

Evaluation of the Efficacy and Safety of Dienogest in the Treatment of Primary Dysmenorrhea: A Study in a District-Level Hospital in Bangladesh

Dr. Najmatun Jikria^{1*}, Dr. Numaya Habib², Dr. Sohely Sultana³, Dr. Sadia Sharmin Suborna⁴

¹Medical Officer, Obstetrics and Gynaecology, 250 Beded Sadar Hospital, Naogaon, Bangladesh

²Medical Officer, Obstetrics and Gynaecology, Maternal and Child Health Training Institute, (MCHTI), Azimpur, Bangladesh

³Medical Officer, Obstetrics and Gynaecology, Taraganj Upazila Health Complex, Taraganj, Rangpur, Bangladesh

⁴Junior Consultant (CC), Obstetrics and Gynaecology, Upzilla Health Complex, Goshairhat, Shariatpur, Bangladesh

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*Corresponding author: Dr. Najmatun Jikria

Medical Officer, Obstetrics and Gynaecology, 250 Beded Sadar Hospital, Naogaon, Bangladesh

Abstract

Background: Dysmenorrhea is a common symptom secondary to various gynecological disorders, but it is also represented in most women as a primary form of disease. Pain associated with dysmenorrhea is caused by hypersecretion of prostaglandins and an increased uterine contractility. The primary dysmenorrhea is quite frequent in young women and remains with a good prognosis, even though it is associated with low quality of life. **Objectives:** The aim of this study is to evaluate the efficacy and safety of dienogest in the treatment of primary dysmenorrhea: a study in a district-level hospital in Bangladesh. **Methods:** The cross-sectional observational study was conducted in the Department of Gynae and Obs, Naogaon Sadar Hospital from July 2022 to June 2023. A total of 100 subjects who received DNG (1 mg/day, orally) were included in the study. Data were collected by face-to-face interview and analyzed by appropriate computer based programmed software Statistical Package for the Social Sciences (SPSS), version 24. **Results:** In this study, most of the patients 43% lies between 21 years to 25 years and body weight of 24% patients were between 51 to 55 kg. In this study, most of the patients 41% body mass index were 18.5 – 24.9 kg/m². Most of the patients' clinical symptoms were cramping pain in the lower abdomen (89%), low back pain (86%), pain spreading down to the leg (73%), fatigue (64%). About (56%) adverse effects were body weight gain and irregular uterine bleeding occurred in 35 of 100 cases (35%). **Conclusion:** Primary dysmenorrhea is one of the most common illnesses in women of childbearing age. When severe, it may interfere with the activities of daily living and may lead to school and work absenteeism. Primary dysmenorrhea is also one of the most underdiagnosed diseases, so clinicians should suspect the diagnosis in a timely manner and provide appropriate treatment.

Keywords: Efficacy, Safety, Dienogest, Dysmenorrhea.

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INTRODUCTION

Dysmenorrhea, which is one of the most common causes of pelvic discomfort and menstrual disorders, is described as the presence of painful cramps of uterine origin that occur during menstruation. The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” [1]. In particular, chronic pelvic pain is located in the pelvic area and lasts for 6 months or longer [2].

The burden of dysmenorrhea is greater than any other gynecological complaint [3]. Dysmenorrhea

is the leading cause of gynecological morbidity in women of reproductive age regardless of age, nationality, and economic status [4–7]. The effects extend beyond individual women to society, resulting annually in an important loss of productivity [8, 9]. Thus, the World Health Organization estimated that dysmenorrhea is the most important cause of chronic pelvic pain [10].

Although estimates of the prevalence of dysmenorrhea vary extensively, they range from 45 to 93% of women of reproductive age with adolescents reporting the greatest rates [11, 12]. Women do not report it or seek medical attention since it is accepted

as a typical part of the menstrual cycle and is therefore tolerated [13, 14]. Some women (3 to 33%) have very severe pain, severe enough to render them incapacitated for 1 to 3 days each menstrual cycle, requiring absence from school or work [15, 16]. Indeed, dysmenorrhea has a high impact on women's lives, resulting in a restriction of daily activities [17, 18], a lower academic performance in adolescents [19,20], and poor quality of sleep [21], and has negative effects on mood, causing anxiety and depression [22].

On the basis of pathophysiology, dysmenorrhea is classified as primary dysmenorrhea (menstrual pain without organic disease) or secondary dysmenorrhea (menstrual pain associated with underlying pelvic pathology) [23]. The cause of primary dysmenorrhea is not well established. However, the responsible cause has been identified on the hyper-production of uterine prostaglandins, particularly of PGF_{2a} and PGF₂, thus resulting in increased uterine tone and high amplitude contractions²⁴. Women with dysmenorrhea have higher levels of prostaglandins, which are highest during the first two days of menses [25]. Prostaglandin production is controlled by progesterone: when progesterone levels drop, immediately prior to menstruation, prostaglandin levels increase. If the exposure of endometrium to luteal phase is crucial for the increased production of progesterone, dysmenorrhea occurs only with ovulatory cycles. This could explain why primary dysmenorrhea onset is shortly after menarche and why dysmenorrhea responds well to ovulatory inhibition. However, multiple other factors may play a role in the perception and the severity of pain, which does not depend only on endocrine factors [26].

Central sensitization, which is linked to structural and functional changes in the central nervous system, is linked to recurring menstrual pain. Menstrual pain must be treated in order to minimize the unpleasant input into the central nervous system, as dysmenorrhea may have significant long-term effects and increase women's vulnerability to other chronic pain problems later in life. The most frequent causes of adenomyosis and endometriosis in young women are secondary dysmenorrhea.

The most prevalent cause of secondary dysmenorrhea is endometriosis, which is defined by the presence of endometrial tissue (stroma and glands) outside the uterine cavity. Endometriosis-affected women's physical and mental health are adversely affected by pain symptoms. Every type of pain is thought to be a stressor because it increases sympathetic nervous system activity, which in turn affects neuromediators, neuroendocrine systems, and hormone secretions.

Dysmenorrhea is frequently linked to heavier and longer-lasting menstrual bleeding. Having children has a significant impact on the decline in dysmenorrhea. While a longitudinal research revealed that the proportion of women with moderate-to-severe dysmenorrhea remained steady with age, increasing age is also linked to less severe dysmenorrhea. A family history of dysmenorrhea is linked to a much higher incidence of dysmenorrhea, and an early beginning of pain is related with more severe pain. Given the frequent correlation between anxiety and depression, dysmenorrhea could be a component of a somatoform syndrome.

Management of dysmenorrhea

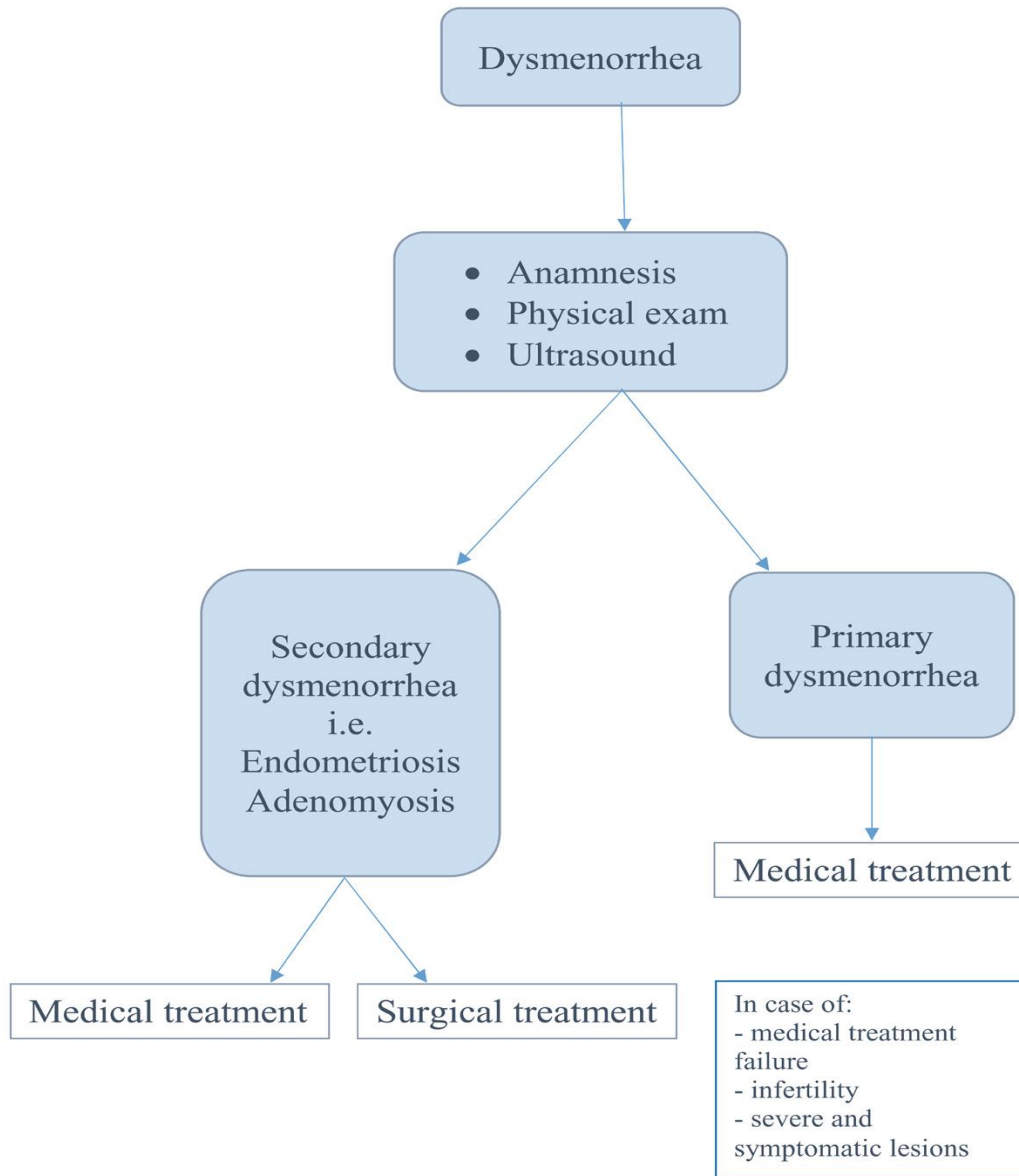


Figure 1: Flowchart for the management of patients with dysmenorrhea

METHODOLOGY

The cross-sectional observational study was conducted in the Department of gynae and obs, Naogaon Sadar Hospital from July 2022 to June 2023. A total of 100 subjects who received DNG (1 mg/day, orally) were included in the study. Patients who gave consent to be included in the study. Patients who were not willing to give consent were excluded. Face to face interview was done to collect data with a semi-structured questionnaire. After collection, the data were checked and cleaned, followed by editing, compiling, coding, and categorizing according to the objectives and variable to detect errors and to maintain consistency, relevancy and quality control. Statistical evaluation of the results used to be obtained via the use

of a window-based computer software program devised with Statistical Packages for Social Sciences (SPSS-24).

RESULT

Table I: Distribution of the patients according to age (n = 100)

Age group	Frequency	%
15 – 20 years	34	34
21 - 25 years	43	43
26 - 30 years	14	14
31 - 35 years	9	9
Total	100	100.0

Table I shows that, maximum 43 (43%) of the patients were within the age group of 21- 25 years and minimum 9 (9%) of the patients were within the age group of 31-35 years

Table II shows that, 24 (24%) of the patient’s body weight were between 51 – 55 kg, 21(21%) of the patients were in between 56 – 60 kg and 19 (19%) of the patients were in between 46 – 50 kg.

Table II: Distribution of the patients according to body weight (n = 100)

Weight (Kg)	Frequency	%
35 – 40 kg	5	5
41 – 45 kg	9	9
46 – 50 kg	19	19
51 – 55 kg	24	24
56 – 60 kg	21	21
61 – 65 kg	12	12
66 – 70 kg	7	7
>70 kg	3	3
Total	100	100.0

Table III: Distribution of the patients according to body mass index (n = 100)

Body Mass Index (kg/m ²)	Frequency	%
<18.5	17	17
18.5 – 24.9	41	41
25.0 – 29.9	20	20
>30	22	22
Total	100	100.0

Table III shows that most of the patients 61 (61%) were in normal range (18.5 – 29.9 kg/m²), 17(17%) of the patients were underweight (<18.5) and 22 (22%) of the patients were overweight (>30).

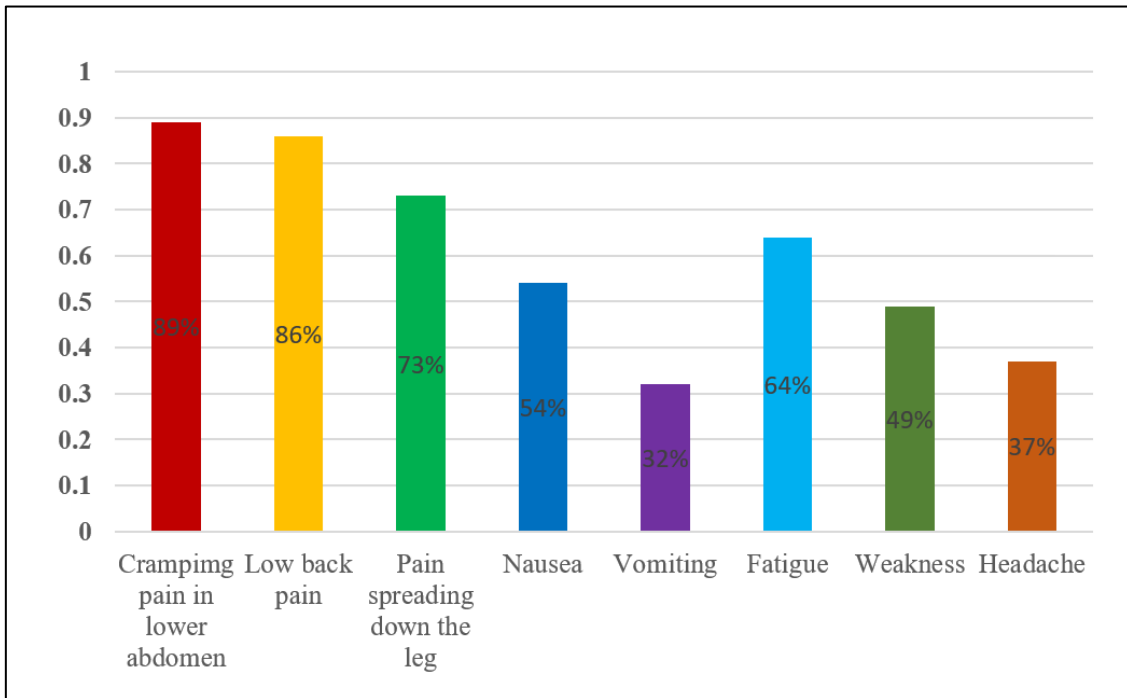


Figure I: Distribution of patients according to clinical symptoms

Figure I shows that, most of the patients clinical symptoms were cramping pain in the lower abdomen (89%), low back pain (86%), pain spreading

down to the leg (73%), fatigue (64%) and some of them complain that they had nausea (54%), weakness (49%), headache (37%) and vomiting (32%)

Table IV: Distribution of the patients according to adverse effects of dienogest treatment (n = 100)

Parameter	Frequency	%
Body weight gain	56	56
Irregular uterine bleeding	35	35
Fatigue	11	11
Insomnia	5	5
Breast discomfort	3	3
Depression	4	4
Dizziness	2	2

Table IV shows that most of the patients' (56%) adverse effects was body weight gain and irregular uterine bleeding occurred in 35 (35%) of 100 cases.

DISCUSSION

Women with dysmenorrhea, compared with women without dysmenorrhea, have greater sensitivity to experimental pain both within and outside areas of referred menstrual pain. Importantly, the enhanced pain sensitivity is evident even in phases of the menstrual cycle when women are not experiencing menstrual pain, illustrating that long-term differences in pain perception extend outside of the painful menstruation phase. This enhanced pain sensitivity may increase susceptibility to other chronic pain conditions in later life; dysmenorrhea is a risk factor for fibromyalgia. Further, dysmenorrheic pain has an immediate negative impact on quality of life, for up to a few days every month. Women with primary dysmenorrhea have a significantly reduced quality of life, poorer mood and poorer sleep quality during menstruation compared with their pain-free follicular phase and compared with the menstruation phase of pain-free control women. The prescribed first-line therapy for menstrual pain remains non-steroidal anti-inflammatory drugs, which are effective in relieving daytime and night-time pain.

The cross-sectional observational study was conducted in the Department of gynae and obs, Naogaon Sadar Hospital from July 2022 to June 2023. A total of 100 subjects who received DNG (1 mg/day, orally) were included in the study to evaluate of the efficacy and safety of dienogest in the treatment of primary dysmenorrhea: a study in a district-level hospital in Bangladesh.

In this study, maximum 43 (43%) of the patients were within the age group of 21- 25 years and minimum 9 (9%) of the patients were within the age group of 31-35 years. In another study shows comparison of basic characteristics between the three cohorts of women assessed at 19 and 24 years of age and there was a successive increase in bodyweight between the three cohorts and the frequency of smoking decreased (P, 0.001) over time. The proportion of women using COCs was lower (P, 0.001) at the age of 24. In this study 24 (24%) of the patient's body weight were between 51 – 55 kg, 21(21%) of the patients were in between 56 – 60 kg and 19 (19%) of the patients were in between 46 – 50 kg and most of the patients 61 (61%) were in normal range (18.5 – 29.9 kg/m²), 17(17%) of the patients were underweight (<18.5) and 22 (22%) of the patients were overweight (>30). In another study patients had mean body weight of 57.9±9.7 kg, mean height of 159.5±5.6 cm, and a body mass index of 22.8±3.6 kg/m². most of the patients' clinical symptoms were cramping pain in the lower abdomen (89%), low back pain (86%), pain spreading down to the leg (73%), fatigue (64%) and some of them

complain that they had nausea (54%), weakness (49%), headache (37%) and vomiting (32%). In another study shows most of the patients' clinical symptoms were cramping pain in the lower abdomen (89%), the dysmenorrhea, and non-menstrual pelvic pain scores, and use of analgesics in 89 patients before and after treatment with DNG. The effective endpoint was the patient response to treatment for dysmenorrhea and pelvic pain associated with endometriosis, as evaluated by the VRS. The analysis assessed changes in symptom severity before and after treatment with DNG. The mean (±standard deviation) score for dysmenorrhea was 1.42±1.1 before treatment and 0.1±0.3 after treatment. The dysmenorrhea score significantly decreased by the end of treatment (P<0.001). The mean non-menstrual pelvic pain score was 0.52±0.6 before treatment and 0.18±0.3 after treatment, a significant difference (P<0.001). The use of analgesics decreased low back pain (86%), pain spreading down to the leg (73%), fatigue (64%). In another study about (56%) adverse effects were body weight gain and irregular uterine bleeding occurred in 35 of 100 cases (35%). In another study conducted by Kim *et al.*, there were a few side effects like irregular uterine bleeding occurred in 28 of 89 cases (31.5%); however, only 1 patient discontinued treatment because of severe uterine bleeding. Moreover, irregular uterine bleeding decreased with continued treatment and resolved by the end of treatment. Another adverse effect was weight gain, a common adverse effect with other progestins used in endometriosis treatment. Weight after treatment (61.1±12.6 kg) was greater than that before treatment (57.9±9.7 kg); the increase was statistically significant (P<0.040). A weight gain of 15 kg was recorded in 1 patient. Other than uterine bleeding and weight gain, no serious adverse events related to DNG use occurred. Laboratory safety parameters showed no clinically relevant changes in serum lipid and liver enzyme levels with DNG treatment [24]. Another study suggested that the extent of suppression of estradiol production by DNG at 1 mg/day was less than that induced by DNG at 2 mg/day. It is believed DNG at 1 mg/day reduces pain by inhibiting the production of prostaglandin due to suppression of ovulation and endometrial proliferation. We found no inconsistency with the results of a phase II study that involved pharmacologic evaluation of DNG for primary dysmenorrhea [27].

In another study reported that regarding safety, the most common adverse drug reaction was irregular uterine bleeding in all DNG arms. Irregular uterine bleeding has been reported generally during the use of progestin products [28, 29], and was also reported in clinical studies of DNG 2 mg/d in patients with endometriosis and adenomyosis [30, 31]. Anemia was not reported as an adverse drug reaction. The number of days with vaginal bleeding was lower in the DNG 1 mg/d arm, although there was no meaningful difference among the doses of DNG. By severity of vaginal bleeding, the proportion of days with spotting and days

with breakthrough bleeding was higher in all DNG arms, which was consistent with the results of a clinical study of DNG 2 mg/d in patients with adenomyosis [31]. Based on the above, the clinically recommended dose of DNG in the treatment of primary dysmenorrhea is considered to be 1 or 2 mg/d because those doses demonstrated superiority to placebo in terms of the dysmenorrhea score, an improvement equivalent to or greater than that achieved by an approved oral contraceptive, and no greater safety risk of problems like irregular uterine bleeding. The optimal and clinically recommended dose of DNG is 1 mg/d because it does not suppress estradiol production.

CONCLUSION

Primary dysmenorrhea is one of the most common illnesses in women of childbearing age. When severe, it may interfere with the activities of daily living and may lead to school and work absenteeism. Its diagnosis is based on a characteristic clinical history, normal physical examination, and absence of pelvic disease. Its management consists of patient education, reassurance, and support. Pharmacological treatment is the most effective and includes NSAIDs or hormonal contraceptives for women who do not wish to become pregnant. Women who do not respond to treatment after 3 months of use should be investigated for suspected secondary dysmenorrhea. Primary dysmenorrhea is also one of the most underdiagnosed diseases, so clinicians should suspect the diagnosis in a timely manner and provide appropriate treatment.

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