Original Research Paper

Volume - 12 | Issue - 11 | November - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Obstetrics & Gynaecology

A PROSPECTIVE OBSERVATIONAL STUDY TO EVALUATE EFFICACY AND SAFETY OF 2 DOSES OF DIENOGEST (2MG VERSUS 4 MG) IN TREATMENT OF ENDOMETRIOSIS

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ABSTRACT **Background:** Endometriosis is a chronic, estrogen-dependent disease that affects 10–15% of women during their reproductive years. Dienogest is a selective progestin that uniquely combines the pharmacological properties of 19-norprogestins and progesterone derivatives, offering a pronounced local effect on endometrial tissue16. It reduces endometriotic lesion by creating a local progesteronic environment, while only moderately suppressing systemic estrogenic levels17.**Aim and Objectives:** The present study compares the efficacy and safety of dienogest at 2mg/day and 4 mg/day over 24 weeks, with the aim to define the lowest effective dose in the treatment of endometriosis. **Material and Methods: Study Area:** Patients attending Gynaecological OPD of M.R. Bangur Hospital, Kolkata between their menarche and menopause, with signs and symptoms of Endometriosis. **Study Period:** February 2020 to July 2021 (18 months). **Study design:** Parallel group, Prospective observational study. **Inclusion criteria:** Women aged 20-45 years experiencing de novo or recurrent pain associated with endometriosis or menorrhagia. **Study group:** Group A = 50 patients (administered with dienogest 2 mg once a day orally), Group B = 50 patients (administered with dienogest 4 mg once a day orally) **Results:** Spotting was observed at the beginning among 3(6%) in Group A and 3(6%) in group B, at 12 weeks among 2(4%) in group A and 2(4%) in group B, at 24 weeks among 2(4%) in group A and 3(6%) in group B. 3(6%) women in Group A and 13(26%) women in Group B had headache after treatment. Headache after treatment in Group B was significantly higher than Group A(p-value 0.006). 3(6%) women in Group A and 10(20%) women in Group B had weight gain after treatment. Weight gain in Group B was significantly higher than Group A(p-value 0.037). 2(4%) women in Group A and 13(26%) women in Group B had decreased libido after treatment. Decreased libido after treatment in Group B was significantly higher than Group A(p-value 0.002). **Conclusion:** We recommend 2 mg dienogest as most effective dose for relief of symptoms in endometriosis and with a greater tolerability than 4 mg.

KEYWORDS : Endometriosis, Dienogest 2mg vs 4mg, treatment of endometriosis.

INTRODUCTION

Endometriosis is a chronic, estrogen-dependent disease that affects 10–15% of women during their reproductive years and is defined by the presence of endometrial-like tissue outside the uterus cavity that induces chronic inflammation, ovarian cyst formation, and fibrosis[1,2].

The etiology of endometriosis is complex and indeed still poorly understood. Various theories have been postulated, such as menstrual blood regurgitation, persistent Müllerian duct abnormality, and coelomic metaplasia[3]. The most commonly accepted theory regarding the origin of endometriosis was first postulated by Sampson in 1927. In his work, Sampson described the elements generally present in this condition: retrograde menstruation, viable cells within retrograde menstruation, and the implantation of viable endometrial tissue within the peritoneum[4]. Retrograde menstruation is the backflow of menstrual blood into the peritoneal cavity through the fallopian tubes. Interestingly, retrograde menstruation is not a unique phenomenon to endometriosis and occurs in most women[5]. Normally, the immune system will eliminate these cells, preventing their implantation in the peritoneal cavity.

Inflammation is now accepted as central in the development and progression of the disease, characterized by an overproduction of inflammatory mediators, such as prostaglandins, metalloproteinases, cytokines, and chemokines[6]. In fact, investigation of the expression of inflammatory cytokines in peritoneal fluid of women with endometriosis has suggested that interleukin (IL)-17A and IL-2 are involved in inflammatory processes underlying endometriosis[7]. Moreover, reactive oxygen species and free radicals may lead to the growth and adhesion of endometrial cells in the peritoneal cavity and thereby disease onset[6].

Typical symptoms of endometriosis include pelvic pain, dysmenorrhea, dyspareunia, premenstrual pain, and lower back pain[8]. These symptoms characteristically impact adversely on physical, mental, and social well-being.

From a woman's perspective, the primary aim of treatment is to reduce the painful symptoms of endometriosis. Nonspecific medical therapies include nonsteroidal anti-inflammatory drugs, which offer short-term analgesia; combined oral contraceptives, which are off label in endometriosis; and more specific therapies producing a hypoestrogenic environment, such as gonadotropin-releasing hormone (GnRH) agonists, androgens (i.e., danazol), and progestins[9,10,11]. No current treatment options can be considered ideal, in part because of their adverse event profiles. For example, danazol may cause undesirable androgenic effects and adverse lipid changes[12], and GnRH agonists in the absence of “add-back” therapy produce a hypoestrogenic state, elevating the risk of bone loss that limits long-term use[13]. Progestins provide effective control of the symptoms of endometriosis, combined with a generally good tolerability profile[14]. The tolerability of progestins is, however, dose dependent and therefore the lowest effective dose should be established for each compound[15].

Dienogest is a selective progestin that uniquely combines the pharmacological properties of 19-norprogestins and progesterone derivatives, offering a pronounced local effect on endometrial tissue[16]. It reduces endometriotic lesion by creating a local progesteronic environment, while only moderately suppressing systemic estrogenic levels[17].

The present study compares the efficacy and safety of dienogest at 2mg/day and 4 mg/day over 24 weeks, with the aim to define the lowest effective dose in the treatment of endometriosis.

AIM & OBJECTIVES:

Primary objectives:

2mg and 4 mg doses will be compared with respect to following symptoms:

1) To study improvement in dysmennorhea in endometriosis from baseline to study end measured on VAS (Visual Analogue Scale) ,a validated measure of endometriosis related pain.

2) To study reduction in pelvic pain.
3) Effect on bleeding patterns.

Secondary objectives:
1) To compare improvement in overall quality of life using questionnaire.
2) Comparison of adverse effects between two doses like headache, weight gain, loss of libido, alopecia, acne.

MATERIALS & METHODS:
Study Area: Patients attending Gynaecological OPD of M.R. Bangur Hospital, Kolkata between their menarche and menopause, with signs and symptoms of Endometriosis.

Study Period: February 2020 to July 2021 (18 months).

Study design: Parallel group, Prospective observational study.

Aim of Treatment: To relieve symptoms with optimum possible dose.

Parameters studied:
1) Endometriosis associated pain assessed by VAS score every 12 weeks for 24 weeks
2) Uterine bleeding pattern assessed over 24 weeks period, women documented presence and intensity of bleeding on daily cards from which the frequency and duration of bleeding events were calculated.
3) Safety variables like tolerability, assessed by directly questioning women on incidences of adverse events commonly associated with endometriosis and hormonal therapy like nausea, vomiting, bloated feeling, headache, depression, acne, hirsuitism, etc.

Inclusion criteria:
Women aged 20-45 years experiencing de novo or recurrent pain associated with endometriosis or menorrhagia.
Exclusion criteria:
1) Contraindications to progestins
2) Severe metabolic diseases
3) Known alcohol or drug abuse
4) Pregnancy
5) Concurrent treatment with other hormonal preparations

Sample Size: 100 patients

Study group:
Group A = 50 patients (administered with dienogest 2 mg once a day orally)
Group B = 50 patients (administered with dienogest 4 mg once a day orally)

Statistical analysis:
For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 27.0. and Graph Pad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. p-value $\leq$ 0.05 was considered for statistically significant.

METHODOLOGY:
Laboratory Investigations:
Routine blood investigations (including): Complete blood count, ABO grouping and RH typing, HbsAg, VDRL, ICTC, Thalessemia screening, FBS/PPBS, Thyroid profile(TotalT4,FT4,TSH) .

Procedure and Intervention:
1) Case Selection
2) History taking of patient in details with clinical examination according to a predesigned proforma and questionnaire
3) Arriving at a Provisional Diagnosis
4) Randomisation into two groups – by lottery system
5) Administering 2 mg daily dose in Group A and 4mg to Group B.
6) Monitoring and recording of the following parameters:
i) Pain intensity by VAS - at the beginning, 12 weeks and 24 weeks
ii) Pelvic pain at 24 weeks
iii) Bleeding pattern - at the beginning, 12 weeks and 24 weeks.
iv) Physical health score – at the beginning, 12 weeks and 24 weeks
v) Any headache / weight gain / decrease in libido / acne / alopecia after therapy
7) Master chart preparation with all the recorded data and analysis of the results
8) Arriving to a conclusion

RESULTS & ANALYSIS:
The mean age(Mean±SD) of patients in Group A was 27.56±3.40 years while mean age of patients in Group B was 27.18±2.97 years. Difference of mean age in two groups was not statistically significant(p-value 0.553).

Mean weight in Group A and Group B was 56.54±5.73 kg and 57±5.73 kg respectively. There was no significant difference in mean weight of two groups(p-value 0.626).

Mean height in Group A and Group B was 152.12 ± 4.92 cm and 153.70 ± 5.54 cm respectively. There was no significant difference in mean height of two groups (p-value 0.135).

Mean BMI in Group A and Group B was 24.8 ± 2.43 kg/m^2 and 24.2 ± 3.33 kg/m^2 respectively. There was no significant difference in mean BMI of two groups (p-value 0.316).

Mean heart rate in Group A and Group B was 79.90 ± 7.21 /min and 78.66 ± 5.53 /min respectively. There was no significant difference in mean heart rate of two groups (p-value 0.337).

Mean arterial pressure in Group A and Group B was 92.07 ± 8.64 mm of Hg and 92.02 ± 6.81 mm of Hg respectively. There was no significant difference in mean arterial pressure of two groups (p-value 0.975).

Mean VAS at the beginning in Group A and Group B was 73.7±13.0 mm and 71.7±14.8 mm respectively(p-value 0.485). Mean VAS at 12 weeks follow-up in Group A and Group B was 46.8±18.6 mm and 46.7±15.1 mm respectively(p-value 0.991). Mean VAS at 24 weeks follow-up in Group A and Group B was 31.0±10.1 mm and 32.28±8.64 mm respectively(p-value 0.497). There was no significant difference in mean VAS among two groups.

At 24 weeks follow-up, there was Mild pelvic pain(VAS 5-44mm) in 46 patients of Group A and 45 patients of Group B. Moderate pelvic pain(VAS 45-74mm) was present in 4 patients of Group A and 5 patients of Group B. There was no patient with Severe pelvic pain(VAS 75-100mm) or absolute resolution of pain(VAS 0-4mm). There was no significant difference in pelvic pain among two groups at 24 weeks of follow-up (p-value 1.000).

Normal bleeding at the beginning was among 32(64%) in Group A and 24(48%) in Group B. Normal bleeding at 12 weeks was among 44(88%) in group A and 46(92%) in Group B. Normal bleeding at 24 weeks was among 48(96%) in group A and 47(94%) in group B. Although normal bleeding improved with drug usage there was no significant difference among the two dose groups.

Prolonged bleeding at the beginning was among 10(20%) in group A and 18(36%) in group B. Prolonged bleeding at 12 weeks was among 2(4%) in group A and 2(4%) in group B. Prolonged bleeding at 24 weeks was not seen in any of the groups. There was no significant difference among the two dose groups.

Irregular bleeding was observed at the beginning in 5(10%) in group A and 5(10%) in group B, at 12 weeks in 2(4%) in group A and 0% in group B. At 24 weeks no irregular bleeding was observed among the two groups. This was also comparable among the two groups.

Spotting was observed at the beginning among 3(6%) in Group A and 3(6%) in group B, at 12 weeks among 2(4%) in group A and 2(4%) in group B, at 24 weeks among 2(4%) in group A and 3(6%) in group B. Statistically it was insignificant but there was slightly more spotting at 24 weeks with 4mg dose.

There was no significant difference in bleeding patten in the beginning(p-value= 0.313), at 12 weeks(p-value= 0.696) and at 24 weeks(p-value= 0.681).

Mean physical health score at the beginning was 43.6±5.57 in Group A and 42.66±6.35 in Group B, at 12 weeks follow-up was 52.22±4.22 in Group A and 52.34 ± 3.66 in Group B, at 24 weeks follow-up was

56.46±3.15 in Group A and 56.64±2.42 in Group B. There was no significant difference in mean physical health score among two groups.

3(6%) women in Group A and 13(26%) women in Group B had headache after treatment. Headache after treatment in Group B was significantly higher than Group A(p-value 0.006).

3(6%) women in Group A and 10(20%) women in Group B had weight gain after treatment. Weight gain in Group B was significantly higher than Group A(p-value 0.037).

2(4%) women in Group A and 13(26%) women in Group B had decreased libido after treatment. Decreased libido after treatment in Group B was significantly higher than Group A(p-value 0.002).

1(2%) women in Group A and 6(12%) women in Group B had developed acne after treatment. There was no significant difference in development of acne among two groups(p-value 0.05).

1(2%) women in Group A and 4(8%) women in Group B had developed alopecia after treatment. There was no significant difference in development of alopecia among two groups(p-value 0.168).

DISCUSSION

Progestins are used as first-line therapy for treatment of endometriosis. They show an antigonadotropic effect, which inhibits ovarian function and creates a hypoestrogenic environment. By directly acting on endometrial progesterone receptors, they induce decidualization of the endometriotic lesion. They also have been shown to reduce peritoneal inflammation.

Our study demonstrated that both the groups were comparable in reduction of pelvic pain in endometriosis but this difference was statistically insignificant giving an impression that both 2mg and 4 mg lead to comparable pain reduction but still 4mg cannot be said to optimum dose as there was greater association of side effects in this group. This finding is of high clinical relevance as pelvic pain is one of the most important symptom of endometriosis. In Kohler et al[18] study Dienogest 2 and 4 mg/day both improved symptoms in substantial proportions of women. Both doses were well tolerated, with low rates of treatment discontinuation due to adverse events.

In this study, before starting the therapy, association of bleeding pattern in two groups was not statistically significant. Change in bleeding Pattern at 12 weeks in two groups was statistically insignificant. Change in bleeding pattern at 24 weeks in two groups was statistically insignificant. So they were comparable. Among 4 mg group most common problem was spotting as complained by these patients thereby showing a better safety profile of 2 mg dose as compared to 4 mg. In a study by Strowitzki et al[19] the bleeding pattern associated with dienogest 2 mg was well tolerated, and only 2(0.6%) women reported bleeding events as the primary reason for premature discontinuation.

In this study, in quality of life analysis, the physical health score improvements in both the groups were comparable. In a study by Caruso et al[20] the progressive reduction of the pain syndrome reported by women over the treatment period could contribute to improve the QoL and sexual life of women on dienogest.

As far side effects were concerned, in this study 26% women in 4mg group had headache after treatment as compared to 6% women, which was significant. Headache after treatment in Group B was significantly higher than Group A. 20% women in 4 mg group had weight gain, while in 2 mg it was just 6%. Weight gain in Group B was significantly higher than Group A. Decreased libido was reported in 26 % women in 4 mg group as compared to 4% women in 2mg group. Decreased libido after treatment in Group B was significantly higher than Group A. There were no significant difference in the development of acne and alopecia among the two groups. Strowitzki et al[19] study showed the most common adverse drug reactions were headache, breast discomfort, depressed mood, and acne, each occurring in <10% of women. All these adverse events were generally of mild-to-moderate intensity and associated with low discontinuation rates.

CONCLUSION

In our study we have evaluated the minimal dose required to relieve the symptoms of endometriosis along with considering the related side effects. This treatment is very effective for young patients who are willing to conserve fertility and not inclined to undergo surgery. It is first kind of study in our population. We recommend 2 mg dienogest as most effective dose for relief of symptoms in endometriosis and with a greater tolerability than 4 mg.

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