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Comparison of Efficacy and Safety between Dienogest and Danazol in Women with Endometriosis

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Abstract **Original Research Article**

Background: Endometriosis is a common gynecologic disease associated with a significant burden on women's health and healthcare systems. Currently approved hormonal treatments for Endometriosis can effectively control symptoms but may have clinically relevant side effects that limit their use. ***Objective:*** This study aimed to compare the Efficacy and safety of commonly used drugs dienogest and danazol in patients with Endometriosis. ***Methods and Material:*** This randomized clinical trial was conducted at the department of Obst and Gynae in Rajshahi Medical College Hospital from June 2020 to May 2021. A total of 100 diagnosed cases of Endometriosis were included in this study according to inclusion and exclusion criteria. The study population was divided into two groups randomly by flipping a coin; group A is the dienogest group (experimental group), and group B is the danazol group (control group). Informed written consent was obtained from all cases. Patients were followed up after 3 months of treatment following a standard management plan. After data collection, data analysis was done using SPSS version 23. ***Result:*** Mean age of the study patients was 28.72±4.71 (SD) years in group A and 29.52±5.23 (SD) years in group B patients with a majority in the age group 26-30 years. Age and other socio-demographic variables were statistically similar in both groups. Symptomatic improvement was observed with statistical significance in both groups regarding visual analog scale (VAS) pain score and severity of dyspareunia and bleeding pattern according to pictorial blood loss assessment chart (PBAC) score ($p<.05$). But post-treatment VAS pain score and severity of dyspareunia and bleeding pattern was similar in both groups ($p>.05$). Pre-treatment size of ovarian endometrioma was 4.02±0.227 cm (SD) in group A patients and 3.98±0.212 cm (SD) in group B patients. After treatment, ovarian endometrioma significantly ($p<.05$) reduced to 1.33±0.698 cm (SD) in group A and 1.47±0.967 cm (SD) in group B. But post-treatment size of endometrioma was similar in both groups ($p>.05$). Pre-treatment CA-125 level was 70.50±7.16 U/mL (SD) in group A patients and 65.85±6.10 U/mL (SD) in group B patients & significantly ($p<0.05$) reduced in both groups. Adverse events including hot flush, joint pain, vaginal dryness, decreased libido, and sleep disorder were significantly higher in patients who received Danazol (group B). ***Conclusion:*** This study demonstrated similar Efficacy of dienogest and danazol in patients with Endometriosis. A higher frequency of adverse events was observed in patients receiving danazol. Still, larger trials are recommended.

Keywords: Dienogest, Endometriosis, Progestins, Long-Term Treatment, Quality of Life, Symptoms, Pain.

INTRODUCTION

Endometriosis is a chronic, estrogen-dependent disease that affects approximately 10% of women of reproductive age, with a peak incidence in the age range of 25– 30 years [1]. Endometriosis is characterized by the formation of endometriotic lesions outside the uterus, including the ovaries and other pelvic structures. These lesions cause a chronic, inflammatory reaction, which can form scar tissue and adhesions [2]. Women with Endometriosis frequently experience symptoms of dysmenorrhea, premenstrual pain, dyspareunia, and chronic fatigue [3]. Endometriosis can also interfere with bowel or bladder functioning, depending on where endometriotic lesions develop. Up to 50% of women with endometriosis experience infertility [4]. However, the clinical presentations of Endometriosis can vary widely, and many affected women are asymptomatic [5]. Quality of life studies show that symptoms of Endometriosis

impact many aspects of a woman's life, including work and education, relationships, social functioning, and mental health.

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. No current treatment options can be considered ideal, in part because of their adverse event profiles [6].

Danazol is an androgen, a synthetic isoxazole derivative related chemically to 17- ethinyl testosterone. Danazol has a complex mechanism of action. The effects of danazol are due to its inherent androgenic properties and its ability to increase free testosterone concentration by binding to sex hormone binding globulin (the concentration of which is decreased by danazol) and thereby displacing testosterone [7]. Furthermore, danazol inhibits steroid production from the ovary, decreasing ovarian estrogen production. In addition, danazol interferes with follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion by the pituitary. Danazol also has a specific inhibitory effect on endometrial growth. Thus, the Efficacy of danazol is based on its ability to produce a high androgen / low estrogen environment (pseudo menopause) which results in the atrophy of endometriotic implants and thus an improvement in painful symptoms [8].

On the other hand, dienogest is a 19-nortestosterone derivative progestogen that is highly selective for progesterone receptors while demonstrating only negligible binding for estrogen, androgen, glucocorticoid, and mineralocorticoid receptors [9]. Furthermore, dienogest does not cause metabolic imbalance, and treatment with dienogest can be prescribed as a continuous regimen. Evidence has supported dienogest's comparable Efficacy with GnRH agonists in controlling endometriosis-associated pain symptoms [10].

However, very few studies have been done in Bangladesh to compare the Efficacy and safety of Dienogest and Danazol in women with Endometriosis. Thus, we aimed this study.

Objectives

General objectives:

- To compare the Efficacy and safety between Dienogest and Danazol for the treatment of Endometriosis.

Specific objectives:

- To assess the Efficacy and safety of Dienogest therapy
- To assess the Efficacy and safety of Danazol therapy
- To determine the socio-demographic characteristics of participants
- To compare the Efficacy and safety between Dienogest and Danazol

LITERATURE REVIEW

Endometriosis is a chronic, incurable condition that causes intense pain and subfertility in approximately 176 million women worldwide. Endometriosis is a common condition affecting 5–15% of women of reproductive age [11].

Prevalence of Endometriosis:

According to the World Bank's population figures for 2017, Endometriosis amounts to nearly 190 million women worldwide. Asymptomatic women have a prevalence of 2-11%, infertile women have a prevalence of 5 to 50%, and women treated with abdominal pain have a prevalence of 5 to 21% Endometriosis is found in 49% of symptomatic adolescents with chronic pelvic pain [12].

In the United Kingdom, Endometriosis is the second most prevalent gynecological disease. Endometriosis affects about 26 million women in India. Infertile women have a 20% to 50% chance of becoming pregnant. According to various reports, Endometriosis is diagnosed by laparoscopy in 34 to 48 percent of Indian women [13]. According to a study conducted at a tertiary referral center for Endometriosis and pelvic pain, the prevalence of Endometriosis is on the rise among women of East and South East Asian origin, and the incidence rate of endometrioma on ultrasonography is also on the rise. In comparison to Caucasians and other ethnicities, 82.9% of East/South East Asian women had extreme Endometriosis [14].

Treatment:

Regulation of symptoms, prevention of further disease development, and maintenance of fertility are the three specific goals of therapy in Endometriosis [15].

Surgical intervention:

Excision or ablation of Endometriosis, drainage/sclerosis/excision of endometriomas, presacral neurectomy or uterosacral nerve ablation, excision of bowel implants, and hysterectomy with or without oophorectomy are among the surgical treatments available. Surgical treatment aims to halt disease development, restore normal anatomy, and prevent a recurrence. Surgical surgery is indicated for failed medicinal therapy, chronic adnexal mass, additional pelvic organ dysfunction such as blockage of the

bladder or intestine, and the requirement for a definite diagnosis.

Drug Therapy

Nonsteroidal anti-inflammatory medications, GnRH agonists, progestins, and oral contraceptive pills are popular treatment choices for reducing pain and disease stress [12]. Danazol, a synthetic androgen that is the 2,3- isoxazole analog of 17-ethynyl T, has been used to treat Endometriosis. The use of progestins in the treatment of Endometriosis is dependent on the inhibition of the hypothalamic-pituitary-ovarian axis, which results in anovulation, lower serum estrogen levels, atrophy of ectopic endometrium and endometriotic lesions, and lower peritoneal inflammatory markers, as well as modulating the immune response involved in endometriosis pathogenesis. Dienogest (DNG) is a fourth-generation selective progestin that incorporates the pharmacological properties of 19-nortestosterone and progesterone derivatives to have a strong local impact on endometriotic lesions while exhibiting little androgenic, estrogenic, glucocorticoid, or mineralocorticoid activity [10].

Mode of action of Dienogest (DNG):

Dienogest has been shown in studies to have anovulatory and antiproliferative effects and inhibit cytokine release in the stroma of endometrial cells. Many doctors believe the medical treatment for Endometriosis should be observational, whether before or after laparoscopic validation. Dienogest attaches to the progesterone receptor with high sensitivity, resulting in a strong progestogenic activity due to the high levels of the unbound molecule in circulation [5]. Endometriotic lesions are reduced by Dienogest by various biological pathways. Dienogest is linked to a mild inhibition of gonadotropin secretion, resulting in a small reduction in endogenous estradiol production.

Mode of action of Danazol:

Danazol binds to androgen receptors, P receptors, and glucocorticoid receptors and is clearly active at several loci. Danazol has a variety of pharmacological effects, including gonadotropin repression, competitive inhibition of steroidogenic enzymes, regulation of immunological activity, and suppression of cell proliferation. 3-hydroxysteroid dehydrogenase (3-HSD), 17-HSD, 17-hydroxylase, 17,20-lyase, 21-hydroxylase, and 11-hydroxylase were all inhibited by danazol. Danazol blocked aromatase function in granulosa cells (GC) but not in human corpus luteum (CL) microsomes [16]. Danazol's effects are due to its inherent androgenic qualities and its potential to raise free testosterone levels by binding to sex hormone binding globulin and thereby displacing testosterone. Danazol also reduces ovarian steroid activity, resulting in a reduction in ovarian estrogen production. Danazol also inhibits the pituitary's development of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Danazol also has a specific endometrial growth inhibitory function [8].

Comparison between Efficacy and safety of Dienogest (DNG) and Danazol: DNG 2 mg/day has been found in studies to be a more effective endometriosis treatment than placebo. Long-term DNG use (52–53 weeks) demonstrated the drug's applicability and effectiveness in clinically reducing endometriosis symptoms such as chronic pelvic pain [10]. Dienogest, like other 19-no progestins, is almost entirely absorbed and has a high bioavailability following oral administration. In woman volunteers given dienogest at doses of 0.5–3 mg daily, a recent pharmacokinetic analysis reported mild suppression of estradiol levels, which remained within the lower end of the normal physiological range. Dienogest at 2 mg and 4 mg daily reduced endometriotic lesions significantly, according to laparoscopy. Furthermore, each of these doses of dienogest increased patient-reported effects, such as the severity of dyspareunia, dysmenorrhea, and diffuse pelvic discomfort [5]. According to a study, the dienogest doses of 2 mg and 4 mg were usually well tolerated, with low rates of discontinuation due to adverse effects. 55.2% of those in the 2 mg group and 68.6 % of those in the 4 mg group recorded irregular uterine bleeding, with all groups showing a tendency toward less intense bleeding over time. Dienogest, at a dosage of 2 mg once daily, was prescribed as the best therapy for Endometriosis based on these findings [6].

Relevant Studies for the Comparison of Efficacy and Safety of Dienogest and Danazol in Case of Endometriosis:

Petraglia *et al.,* (2012) performed an expansion study involving 152 women with confirmed Endometriosis who had previously taken part in a study that compared DNG 2 mg/day to placebo. 168 women joined the extension trial, and 152 completed it out of the 188 who completed the placebo-controlled study. These patients were assigned to receive DNG 2 mg/daycare for 36 or 52 weeks. Both the group that had previously been treated with DNG and the group that had previously been treated with placebo reported an increase in pain after the procedure. Breast pain, nausea, and irritability were recorded by 27 of the 168 women who took part in the study. They concluded that long-term Dienogest showed a favorable efficacy and safety profile, with progressive decreases in pain and bleeding irregularities during continued treatment; the decrease of pelvic pain persisted for at least 24 weeks after treatment cessation [17].

According to Schindler *et al.,* (2011), two research programs, including dose-ranging, placebo-controlled, successful comparator-controlled, and long-term (up to 65 weeks) tests, were conducted in Europe and Japan. Dienogest 2 mg daily successfully relieves the debilitating effects of Endometriosis, decreases endometriotic lesions, and increases indices of quality

of life, according to these findings. Dienogest demonstrated a favorable safety and tolerability profile in these trials, with predictable adverse effects, high patient compliance, and low withdrawal rates [5].

According to a report by Selak *et al.,* (2007), danazol (alone or as an adjunctive treatment) was equivalent to placebo or no therapy in randomized controlled trials. Six months of danazol treatment was shown to be significantly better than placebo at relieving debilitating symptoms in the studies used. Six months after the treatment was discontinued, the difference was already visible. Danazol substantially impacts AFS ratings, CA-125 levels, and the free androgen index, among other things (FAI). Patient satisfaction was slightly higher with danazol than with placebo after six months. However, this beneficial impact may be counterbalanced because danazol has produced many side effects that were not expected [8].

METHODOLOGY

Study design: Randomized clinical trial.

Study place: Department of Obs. & Gynae, Rajshahi Medical College Hospital, Rajshahi.

Study period: 12 Months (from June 2020 to May 2021).

Study population: Women aged 18-45 years with Endometriosis who are attending in the department of Obs. & Gynae (both indoor and outdoor) in RMCH.

Sampling method: Convenient sampling.

Sample size: Sample size was determined by comparison of two means.

$$n = \frac{(Z_\alpha + Z_\beta)^2 \times (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

μ1= mean VAS score of chronic pelvic pain after treatment with Danazol is 3.06 (Rasul *et al.*, 2017).
σ1= SD of μ1 is 1.23 (Rasul *et al.*, 2017).
μ2= mean VAS score of chronic pelvic pain after treatment with Dienogest is 2.49 (Lee *et al.*, 2018).
σ2= SD of μ2 is 1.27 (Lee *et al.*, 2018).
μ1-μ2 is equivalent to effective size (d)
Zα = 1.96 at 5% level, Zβ = 0.84

$$= \frac{(1.96 + 0.84)^2 \, x \left\{(1.23)^2 + (1.27)^2\right\}}{(3.06 - 2.49)^2}$$

n = 98.02

Data processing and analysis

Following data collection, the collected data were assessed for completeness, accuracy, and consistency before the commencement of the analysis. Data analysis was carried out by using SPSS version 23 (IBM Corp., Armonk, NY). The test statistics used to analyze the data were descriptive statistics, Chi-square ($\chi 2$) Test, and Paired t-Test. While the categorical variables were expressed using frequency, and corresponding percentages were compared between groups using Chi-square ($\chi 2$) Test, and the continuous variable was expressed as mean and standard deviation and was compared between groups using the Student's t-Test. The level of significance was set at 5%, and $p< 0.05$ was considered statistically significant.

Ethical Consideration

The researcher was concerned about the ethical issues related to the study. In this study, the following criteria were followed to ensure maintaining ethical values.

- Formal ethical clearance was taken from the ethical review committee of the RMCH for conducting the study
- Confidentiality of the person and the information was maintained, observed and unauthorized persons didn't have any access to the data
- Informed written consent was taken from the subject
- The content of the consent requirements was as such:
- Explanation of the nature & purpose of the study
- Explanation of the procedure of the study
- The explanation is that they have the right to refuse, accept & withdraw to participate in the study
- The participants didn't gain financial benefit from this study

Therefore, for this study total 100 patients were included. Among them, 50 subjects were enrolled in each group.

Selection Criteria:
Inclusion criteria:

- Age: 18-45 years
- A patient diagnosed with Endometriosis
- Willing to participate

Exclusion criteria:

- Pregnant and nursing mother
- H/O amenorrhea within 3 months of screening
- Menopausal or postmenopausal women
- Use of estrogen, progesterone, or contraceptive steroids in the previous 3 months due to any clinical condition
- An abnormal cervical cytological smear in the last 3 months
- Impaired hepatic or renal function or cardiovascular disease
- Risk factors for decreased BMD (such as the family history of osteoporosis or use of anticonvulsants or corticosteroids.

RESULTS

This randomized clinical trial was conducted in the Department of Gynae & Obstetrics, Rajshahi Medical College Hospital, Rajshahi. A total of 100 patients diagnosed with Endometriosis were taken in this study. Patients were divided into group A (Experimental group) and group B (Control group). Group A patients received dienogest for 3 months, and group B received danazol for 3 months Majority of the study population were aged 26-30 years in both groups (42% in group A and 32% in group B). The mean age of the study population was 28.72±4.71 (SD) years among group A patients and 29.52±5.23 (SD) years among group B patients. No significant difference was observed between groups (p>.05)

Table 1: Distribution of the respondents according to age (N=100)

Age group	Group A n=50 (%)	Group B n=50 (%)	N=100 (%)	p-value
18-20	1 (2)	0	1(1)	
21-25	12 (24)	14 (28)	26 (26)	
26-30	21 (42)	16 (32)	37 (37)	
31-35	11 (22)	13 (26)	24 (24)	.550*
36-40	5 (10)	5 (10)	10 (10)	
41-45	0	2 (4)	2 (2)	
Mean±SD	28.72±4.71	29.52±5.23	29.12±4.97	.424**
Total	50	50	100	

Group A: Patients with Endometriosis receiving Dienogest
Group B: Patients with Endometriosis receiving Danazol
p-value was determined by chi-square test* and independent student t-test**

The Majority of the respondents were housewives (64% and 60%). No significant difference was observed between groups (p>.05).

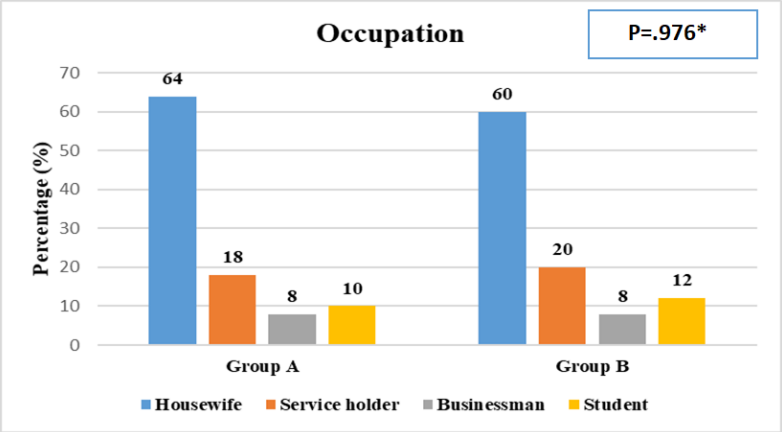

Figure 1: Distribution of the study respondents by occupation (N=100)

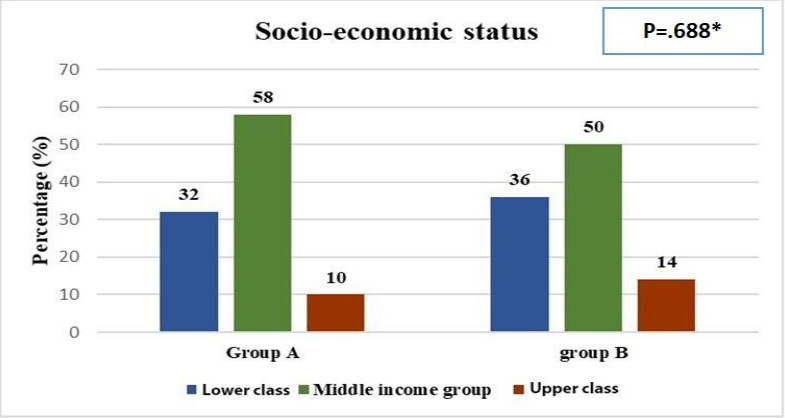

Figure 2: Distribution of the respondents by socio-economic class (N=100)

The Majority of the patients belonged to the middle socio-economic class (58% in group A and 50% in group B). No significant difference was observed between groups (p>.05).

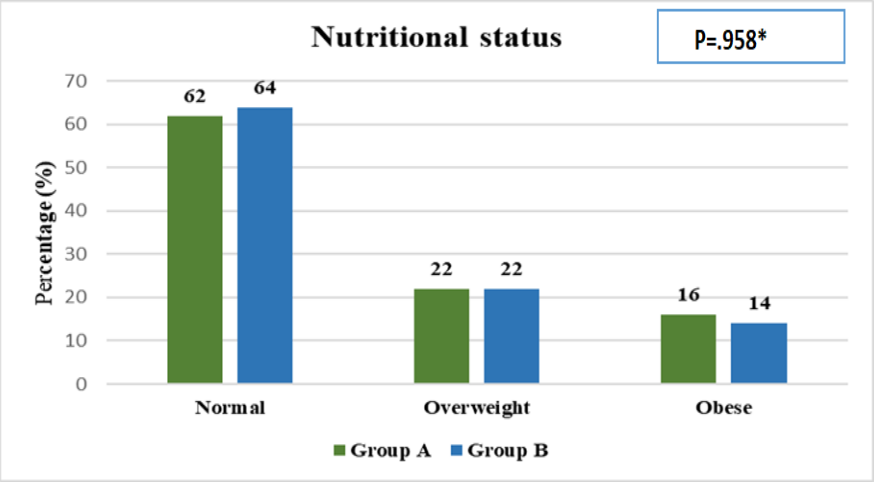

Figure 3: Distribution of the respondents by nutritional status (N=100)

The Majority of the respondents had normal BMI (62% in group A and 64% in group B). No significant difference was observed between groups (p>.05).

The clinical presentations are tabulated below. No significant difference was observed between groups (p>.05).

Table 2: Clinical presentations among the study participants (N=100)

Clinical presentations	Group A n=50 (%)	Group B n=50 (%)	Total N=100 (%)	p value*
Pelvic pain	46 (92)	43 (86)	89 (89)	.476
Infertility	16 (32)	14 (28)	30 (30)	.663
Dysmenorrhoea	40 (80)	37 (74)	77 (77)	.640
Dyspareunia	37 (74)	39 (78)	76 (76)	.373
Cyclical intestinal complaints	4 (8)	5 (10)	9 (9)	.727
Irregular menstruation	16 (32)	12 (24)	28 (28)	.689
Profuse bleeding	1 (2)	1 (2)	2 (2)	1
Cyclical urinary complaints	2 (4)	1 (2)	3 (3)	.553
Asymptomatic	3 (6)	2 (4)	5 (5)	.341

Group A: Patients with Endometriosis receiving Dienogest
Group B: Patients with Endometriosis receiving Danazol
***p value was determined by chi-square test**

VAS score were significantly reduced after treatment in both groups (p<.05). But VAS score was statistically similar among patients of both groups before treatment and after treatment (p>.05).

Table 3: Comparison of VAS scores before and after treatment in the study participants (N=100)

VAS Score	Group A Mean±SD	Group B Mean±SD	p-value*
Before treatment	55.60±22.80	51±24.28	.544
After treatment	26.00±12.77	24.80±12.20	.632
p-value**	<.001	<.001	

Group A: Patients with Endometriosis receiving Dienogest
Group B: Patients with Endometriosis receiving Danazol
p-value was determined by independent student test* and paired t-test**

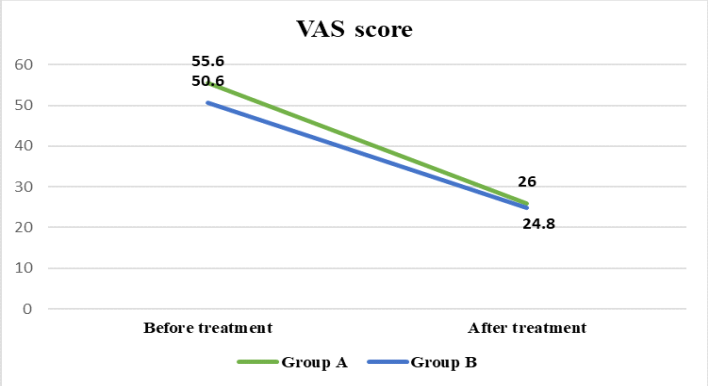

Figure 4: VAS score before and after treatment (N=100)
VAS score reduces in both groups after treatment.

The severity of dyspareunia reduced after treatment in patients of both groups statistically (p<.05). But severity was statistically similar after treatment in both groups (p>.05).

Table 4: Dyspareunia according to Biberoglu and Behrman scale among the respondents before and after treatment (N=100)

Group A				**Group B**			
Dyspareunia	**Before treatment**	**After treatment**	**p1***	**Before treatment**	**After treatment**	**p2****	**p3*****
No	13	14	<.001	11	23	<.001	.118
Mild	11	30		13	20		
Moderate	13	6		14	7		
Severe	13	0		12	0		

Group A: Patients with Endometriosis receiving Dienogest
Group B: Patients with Endometriosis receiving Danazol
p1* indicates the statistical association of dyspareunia before and after treatment in patients of group A.
p2** indicates the statistical association of dyspareunia before and after treatment in patients of group B.
p3*** indicates the statistical association of dyspareunia after treatment between groups A and B patients.

PBAC's total score was 147.06±12.05 among group A patients and 143.89±14.76 among group B patients before treatment. After treatment, the PBAC score was significantly reduced (p<.05) to 42.72±4.98 and 43.72±4.98. No significant difference was observed between the two groups (p>.05).

Table 5: Bleeding pattern of the patients before and after treatment (N=100)

PBAC Score	**Group A Mean±SD**	**Group B Mean±SD**	**p-value***
Before treatment	147.06±12.05	143.89±14.76	.231
After treatment	42.72±4.98	43.72±4.98	.351
p-value**	<.001	<.001	

Group A: Patients with Endometriosis receiving Dienogest
Group B: Patients with Endometriosis receiving Danazol
p-value was determined by independent sample t-test* and paired t-test**

The size of endometrioma reduced after treatment in both groups of patients with statistical significance(p<.05). But the size of endometrioma was statistically similar in both groups before and after treatment(p>.05).

Table 6: Size of endometrioma among the study participants before and after treatment (N=100)

Size of endometrioma (cm)	**Group A Mean±SD**	**Group B Mean±SD**	**p-value***
Before treatment	4.02±.227	3.98±.212	.366
After treatment	1.33±.698	1.47±.967	.423
p-value**	<.001	<.001	

Group A: Patients with endometrioma receiving Dienogest
Group B: Patients of endometrioma receiving Danazol
p-value was determined by independent student test* and paired t-test**
CA-125 is significantly reduced after treatment in both groups of patients (P<.05).

Table 7: CA-125 level (U/mL) among respondents before and after receiving treatment (n=100)

CA-125	Group A n=50 Mean±SD	Group B n=50 Mean±SD	p-value*
Before treatment	70.50±7.16	65.85±6.10	.012
After treatment	41.76±3.94	40.57±4.72	.177
p-value**	<.001	<.011	

Group A: Patients with Endometriosis receiving Dienogest
Group B: Patients with Endometriosis receiving Danazol
p-value was determined by independent sample t-test* and paired t-test**

Hot flush (0 Vs. 22%), joint pain (2% Vs. 14%), vaginal dryness (4% Vs. 18%), decreased libido (4% Vs. 20%), and sleep disorder (4% Vs. 22%) were significantly higher in patients who received Danazol (group B) in comparison to the patients who received Dienogest (group A).

Table 8: Adverse events among the study participants during treatment (N=100)

Adverse Events	Group A n=50 n (%)	Group B n=50 n (%)	p-value*
Irregular bleeding	3 (6)	0	.079
Hot flushes	0	11 (22)	<.001
Headache	3 (6)	2 (4)	.646
Joint pain	1 (2)	7 (14)	.027
Alopecia	2 (4)	6 (12)	.140
Weight gain	3 (6)	1 (2)	.169
Vaginal dryness	2 (4)	9 (18)	.008
Decreased libido	2 (4)	10 (20)	.014
Sleep disorder	2 (4)	11 (22)	.004
Mastalgia	3 (6)	0	.079

Group A: Patients with Endometriosis receiving Dienogest
Group B: Patients with Endometriosis receiving Danazol
***p value was determined by chi-square test**

DISCUSSION

Endometriosis is a chronic, estrogen-dependent disease that affects approximately 10% of women of reproductive age. Though there is no permanent cure for Endometriosis, women with Endometriosis require ongoing, collaborative, and supportive management of their condition to minimize the significant impact of this condition on their quality of life. According to the American Society for Reproductive Medicine, "Endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures" (*American Society for Medicine 2008*). The goal of the management of Endometriosis is to alleviate pain and other symptoms, as well as reduce endometriotic lesions and improve the quality of life. Several medical and surgical therapies are available to treat Endometriosis, and no single treatment is ideal for all patients. The management approach should be chosen according to each patient's individual needs. As Endometriosis is a chronic condition, Efficacy, long-term safety, and tolerability are also considered carefully. Along with Nonsteroidal anti-inflammatory drugs, various medical therapies are approved for the treatment of Endometriosis, including gonadotropin-releasing hormone (GnRH) agonists, danazol, and certain progestins. Danazol is an androgenic steroid that is effective in treating the signs and symptoms of Endometriosis, but its use is limited due to its adverse effects [18]. Dienogest is an oral progestin investigated extensively in some clinical programs performed in different countries. In those studies, dienogest showed a favorable safety and tolerability profile with predictable adverse effects, high patient compliance rates, and low withdrawal rates. The present study investigated the Efficacy and safety of Dienogest and Danazol among patients with Endometriosis and their comparison.

The average age of the study patients who have Endometriosis was 28 years, with the Majority in the age group 26-30 years. A study conducted on endometriosis patients of Bangladesh by Chowdhury, Chowdhury, and Mahmud also found 40% of the same age were the Majority [19]. Even if the age of onset of menstrual pain is early, there is usually a significant delay of 7–11 years before the average woman is diagnosed. In two different studies, Propst and Yeung also showed that among adolescents who complained of dysmenorrhea, approximately 70% eventually were diagnosed with Endometriosis, so this symptom warrants special attention in young women [20]. Age distribution was statistically the same in both groups.

About two-thirds of the patients hailed from rural areas. The Majority of the patients completed SSC, while nearly two-thirds of them were housewives. Most of the patients belonged to the lower-middle class of society. This study was conducted in Rajshahi

Medical College Hospital, Rajshahi, a Government-facilitated tertiary level hospital in Northern Bangladesh. So, most of the people visiting this hospital belonged to the lower-middle class population in the surrounding area, which is reflected in the socio-demographic picture of this study population. Socio-demographic features were statistically similar in both groups. In this study, nearly two-thirds of the respondents had normal BMI in both groups. A study didn't find any relation between BMI and Endometriosis [21]. BMI was statistically similar in both groups.

Presenting features among the patients with Endometriosis were pelvic pain, infertility, dysmenorrhea, dyspareunia, cyclical intestinal complaints, irregular menstruation, profuse bleeding, and cyclical urinary complaints. Among these, pelvic pain, dysmenorrhea, and dyspareunia were major features. No significant difference was observed in clinical features between groups. About 6% of patients in group A and 4% in group B were asymptomatic. Endometriosis is characterized by the formation of endometriotic lesions outside the uterus, including the ovaries and other pelvic structures, which cause a chronic, inflammatory reaction that results in the formation of scar tissue and adhesions. Women with Endometriosis frequently experience symptoms of dysmenorrhea, premenstrual pain, dyspareunia, and chronic fatigue, and it may also interfere with the functioning of the bowel & bladder [3]. However, the clinical presentations of Endometriosis can vary widely, and many affected women are asymptomatic, and no clear relationship exists between the extent of endometriotic lesions and a woman's symptoms [22]. In this study, symptomatic improvement was observed with statistical significance in both groups regarding VAS pain score and severity of dyspareunia and bleeding pattern according to PBAC score ($p<.05$). But post-treatment VAS pain score and severity of dyspareunia and bleeding pattern was similar in both groups ($p>.05$). Pre-treatment size of ovarian endometrioma was 4.02±0.227 cm (SD) in group A patients and 3.98±0.212 cm (SD) in group B patients. After treatment, ovarian endometrioma significantly ($p<.05$) reduced to 1.33±0.698 cm (SD) in group A and 1.47±0.967 cm (SD) in group B. But post-treatment size of endometrioma was similar in both groups ($p>.05$). Pre-treatment CA-125 level was 70.50 ±7.16 U/mL (SD) in group A patients and 65.85±6.10 U/mL (SD) in group B patients & significantly ($p<0.05$) reduced in both groups. Adverse events, including hot flush, joint pain, vaginal dryness, decreased libido, and sleep disorder, were significantly higher in patients who received Danazol (group B). Hirsutism is also a well-known side effect of Danazol, but we didn't observe hirsutism in the present study. The shorter follow-up period may be the reason behind this.

Danazal has been considered an effective treatment for Endometriosis [8]. Though this androgenic steroid is effective in treating the signs and symptoms of Endometriosis, various adverse effects were reported on lipid metabolism, including weight gain, edema, acne, vaginal dryness, hot flushes, oily skin, hirsutism, liver toxicity, and breast atrophy [18]. On the other hand, dienogest demonstrated effectiveness in endometriosis patients [10]. Kohler *et al*., stated that dienogest is the best therapy for Endometriosis based on their study findings [6]. These study findings corroborated with the present study.

CONCLUSION

In this study, in the management of Endometriosis, both danazol and dienogest demonstrated similar Efficacy. But regarding safety, adverse events were statistically higher in patients receiving danazol. Endometriosis is a chronic condition that needs a life-long management approach, drugs with lesser adverse events should be considered during long-term therapy. However, further extensive study is recommended before validating these findings.

Limitation

- All samples were collected from a single site
- The sample size was not representative to generalize the findings

Recommendations:

- Further studies with a larger sample size are recommended

Conflict of Interest: None.

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