: "*" represents marked discrepancy compared with pre-treatment, P<0.05.

Table 6: Immune indexes ($\bar{x}$±s)

Norm	Time	CC group	ND group	*t*	*P*
$CD4^+$ T cells (%)	Pre-treatment	36.68±3.01	36.27±2.94	-0.755	0.452
	Post-treatment	25.84±2.13*	28.80±1.62*	8.568	<0.001
$CD8^+$ T cells (%)	Pre-treatment	24.31±1.96	24.06±2.08	-0.678	0.499
	Post-treatment	19.66±1.28*	21.14±1.07*	6.872	<0.001
$CD4^+/CD8^+$	Pre-treatment	1.52±0.20	1.48±0.19	-1.123	0.264
	Post-treatment	1.19±0.11*	1.28±0.14*	3.916	<0.001

Note: "*" represents marked discrepancy compared with pre-treatment, $P<0.05$.

Table 7: Occurrence of adverse reactions

	CC group	ND group	x^2	*P*
Nausea/vomiting	2 (3.33)	1 (1.67)	0.205	0.651
Hot flashes/sweating	0 (0.00)	1 (1.67)	2.020	0.155
Headache	1 (1.67)	2 (3.33)	0.205	0.651
Vaginal discomfort	0 (0.00)	1 (1.67)	2.020	0.155
Pelvic inflammatory disease	0 (0.00)	1 (1.67)	2.020	0.155
Itchy skin	1 (1.67)	2 (3.33)	0.205	0.651
Urinary tract infection	2 (3.33)	1 (1.67)	0.205	0.651
Joint pain	1 (1.67)	0 (0.00)	2.020	0.155
Overall incidence (*n*, %)	7 (11.67)	9 (15.00)	0.782	0.376

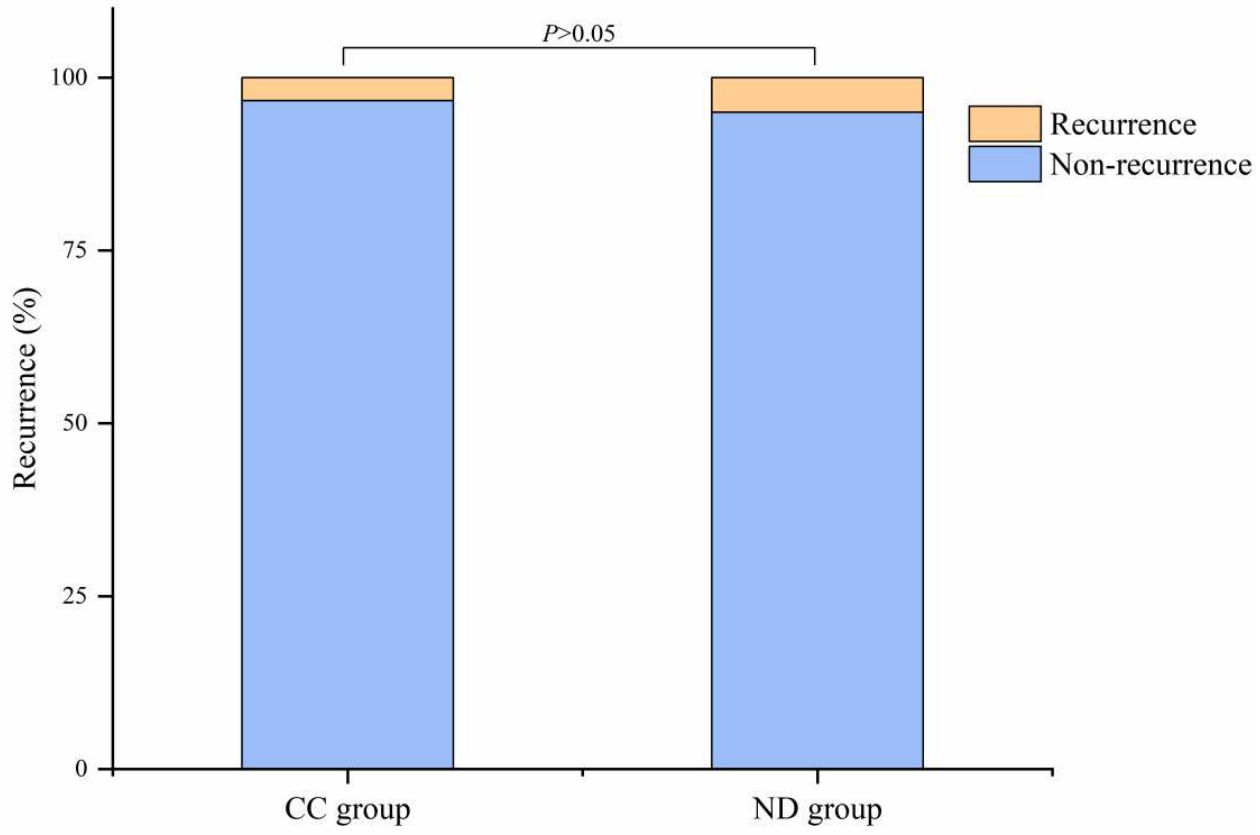

Fig. 2: Recurrence rate

The FSH, LH and E2 of patients in the CC group were 2.17±0.31 U/L, 2.41±0.76 U/L and 94.59±7.80 pmol/L, respectively, which were markedly below the ND group's 3.51±0.33 U/L, 3.94±1.11 U/L and 141.03±7.60 pmol/L ($P<0.05$). It indicated that the sex hormone levels of both groups were decreased remarkably after treatment and the CC group was better in terms of significant improvement of sex hormone levels.

Clinical efficacy

Combined with the patients' drug treatment effect, we analyzed the clinical efficacy of the both groups and the results of the analysis are presented in table 4. The total efficacy rate of CC group patients was 91.67% (55/60) and that of ND group was 73.33% (44/60), with a marked discrepancy among the groups (P<0.05). The results showed better efficacy in CC group patients, indicating that the clinical efficacy of compound oral contraceptives in the treatment of dysmenorrhea was better than NSAIDs.

Secondary results

CA125 and BGP levels

The results of the comparison of CA125 and BGP levels in the both groups are demonstrated in table 5. Before treatment, no remarkable discrepancy was found in the comparison of CA125 and BGP levels of the both groups of patients (P>0.05). After treatment, the CA125 levels of the both groups of patients were remarkably reduced (P<0.05.). The CA125 level of patients in the CC group was 23.12±5.49 IU/L markedly below the 26.44±5.86 IU/L in the ND group (P<0.05). After treatment, the BGP level of CC patients was 3654.60±1801.57 ng/L and the ND group's was 3620.73±1906.51 ng/L and no obvious differences were found in the comparison of the both groups (P>0.05). This indicates that CA125 levels were significantly reduced after treatment in patients in the CC group and no obvious discrepancy was found in the BGP level of the both groups.

Immune indexes

We analyzed and compared the results of the immune function indexes of the both groups as demonstrated in table 6. Before treatment, the comparison results of the immune function indexes of the both groups were not statistical significant (P>0.05). After treatment, the percentages of $CD4^+$ T cells, $CD8^+$ T cells and $CD4^+/CD8^+$ in CC group were 25.84±2.13%, 19.66±1.28% and 1.19±0.11 and in ND group were 28.80±1.62%, 21.14±1.07% and 1.28±0.14, respectively, all of them were obviously decreased compared with the pre-treatment (P<0.05). The changes in immunity indexes of CC group were superior to ND group (P<0.05). It indicates that the immunotherapy of both groups improved markedly after treatment and the improvement of immune function of CC group patients was more remarkable.

Adverse reactions

We followed up the patients to observe the adverse reactions. Adverse reactions of varying degrees such as nausea/vomiting during treatment in both groups are shown in table 7. The total incidence of adverse reactions in patients in the CC group was 11.67% (7/60) and in the ND group was 15.00% (9/60) and there was no marked discrepancy in the total incidence of adverse reactions among the two groups (P>0.05), indicating that no marked discrepancy was found among the two treatments in terms of adverse reactions.

Recurrence rate

We recorded the recurrence of patients in both groups during the follow-up period, as demonstrated in Fig. 2. The recurrence rate of patients in CC group was 3.33% (2/60) and that of ND group was 5.00% (3/60), with no obvious discrepancy among the both groups (P>0.05). It shows that all the treatments used in this study can effectively reduce the recurrence rate of patients after treatment.

DISCUSSION

Dysmenorrhea, as an extremely common gynecological symptom, bothers many women. According to domestic and international literature, dysmenorrhea is defined as pain and swelling in the lower abdomen, often accompanied by back pain or other discomfort, that occurs in women before, during, or after menstruation. Severe dysmenorrhea can have a significant negative impact on a woman's quality of life, work efficiency and study status (Kulkarni and Deb, 2019). Primary dysmenorrhea, which accounts for more than 90% of dysmenorrhea cases, has an unknown cause and most often begins in adolescence, often associated with overproduction of prostaglandins by the endometrium during menstruation. Excessive prostaglandins cause overly strong contraction of the uterine smooth muscle, triggering vasospasm, which in turn causes uterine ischemia and hypoxia, resulting in pain (Tataj-Puzyna *et al.*, 2021). Secondary dysmenorrhea is caused by organic pelvic diseases, such as endometriosis, which irritates the surrounding tissues and causes pain, which tends to worsen with the progression of the disease and is often accompanied by increased menstrual flow and prolonged menstrual periods (Serrahima and Martínez, 2023).

NSAIDs are commonly used in clinical practice for the treatment of dysmenorrhea relief. During women's menstruation, the endometrium synthesizes and releases prostaglandins, of which increased levels of prostaglandin F2α and prostaglandin E2 are the main cause of primary dysmenorrhea (Thakur and Pathania, 2022).

NSAIDs can inhibit the activity of COX, a key enzyme that catalyzes the conversion of arachidonic acid to prostaglandins and NSAIDs reduce prostaglandin synthesis by blocking its action, which in turn reduces the contraction and spasm of uterine smooth muscle and achieves pain relief. However, long-term use can damage the gastrointestinal tract and liver and kidneys and there are more adverse reactions, which has certain limitations (Rani *et al.*, 2024). Compound oral contraceptives were originally used as second-line drugs for the treatment of endometriosis, but with the continuous progress of research in recent years, their use in the treatment of endometriosis has been gradually emphasized. Compound oral contraceptives are estrogen and progestin compound preparations and their main mechanism of action in the treatment of endometriosis is to inhibit ovarian ovulation

through negative feedback effects, shrink the ectopic endometrium, reduce the menstrual flow and effectively relieve dysmenorrhea through the inhibition of prostaglandin synthesis (Rapisarda *et al.*, 2019). It is well documented that long-term use of oral contraceptives does not increase the incidence of genital malignancies. However, long-term use of the drug is associated with some adverse effects, such as menstrual cycle disorders, irregular vaginal bleeding, weight gain and high mood swings (Coelingh Bennink *et al.*, 2024). Therefore, both treatment modalities should be fully communicated before medication to reduce concerns and achieve the goal of increasing the controllability of treatment. Therefore, this study focuses on the treatment of pain and menstrual discomfort caused by dysmenorrhea by compound oral contraceptives and NSAIDs and compares them with clinical efficacy, observes the pain condition and sex hormone condition after treatment, with the aim of providing more references to the clinic.

The results of this study showed that after treatment, the indicators of the both groups were statistical significant as compared to pre-treatment. The scores of dysmenorrhea, sexual intercourse and pelvic pain of patients in the CC group were remarkably below the ND group (P<0.05), indicating that compound oral contraceptives were effective in reducing the level of pain. Biologically, sex hormone levels vary cyclically during a woman's menstrual cycle, with oestrogen and progesterone relieving dysmenorrhoea by regulating prostaglandin synthesis in the endometrium and inhibiting excessive uterine contractions. Compounded oral contraceptives, through exogenous supplementation of oestrogen and progesterone, can inhibit ovulation and stabilise hormone levels, thereby reducing inflammatory responses and pain signalling during endometrial shedding (Abo *et al.*, 2022). This result suggests that the reduction in sex hormone levels may alleviate dysmenorrhoea symptoms by inhibiting the activity of endometriotic foci and, in turn, relieving dysmenorrhoea. As a glycoprotein secreted by the epithelial cells of the corpus cavernosum, the level of CA125 fluctuates physiologically during the normal menstrual cycle and can be abnormally elevated due to focal stimulation in diseases such as endometriosis. In this study, the CA125 level was significantly lower in the CC group than in the ND group after treatment (P<0.05), which may be related to the inhibition of ectopic endometrial proliferation and the reduction of local inflammatory response by compound oral contraceptives. It has been shown that the level of CA125 is positively correlated with the activity of endometriosis foci and the degree of pain and the decrease in its level may reflect the atrophy of ectopic foci or the reduction of inflammation, which forms a mechanistic correlation with the results of better clinical efficacy in the CC group (Funston *et al.*, 2020). BGP is a non-collagenous protein synthesised and secreted by osteoblasts, which plays an important role in bone metabolism and physiological functions. There was no significant difference in the levels of BGP as a bone metabolism marker secreted by osteoblasts between the two treatment groups (P>0.05). It is suggested that the two treatments have less effect on bone metabolism, which is consistent with previous studies that short-term use of non-steroidal anti-inflammatory drugs (NSAIDs) or compound oral contraceptives had no significant effect on bone density (Nowicki and Jakubowska-Pietkiewicz, 2024). Wang and Zhou (2019). reported similar findings in their analysis of the efficacy of different dosing methods of compound oral contraceptives on dysmenorrhea in endometriosis.

$CD4^+$ is a key cell in the human immune system and changes in its number and function are closely associated with a variety of diseases. $CD8^+$ cells are mainly cytotoxic T cells with killing effects on virus-infected cells and tumor cells. The $CD4^+/CD8^+$ ratio is an important indicator reflecting the immunoregulatory status of the body. It has important clinical value for monitoring the development of disease and prognosis judgment (Obeagu and Chukwu, 2024). It was found that the immune indicators of patients in the CC group were lower than those in the ND group (P<0.05), which may be related to the fact that compound oral contraceptives inhibit excessive immune-inflammatory responses by regulating the balance of immune cytokines. It indicates that the use of compound oral contraceptives can ensure efficient analgesic effect while protecting cellular immunity when compared with oral NSAIDs. During the study, the adverse effects of these two drugs were nausea/vomiting and hot flashes/sweating, etc. and no marked discrepancies were found in the comparison of the total incidence of adverse reactions and the recurrence rate of the two treatment modalities. The results of the study showed that compound oral contraceptives improve dysmenorrhoea symptoms through multiple mechanisms: Inhibiting uterine contraction and ectopic lesion activity by regulating sex hormone levels, lowering CA125 levels reflecting reduced lesion inflammation and reducing local inflammatory responses through immunomodulation, which is worthy of clinical promotion and application.

This study has some limitations. The sample size was relatively small and failed to cover the different conditions of all dysmenorrheal patients, which may lead to biased findings and affect the extrapolation and reliability of the conclusions. In the design of retrospective studies, the effect of the different phases of the menstrual cycle on the levels of biomarkers such as sex hormones, CA-125, etc., was not adequately taken into account and the phase of the cycle at which the biomarkers were measured was not documented, standardised or taken into account in detail, which may have led to significant confounding of the data and compromised the validity of the results. There were differences in the patients' own underlying conditions, which may affect the generalizability of the study results.

In addition, the follow-up period was relatively short, which could not adequately assess the long-term effects and safety of the treatment. Therefore, future studies should further expand the sample size and extend the follow-up period to more comprehensively assess the efficacy and safety of combined oral contraceptives and NSAIDs in treating patients with dysmenorrhea.

CONCLUSION

This study analyzed the clinical efficacy of compound oral contraceptives and NSAIDs in treating patients with dysmenorrhea, in order to provide a new drug pathway for the treatment of this type of disease. The results showed that after treatment, all the indicators of patients in both groups improved. The pain scores, sex hormone levels, CA125 levels and immune indicators of patients in the CC group were below the ND group and the clinical efficacy was superior to the ND group. No obvious differences were found among the two groups in terms of BGP level, incidence of adverse reactions and recurrence rate. This indicates that both treatment modalities have certain efficacy in treating dysmenorrhea and the efficacy of compound oral contraceptives is significant, which can better reduce the pain level, improve the patients' sex hormone level and immune indexes and provide a new reference method for the clinical treatment of related diseases. However, the present study has a small sample size and a short course of clinical medication, failing to observe the long-term effectiveness of this method of treatment. Due to the limitation of conditions, more specific indicators such as others could not be added. Multi-center, large-sample, high-quality clinical studies can be carried out in the later stage for validation.

Acknowledgment
None

Author's contribution
Meiyi Ren, Yi Yang: Developed and planned the study, performed experiments and interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions.
Huifen Xu: Participated in collecting, assessing and interpreting the date. Made significant contributions in the interpretation and manuscript preparation.

Funding
None.

Data availability statement
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethical approval
This study was approved by the Ethics Committee of the People's Hospital of Xiaodian District (Approval No.: ZL--20240513).

Conflict of interest
The authors declare that they have no financial conflicts of interest.

Consent to participate
We secured a signed informed consent form from every participant.

REFERENCES

Abo S, Smith D, Stadt M and Layton A (2022). Modelling female physiology from head to toe: Impact of sex hormones, menstrual cycle and pregnancy. *J. Theor. Biol.,* **540**: 111074.

Aljabr W, Al Amari A, Abbas B, Karkashan A, Alamri S, Alnamnakani M and Al Qahtani A (2022). Evaluation of the levels of peripheral CD3+, CD4+ and CD8+ T cells and IgG and IgM antibodies in COVID-19 patients at different stages of infection. *Microbiol. Spectr.,* **10**(1): e00845-00821.

Barbosa-Silva J, Avila M A, de Oliveira R F, Dedicacao A C, Godoy AG, Rodrigues JC and Driusso P (2024). Prevalence, pain intensity and symptoms associated with primary dysmenorrhea: A cross-sectional study. *BMC Women's Health,* **24**(1): 92.

Bielewicz J, Daniluk B and Kamieniak P (2022). VAS and NRS, same or different? Are visual analog scale values and numerical rating scale equally viable tools for assessing patients after microdiscectomy? *Pain Res. Manag.,* **2022**(1): 5337483.

Charkhchi P, Cybulski C, Gronwald J, Wong FO, Narod S A and Akbari MR (2020). CA125 and ovarian cancer: A comprehensive review. *Cancers,* **12**(12): 3730.

Coelingh Bennink HJ, van Gennip FA, Gerrits MG, Egberts J F, Gemzell-Danielsson K and Kopp-Kallner H (2024). Health benefits of combined oral contraceptives–A narrative review. *Eur. J. Contracep. Repr.,* **29**(2): 40-52.

Cortes H, Hernandez-Parra H, Bernal-Chavez SA, Caballero-Floran IH, Aguilar-Vazquez R, Del Prado-Audelo ML, Gonzalez-Torres M, Reyes-Hernandez OD, Figueroa-Gonzalez G and Leyva-Gomez G (2023). Current status of the therapeutic approach for dysmenorrhea. *Cell. Mol. Biol.,* **69**(3): 52-63.

Ferries Rowe E, Corey E and Archer JS. (2020). Primary dysmenorrhea: Diagnosis and therapy. *Obstet. Gyneco.,* **136**(5): 1047-1058.

Fitrianingsih ADR and Santanu AM (2021). Primary dysmenorrhea risk based on characteristics, dietary habits and types of exercise. *J. Ilmu Kesehat. Masy.,* **12**(1): 21-37.

Funston G, Hamilton W, Abel G, Crosbie EJ, Rous B and Walter FM (2020). The diagnostic performance of CA125 for the detection of ovarian and non-ovarian cancer in primary care: A population-based cohort study. *PLoS Med.,* **17**(10): e1003295.

Gutman G, Nunez AT and Fisher M (2022). Dysmenorrhea in adolescents. *Curr. Prob. Pediatr. Ad.,* **52**(5): 101186.

Itani R, Soubra L, Karout S, Rahme D, Karout L and Khojah HM (2022). Primary dysmenorrhea: Pathophysiology, diagnosis and treatment updates. *Korean J. Fam. Med.,* **43**(2): 101.

Karout S, Soubra L, Rahme D, Karout L, Khojah HM and Itani R (2021). Prevalence, risk factors and management practices of primary dysmenorrhea among young females. *BMC Women's Health,* **21**: 1-14.

Krzemińska P, Kołodziej J and Biniewicz A (2024). Primary and secondary dysmenorrhea: Symptoms, risk factors, diagnosis and treatment–review. *Quality in Sport,* **21**: 53346.

Kulkarni A and Deb S. (2019). Dysmenorrhoea. *Obstet. Gynaecol. Reprod. Med.,* **29**(10): 286-291.

Lin Y, Wang J and Lin M. (2021). Stroke risk associated with NSAIDs uses in women with dysmenorrhea: A population-based cohort study. *PloS One,* **16**(11): e0259047.

Martire F G, Piccione E, Exacoustos C and Zupi E (2023). Endometriosis and adolescence: The impact of dysmenorrhea. *J. Clin. Med.,* **12**(17): 5624.

McKenna KA and Fogleman CD. (2021). Dysmenorrhea. *Am. Fam. Physician,* **104**(2): 164-170.

Nie W, Xu P, Hao C, Chen Y, Yin Y and Wang L (2020). Efficacy and safety of over-the-counter analgesics for primary dysmenorrhea: A network meta-analysis. *Medicine,* **99**(19): e19881.

Nowicki J K and Jakubowska-Pietkiewicz E (2024). Osteocalcin: Beyond bones. *Endocrinol. Metab.*, **39**(3): 399-406.

Obeagu E and Chukwu P. (2024). CD4/CD8 ratios as predictors of immune resilience in HIV: A Review. *Lifeline Immunology,* **2**(1): 23-33.

Rani V I, Dash B, Lal M N, Bagchi S, Aruna V and Prabha K S. (2024). Dysmenorrhea and recent treatment options in adolescents and young adults. *Universa. Med.,* **43**(3): 349-362.

Rapisarda A M, Brescia R, Sapia F, Valenti G, Sarpietro G, Di Gregorio L M, Della Gatta A N, La Rosa V L, Sergiampietri C and Corte L D. (2019). Combined oral contraceptive in adolescent and young adult women: Current evidence and future perspectives. *Curr. Women's Health R.,* **15**(2): 109-118.

Schroll JB, Black AY, Farquhar C and Chen I (2023). Combined oral contraceptive pill for primary dysmenorrhoea. *Cochrane Database Syst. Rev*., (7): 1-83.

Serrahima C and Martinez M (2023). The experience of dysmenorrhea. *Synthese,* **201**(5): 173.

Targonskaya A and Maslowski K. (2023). Gonadotropin and Ovarian Hormone Monitoring: Lateral flow assays for clinical decision making. *Women,* **3**(4): 471-485.

Tataj-Puzyna U, Ilczuk P, Kalita-Kurzynska K and Gotlib J. (2021). Women's experiences of dysmenorrhoea–Preliminary study. *Menopause. Rev.,* **20**(3): 133-139.

Thakur P and Pathania AR (2022). Relief of dysmenorrhea–A review of different types of pharmacological and non-pharmacological treatments. *Mater. Today,* **48**: 1157-1162.

Wang X, Zuo G, Liu J, Zhang J, Shi X, Fan X, Li X, Gao Y, Chen H and Liu C (2023). Skin temperature of acupoints in health and primary dysmenorrhea patients: A systematic review and meta-analysis. *J. Pain Res.,* **16**: 2027-2046.

Wang Y and Zhou P (2019). Curative effect analysis on different administration methods of combined oral contraceptives in the treatment of dysmenorrhea caused by endometriosis. *Anhui Med Pharm J.,* **23**(06): 1226-1230.

Zhou Z, Lin Y, Pan C, Wang N, Zhou L, Shan H, Gao Y and Yu X (2020). IL-15 deficiency alleviates steroid-induced osteonecrosis of the femoral head by impact osteoclasts via RANKL-RANK-OPG system. *Immun. Ageing,* **17**: 1-9.