

Comparison of the Efficacy and Safety between Dienogest and Dydrogesterone in Treatment of Endometriosis: Prospective Study

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Abstract: *Endometriosis is a common benign gynecologic disorder; which found in reproductive-aged women due to its hormonal dependent nature. Objective: compare the efficacy and safety of Dienogest to dydrogesterone in management of endometriosis. Patients & Methods: A prospective open-label study, conducted in an out-patient gynecologist clinic for one year starting from 1st Jan-2015 till 1st Jan-2016, included 40 healthy women without signs and symptoms of metabolic disturbances, with proven endometriosis. Results: both treatments were effective in reducing pain after 12 weeks dydrogesterone (62.3 to 35.34 mm) and dienogest (60.97 to 26.67 mm) p-value <0.001, with p-value of interaction = 0.004. 12/20 patients using dienogest achieve <30 mm VAS score while 5/20 of the patients using dydrogesterone achieve pain reduction (<30 mm) after 12 weeks. Total cholesterol, LDL, HDL, triglyceride did not differ significantly after 12 weeks for either drug p-value < 0.05. Conclusion: The results of this study demonstrated that dienogest 2 mg/day orally is more effective than dydrogesterone ten mg/day twice daily orally for relieving endometriosis-associated pelvic pain, with comparable safety profile.*

Keywords: dienogest, dydrogesterone, VAS score, endometriosis

1. Introduction

Endometriosis considered as a common benign disorder which can define as the presence of endometrial tissues (glands and stroma) outside the normal physiological sites. Endometriosis is most commonly found on the pelvic peritoneum but may also found on the ovaries, rectovaginal septum, and ureter, and rarely in the bladder, pericardium, and pleura. Endometriosis is a hormonally dependent disease and as a result, is chiefly found in reproductive-aged women. (1)

It is estimated to occur in 6–10% of women. The exact incidence in the general population remains unknown, due to difficulty in establishing definite diagnosis which requires visualization of the endometriotic implants using laparoscopy or laparotomy. (2) However, because of its link with pelvic pain and infertility, its prevalence is more in subpopulations of women with these complaints. In infertile women, the prevalence has been reported to be between 20 and 50 percent and in those with pelvic pain between 40 and 50 percent. (3)

Several risk factors for endometriosis: family history of endometriosis, early age of menarche, inverse relationship to parity, heavy bleeding during menses, defects in the uterus or fallopian tubes, delayed childbearing, short menstrual cycles (less than 27 days) and long duration of menstrual flow (more than seven days). (4-6)

Although women with endometriosis may be asymptomatic, symptoms are common and typically include chronic pelvic pain and infertility. The pain associated with endometriosis is

depending on the depth of the invasion of the endometrial implants rather the superficial lesions. (7) Pelvic pain is the most common symptoms that occur as a stabbing or cramping pain in both sides of the pelvis and may radiate to the back and the rectal area. (1) The underlying cause of this pain is unclear, but pro-inflammatory prostaglandins and cytokines released by endometriotic implants into the peritoneal fluid may be one source. (8) Also, evidence suggests that pain from endometriosis correlates with depth of invasion and that the site of pain may indicate lesion location. (9)

Although the mechanisms by which endometriosis may cause infertility is not clearly understood, particularly when the extent of endometriosis is low, (10) there is a possible mechanism include: anatomical distortions and adhesions (the fibrous bands that form between tissues and organs following recovery from an injury), the release of several factors from endometriotic cysts which are detrimental to gametes or embryos is another possible mechanism. An endometriotic cyst contains free reactive oxygen species, iron, inflammatory molecules and proteolytic enzymes. (11) Follicular density in tissue surrounding the endometriotic cyst has been consistently shown to be significantly lower than in healthy ovaries, and to the degree, that does not appear to be caused merely by the stretching of surrounding tissues owing to the presence of a cyst. (11)

Endometriosis may more likely develop in women who fail to conceive for other reasons and thus be a secondary phenomenon. For this reason, it is preferable to speak of "endometriosis-associated infertility" rather than any definite "infertility caused by endometriosis" by the same reason that association does not imply causation. (12)

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Women with endometriosis may be asymptomatic, or they may present with pain, infertility, or a combination of both, the goals of the treatment depend on the patient presentation; which include: minimization or removal of endometrial deposits, prevention of disease progression, minimization of associated pain and prevention or correction of associated infertility. (13)

Progestins act by antagonizing the estrogenic effect on the endometrium; which causes decidualization; which produces endometrial atrophy. Progestins have been shown to reduce nerve fiber density and nerve growth factor expression in endometriotic lesions. (14)

Dienogest is an orally active semisynthetic, steroidal progestogen, (15) it is a 19-norprogestin that derived from the steroid 19-nortestosterone. (16) It differs from other 19-norprogestins by possessing a cyanomethyl group instead of an ethinyl group at the 17a position. Progestins may be classified based on their molecular structure and associated functional characteristics. Progesterone derivatives, such as MPA and megestrol acetate, offer a range of progestogenic and androgenic actions. Newer 19-norprogestins have a strong progestogenic effect on the endometrium, with little androgenic, estrogenic or glucocorticoid activity. (17) Dienogest combines the pharmacodynamic advantages of progesterone derivatives with the pharmacological benefits of 19-norprogestins. (18) Although it is related to testosterone structure, dienogest has anti-androgenic activity, which is approximately one-third that of the progesterone derivative, cyproterone acetate. It has no mineralocorticoid or glucocorticoid activity in vivo. In contrast, many other progestins characterized by adverse effects that are androgenic.(18)

This study aimed to compare the efficacy and safety of dydrogesterone with that of Dienogest in the treatment of endometriosis.

2. Patients and methods

This study conducted in an out-patient gynecologist clinic for one year starting from 1st Jan-2015 till 1st Jan-2016, with follow up 12 weeks for each participant. The study included 40 healthy women without signs and symptoms of metabolic disturbances, with proven endometriosis (20 patients in each group). The women's age between 20 to 45 years, patients will be randomized (using a computer program) to treatment with dienogest (2 mg/day, orally) or dydrogesterone (10 mg/twice per day, orally) for 12 weeks.

The patients were advised to adhere to a heart-healthy diet (i.e., increased vegetables, fruits, whole grains; limited sodium, sweets, sugar-sweetened beverages, red meats, saturated/trans fats), maintain regular aerobic physical activity (i.e., moderate-to-vigorous intensity physical activity, 3-4 sessions per week, averaging 40 minutes per session), avoidance of tobacco products, and maintenance of a healthy weight. This study approved by the Iraqi council of medical specialty and all procedures were by Helsinki Declaration, informed consent obtained from all patients that included in

this study.

Inclusion criteria: patients with endometriosis aged 20-45 year old.

Exclusion criteria: patients with hypo- or hyperthyroidism, patients with Diabetes Mellitus, patients taking drugs affect lipid metabolism and patients with lipid metabolism disorders.

The primary endpoint: absolute change in pelvic pain from baseline to end of treatment, assessed by using visual analog scale (VAS) at baseline, 4, 8, and 12 weeks of treatment.

Secondary endpoint: Safety variables include adverse event profile, laboratory parameters, total cholesterol, Triglycerides, HDL-cholesterol and LDL-cholesterol, these variables will be taken before the treatment (at the baseline), after 4 and 12 weeks

Laboratory analysis: Laboratory analysis was carried out in private laboratory, using SIEMENS device: Dimension® clinical chemistry system using a Flex® reagent cartridge for quantitative termination of lipid profile.

Statistical analysis: Continuous variables presented by mean and standard deviation (age, ALT, AST, cholesterol, HDL, LDL, and triglyceride); while discrete variables (gender) presented using number and percentage, chi-square test and Fisher exact test (for 2 x 2 tables) when possible to analyzed the discrete variables. One variable trend ANOVA was used to analyze continuous variables throughout baseline, four weeks, eight weeks and 12 weeks to see the change in their mean effect through the study. Mixed repeated measure two way ANOVA was used to analyze the continuous (comparison between the two drugs) data using time as within group variable and treatment type as between group variables, Mauchly's test of sphericity was used to test sphericity assumption; when significant lower bound correction method used to test within groups significance, if not significant sphericity assumption is preserved and p-value calculated. P value was considered to be significant when it is less than 0.05; all data analyzed using SPSS 20 software package.

3. Results

Mean age of patients received either dydrogesterone (29.85 ± 5.18) years and dienogest (27.7 ± 4.96) years was not statistically significant p = 0.188. Both treatments were significantly effective in reducing pain through the study period, however; when the effect of both treatments compared to each other, the trend in reduction of pain in dienogest was more significant than the trend of reduction of dydrogesterone (p-value of interaction 0.004). Of notice, after eight weeks the difference in reduction become significant (p-value 0.019) and continue after that while at the four weeks the pain reduction was not significant between the two drugs as illustrated in table 1 and figure 1. Both treatments did not cause a significant effect on lipids from baseline to the end of the study as illustrated in table 2.

Table 1: comparison of the effect of both treatments on pain score

Drug	Baseline	Four weeks	Eight weeks	12 weeks	P-value
A	62.30 ± 12.26	45.61 ± 10.19	39.85 ± 8.52	35.34 ± 7.11	<0.001
B	60.97 ± 12.74	39.60 ± 10.0	32.80 ± 9.72	26.67 ± 8.99	<0.001

Trend ANOVA
 Data presented as mean ± standard deviation
 A: Dydrogesterone, B: Dienogest

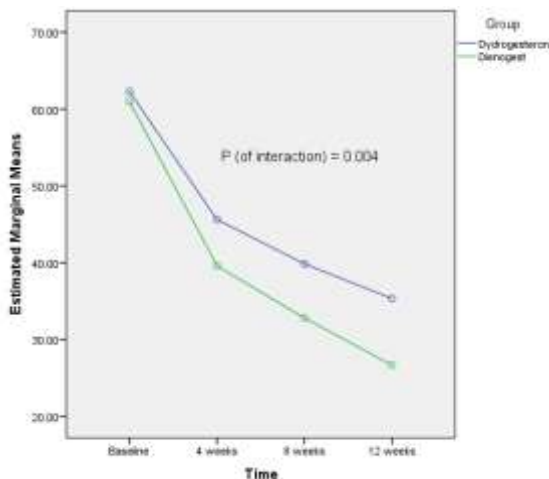


Figure 1: pain score of both dydrogesterone and dienogest using marginal mean

Table 2: Effect of both treatments on lipid panels

Lipid	Drug	Baseline	4 weeks	12 weeks	P value
TC	A	166.5 ± 11.62	167.45 ± 11.82	169.5 ± 11.55	0.419
	B	169.2 ± 12.99	170.4 ± 13.28	171.4 ± 12.95	0.597
TG	A	112.1 ± 27.49	113.75 ± 27.61	114.95 ± 27.71	0.745
	B	101.8 ± 22.89	102.95 ± 23.16	104.4 ± 23.22	0.723
HDL	A	50.3 ± 6.09	49.7 ± 6.39	49 ± 6.69	0.537
	B	47.5 ± 3.05	47.25 ± 2.95	46.9 ± 3.16	0.523
LDL	A	93.78 ± 15.7	95 ± 16.28	97.51 ± 16.3	0.467
	B	101.15 ± 11.7	101.75 ± 11.84	103 ± 11.49	0.618

Trend ANOVA
 Data presented as mean ± standard deviation
 A: Dydrogesterone, B: Dienogest
 TC: Total cholesterol, TG: Triglyceride

4. Discussion

This 12-week, open label, head-to-head comparison study between dydrogesterone and dienogest in women with clinically proven endometriosis, concerning efficacy in reducing pain each individual drug were able to ameliorate endometriosis associated pain within 12 weeks of treatment to significant levels. The results of this study agree with previous studies which investigated the efficacy of dydrogesterone in relieving the symptoms of endometriosis, in an open, prospective, multicenter study (19) which assessed the efficacy and safety of dydrogesterone in post laparoscopic treatment of endometriosis in India, ninety-eight patients, with or without infertility, suffering from minimal, mild, moderate or severe endometriosis, who had undergone laparoscopy, the patients treated with dydrogesterone 10 mg per day (or 20 mg per day in severe cases) orally from day five to twenty-five day of each cycle for 3 to 6 months, the pelvic pain, dysmenorrhea and dyspareunia improved

significantly after the first cycle of treatment. At the end of the 6th cycle, the reduction in pelvic pain was 95%, in dysmenorrheal was 87% and in dyspareunia was 85%. (19) In another study which investigate 49 patients with endometriosis administered 10 mg per day dydrogesterone (5mg twice daily), most subjective (including the pain) symptoms had disappeared within four to eight weeks of treatment (89% pain-free; 53% pregnancy rate; of 32 patients who underwent laparoscopy, 21 were cured, 9 had regression and 2 were unchanged), all but five patients were symptom-free after nine months of therapy. (20) In the above studies the dose of dydrogesterone was ranged from 10 to 20 mg per day and both studies demonstrate a significant pain relief after the first month of administration of dydrogesterone. Dydrogesterone was used at a dose 10 mg twice daily in this study, (the pretreatment VAS scores was 62.30 ± 12.26 mm) which cause significant pain relief after the first 4 weeks of treatment observed by the reduction in the mean VAS score of 16.69 mm (26.78% from baseline) and the improvement continued through the 12-weeks study period the total reduction in mean VAS scores was 26.96 mm (43.27% from baseline).

Dienogest showed significant decrease in pain intensity in which VAS score (60.97 mm at baseline) decreased by 21.37 mm (i.e. 35%) at the end of 4-week treatment (39.6 mm) and by 34.3 mm (i.e. 56.2%) at the end of 12 weeks of treatment (26.67 mm), this efficacy of dienogest in this study support the results of previous studies, in a study in 2010 compared the efficacy of dienogest with that of leuprolide showed that in the dienogest group the VAS scores decreased from 60.2 ± 24.2 mm (the baseline) to 12.7 ± 20.3 mm along 24 week of treatment with 2 mg dienogest per day (which represent a decrease in total pain by 70%), the significant pain relief occurred after just the first 4weeks (more than 39% decrease in VAS scores) and by week 12 the decrease in VAS scores was more than 55%. (21) Strowitzki *et al* (22) in 2010 showed that the efficacy of dienogest in endometriosis compare with placebo in 12-week study and the result showed dienogest reduce pain intensity significantly from the first week of treatment. In this 12-week, randomized, double-blind, placebo-controlled, multicenter (n = 33) study in Germany, Italy, and Ukraine of 198 women aged 18–45 years with laparoscopically confirmed endometriosis and EAPP score ≥30 mm on a visual analog scale (VAS). Dienogest 2 mg or placebo was administered orally once daily. The primary efficacy variable was absolute change in EAPP from baseline to Week 12, mean reductions in VAS score between baseline and Week 12 in the full analysis set were 27.4 mm and 15.1 mm in the dienogest and placebo groups, respectively—a significant score difference of 12.3 mm in favor of dienogest. The primary efficacy measure of absolute change in EAPP demonstrated the superiority of dienogest over placebo. Dienogest was generally well tolerated and few adverse events were associated with therapy. (22) Both dydrogesterone and dienogest were effective in reducing pain associated with endometriosis, however dienogest associated with more significant reduction of pain compared to dydrogesterone (primary end point of the study); since there are no previous study comparing these two drugs head to head our finding represent the first data to support efficacy of dienogest in pain associated with endometriosis.

Overall both drugs show similar effect on lipid profile and their mean effect were not clinically significant, despite dydrogesterone show more effect on lipid effect compared to dienogest this effect were not significant. Adverse effect associated with dienogest was mild and only 2 patients developed adverse effects. One patient develop headache and the other patient developed transient nausea, but these adverse effects were mild and did not affect the treatment plan. Adverse effects associated with dydrogesterone were generally mild and only one patient from 20 patients treated with dydrogesterone suffered from headache and transient mastalgia.

5. Conclusion

The results of this study demonstrated that dienogest 2 mg/day orally is more effective than dydrogesterone 10 twice daily orally for relieving endometriosis-associated pelvic pain, with comparable safety profile. This finding is of high clinical relevance, as pelvic pain is one of the most important symptoms of endometriosis.

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