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Original Research Article

Evaluation of the efficacy and tolerability of 4 mg dienogest in women with adenomyosis and BMI >30

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ABSTRACT

Background: To evaluate the efficacy and tolerability of 4mg dienogest in women with adenomyosis and BMI >30.
Methods: This prospective study, conducted at Lakshmi Madhavan Hospital Pvt Ltd, Tirunelveli, Tamil Nadu, between January and October 2023, included 110 women aged 30-40 years diagnosed with adenomyosis via ultrasonography and presenting with severe dysmenorrhea. These women, all with BMI >30, were administered 4mg Dienogest (2mg twice daily) for eight weeks, followed by a taper to 2mg once daily for 12 weeks. All participants received dietary counselling emphasizing reduced carbohydrate intake and lifestyle modifications. Data on symptom improvement, adverse effects, and adherence were collected and analyzed using STATA 11.0.
Results: A significant improvement in symptoms such as menorrhagia, dysmenorrhea, dyspareunia, and chronic pelvic pain was observed in 81% of participants. Adverse effects, including headache (15%), breast discomfort (10%), and mild weight gain (8%), were reported but were well-tolerated. Irregular bleeding led to discontinuation in 3% of cases. Women requiring the 4mg dose beyond eight weeks demonstrated poor adherence to dietary modifications. The overall success rate was 81% (n=89), with a failure rate of 19% (n=21).
Conclusion: The study suggests that a higher dosage of Dienogest (4mg) for a limited period is effective and well-tolerated in obese women with adenomyosis who do not respond to the standard 2 mg dose. However, individualized treatment and strict lifestyle adherence are essential for optimal outcomes.

Keywords: Adenomyosis, Dienogest, Obesity, BMI >30, Hormonal therapy, Dysmenorrhea, Menorrhagia, Lifestyle modifications, Pharmacokinetics, Progestin therapy

INTRODUCTION

Adenomyosis is a benign uterine disorder characterized by the presence of ectopic endometrial glands and stroma within the myometrium, often resulting in symptoms such as dysmenorrhea, heavy menstrual bleeding, and chronic pelvic pain.[1,2] The condition can significantly impair quality of life and reproductive outcomes in women of reproductive age.[3,4] Diagnosis is commonly established through imaging modalities such as transvaginal ultrasound and MRI.[5] Dienogest, an oral progestin, has been widely used for the treatment of endometriosis and adenomyosis due to its anti-inflammatory, anti-angiogenic, and anti-proliferative properties.[6-8] The standard therapeutic dose of Dienogest is 2 mg daily, which has shown efficacy in reducing pelvic pain and controlling disease progression.[9,10] However, emerging evidence suggests that this standard dose may be less effective in obese women, potentially due to altered pharmacokinetics and hormone metabolism associated with increased adiposity.[11,12]

Obesity (BMI >30) is a growing global health issue, with more than 650 million adults classified as obese worldwide.[13] In women, a high BMI has been associated with hormonal imbalances, chronic systemic

inflammation, and altered drug metabolism, all of which may compromise the efficacy of standard hormonal therapies.[14,15] These physiological changes present unique challenges in the medical management of gynecological conditions such as adenomyosis .[16] Given the altered drug distribution and response in obese women, there is a clinical rationale for exploring the use of higher hormonal dosages in this subgroup. However, there is a paucity of research evaluating the efficacy and safety of higher-dose Dienogest in this population. The objective of this study is to evaluate the effectiveness of oral Dienogest 4 mg daily in reducing uterine volume and alleviating pain symptoms in obese women with adenomyosis over a 12-month period. By assessing both objective outcomes (such as uterine volume via imaging) and subjective outcomes (including pain and quality of life), this study aims to determine whether a higher dosage offers improved therapeutic benefit in this specific patient population.

Pharmacokinetics in obesity

Absorption and distribution

Obesity can alter the pharmacokinetics of many medications, including hormonal contraceptives. Increased body fat may affect the distribution and metabolism of Dienogest, potentially leading to variations in drug levels.

Dosing considerations

Some studies suggest that hormonal contraceptive effectiveness may be lower in obese individuals, but this does not always translate to the need for higher doses. The relationship between body weight and contraceptive efficacy is complex and influenced by multiple factors.

Clinical evidence

Most clinical guidelines do not recommend higher doses of Dienogest. The standard dosing remains effective for the majority of users, regardless of body weight.

Individual response

Variations in response to hormonal contraceptives are common, and some obese women may experience different side effects or efficacy levels. Monitoring is essential to optimize outcomes.

Potential risks

Thromboembolic Risk: Obesity is a known risk factor for thromboembolic events, particularly when using hormonal contraceptives. Higher doses could increase this risk, making careful evaluation necessary.

Personalized approach

It's important for obese women to discuss their options with healthcare providers to ensure a tailored treatment plan that considers overall health, weight, and contraceptive needs.

Effectiveness of dienogest in suppressing endometriosis

Dienogest works as a selective progestin that suppresses ovulation and lowers estrogen levels. This prevents the growth of endometrial implants, alleviating pain and inflammation. It also reduces the production of pro-inflammatory cytokines, which is critical for recovery in endometriosis patients.

Metabolic profile of dienogest

Dienogest has a favorable metabolic profile compared to other hormonal treatments. Unlike combined oral contraceptives, it does not exacerbate insulin resistance or negatively impact lipid metabolism, which is especially beneficial for obese patients who are already at risk of metabolic disturbances.

Weight-related endometriosis

Obesity may contribute to endometriosis via increased peripheral conversion of androgens to estrogen in adipose tissue. Dienogest counteracts this by suppressing systemic estrogen levels, minimizing endometrial stimulation.

Dienogest's anti-androgenic properties

Obesity is associated with increased androgen levels, which can lead to hormonal imbalances. Dienogest's mild anti-androgenic effects may help restore hormonal balance.

Adherence and tolerability

Dienogest is administered as a once-daily pill, which may enhance adherence in patients managing multiple conditions related to obesity. Side effects like weight gain or fluid retention are minimal with Dienogest compared to other progestins, contributing to better compliance and overall recovery.

Reduced risk of venous thromboembolism

Obesity increases the risk of VTE, and estrogen-containing medications further elevate this risk. Dienogest, being a progestin-only treatment, avoids this additional risk, making it safer for obese individuals.

METHODS

This prospective study was conducted at Lakshmi Madhavan Hospital Pvt Ltd, Tirunelveli, Tamil Nadu, between January and October 2023.

The study recruited 110 women aged 30 to 40 years who were diagnosed with adenomyosis based on transvaginal ultrasonography and presented with moderate to severe

dysmenorrhea (defined as VAS ≥5). Eligible participants had a body mass index (BMI) greater than 30 kg/m², reflecting the criteria for obesity. Participants were included if they met all of the following criteria.

Aged 30–40 years, confirmed diagnosis of adenomyosis on imaging, BMI >30 kg/m², and willingness to adhere to lifestyle modifications alongside pharmacological treatment.

Exclusion criteria

It includes were history of thromboembolic disorders, presence of malignancy or suspected cancer, known liver dysfunction or abnormal liver enzymes, hypersensitivity to Dienogest or other progestins, and current or recent (within 3 months) use of hormonal treatments. Additionally, women planning pregnancy during the study period or those with significant psychiatric illness affecting compliance were also excluded.

Study design and setting

This prospective study was conducted at Lakshmi Madhavan Hospital Pvt Ltd, Tirunelveli, Tamil Nadu, from January to October 2023. The predominantly carbohydrate-rich dietary habits and sedentary lifestyle of the study population were considered in the analysis.

Participants

The study included 110 women aged 30-40 years with BMI >30, presenting with severe dysmenorrhea and confirmed adenomyosis via ultrasonography. Exclusion criteria included a history of thromboembolic disorders, malignancy, or contraindications to progestin therapy.

Intervention

Participants were administered dienogest 4 mg daily (2 mg twice daily) for eight weeks, followed by 2 mg once daily for 12 weeks. All women received counselling on lifestyle modifications, including dietary changes (reduced carbohydrates) and increased physical activity.

Data collection

Symptoms, side effects, and adherence were documented at monthly follow-ups. Pain severity was assessed using a visual analog scale (VAS), and data were analyzed using STATA 11.0.

RESULTS

The study included 110 women with a mean age of 36.24 years and a mean BMI of 31.36.

Table 1 shows the summary of most participants (64%) were from rural areas, and dietary habits showed 71% consumed a mixed diet while 29% were vegetarian. The intervention demonstrated an 81% success rate in symptom relief, with significant reductions in pain scores (VAS mean 6.7 to 2.1, $p<0.05$). Adverse effects such as mild headache, breast discomfort, and weight gain were reported but were generally well-tolerated.

Table 1 shows the summary of irregular bleeding led to drug discontinuation in 3% of cases, while no severe adverse events were observed. Lifestyle adherence played a crucial role, as 30% of women required the higher dose of 4mg beyond 8 weeks due to poor compliance with dietary and exercise recommendations.

Table 1: Baseline characteristics.

Characteristics	Stats
No. of subjects	110
Age (in years)	
Mean (SD)	36.24 (6.72)
Min-max	31–52
Food, N (%)	
Veg	32 (29)
Mixed	78 (71)
Marital status, N (%)	
Yes	105 (95)
No	5 (5)
Area	
Rural	70 (64)
Urban	40 (36)
Symptoms, N (%)	
Menorrhagia with dysmenorrhea	34 (31)
Sever pain abdomen	17 (15)
Dysmenorrhea	12 (11)
Back pain	11 (10)
Anxious to conceive	10 (09)
Chronic pelvic pain	12 (11)
Irregular periods	05 (05)
Dyspareunia	02 (02)
Others	07 (06)
Pain scale	
Mean (SD)	6.7 (0.851)
Min-Max	4–8
Duration, months	
Mean (SD)	4.17 (2.25)
Min-Max	03-08
Diagnosis, N (%)	
Adenomyosis	36 (33)
Endometriosis cyst	27 (25)
Bulky uterus	25 (23)
Infertility	10 (09)
Fibroid uterus	10 (09)
Others	02 (01)
BMI	
Mean (SD)	31.36 (1.58)
Min-Max	27-35

Table 2: Complication details.

Complication	No. of patients	%
No	92	85
Yes	18	15
Total	110	100

Table 3: Outcome measures.

Outcome	No. of patients	%
Success	89	81
Failure	21	19
Total	110	100

Table 1 shows the summary of at baseline, the most common symptoms included menorrhagia with dysmenorrhea (31%), severe abdominal pain (15%), and chronic pelvic pain (11%), with a smaller percentage reporting dyspareunia (2%). After treatment with 4mg Dienogest, 81% of participants experienced significant symptom improvement, including reduced pain scores (VAS mean improved from 6.7 to 2.1, $p<0.05$). Adverse effects such as mild headache (15%), breast discomfort (10%), and weight gain (8%) were reported but generally well-tolerated. Irregular bleeding led to discontinuation in 3% of cases. Overall, the treatment was effective in alleviating symptoms, with lifestyle adherence identified as a key factor for optimal outcomes.

The primary symptoms reported at baseline included menorrhagia with dysmenorrhea (31%), severe abdominal pain (15%), chronic pelvic pain (11%), and dyspareunia (2%). Table 3 shows the summary of following treatment with 4mg dienogest, 81% of participants experienced significant improvement in these symptoms, with a notable reduction in pain scores (VAS mean reduced from 6.7 to 2.1, $p<0.05$). Mild adverse effects, such as headache (15%), breast discomfort (10%), and weight gain (8%), were observed, with irregular bleeding leading to discontinuation in 3% of cases. The treatment was well-tolerated overall and effectively alleviated symptoms in the majority of participants.

DISCUSSION

The findings suggest that higher doses of dienogest (4 mg daily) effectively manage adenomyosis in obese women, likely due to altered pharmacokinetics and increased estrogen production in adipose tissue.[5,6] While adverse effects were mild, strict lifestyle adherence played a crucial role in achieving optimal outcomes.[17-24] Pharmacokinetics in obesity, including altered drug absorption and distribution, may necessitate dose adjustments in some individuals.[5,6]

This study has several limitations that should be acknowledged. First, the relatively small sample size may limit the generalizability of the findings, particularly to broader populations with varying degrees of obesity or different ethnic backgrounds.[1] Second, the study did not include a control group receiving the standard 2 mg dose of dienogest, which would have allowed for a direct comparison of efficacy and safety.[8,9] Third, adherence to medication was based on self-reporting, which may introduce bias. Additionally, while imaging was used to assess uterine volume, inter-observer variability in measurements may have affected the accuracy of these outcomes.[4] Finally, the study did not assess long-term side effects beyond the 12-month treatment period, so further research is needed to evaluate the sustainability and safety of high-dose Dienogest over longer durations.[11-14]

This study assessed the efficacy and tolerability of dienogest 4 mg daily in obese women (BMI >30 kg/m²) with adenomyosis, a subgroup often underrepresented in clinical trials. Our findings suggest that dienogest at this higher dose effectively reduced pelvic pain and uterine volume over a six-month period, with acceptable side effect profiles. These results offer insight into an important intersection of hormonal therapy, adenomyosis, and obesity a triad of growing clinical relevance.

Dienogest has been well-established as a treatment for endometriosis and adenomyosis due to its selective progestin activity, effective endometrial suppression, and good safety profile.[7,8,10] Most previous trials have used 2 mg daily doses in average-weight women. In our study, the higher dose of 4 mg was chosen in consideration of altered pharmacokinetics in obese patients, a phenomenon documented in contraceptive and hormonal therapies.[5,6] Our results corroborate earlier findings that higher BMI can impair the efficacy of standard hormonal regimens, necessitating dose adjustments for optimal outcomes.

Notably, the reduction in pain scores observed in our cohort is consistent with the findings of Muzii et al and Maiorana et al, who reported significant decreases in dysmenorrhea and chronic pelvic pain with long-term dienogest use.[7,12] Furthermore, we found a statistically significant decrease in uterine volume, aligning with the results of previous studies where dienogest led to the shrinkage of adenomyotic lesions through decidualization and atrophy of ectopic endometrium.[11,13]

A point of divergence in our study is the higher rate of breakthrough bleeding and breast tenderness compared to previous studies.[14,15] This could be attributed to both the higher dose and the metabolic milieu associated with obesity. Despite these side effects, the discontinuation rate remained low, suggesting good overall tolerability-a finding echoed in long-term follow-up studies by La Torre et al.[11]

Our study adds to the growing body of evidence that individualized hormonal treatment strategies may be necessary for obese women with endometriosis or adenomyosis. Obesity is known to alter steroid metabolism and increase peripheral aromatization, potentially blunting the effectiveness of standard-dose progestins.[17-19] While

lifestyle modification remains a cornerstone in the management of obesity, its integration with pharmacological therapies like dienogest can offer more immediate symptom control.[20-24]

In summary, our findings support the hypothesis that a 4 mg daily dose of dienogest may be more suitable for obese women with adenomyosis, providing enhanced symptom control without significantly compromising tolerability. However, randomized controlled trials with larger sample sizes and longer follow-up periods are necessary to validate these observations.

The study demonstrated that a higher dose of Dienogest (4 mg) was effective in managing symptoms of adenomyosis in women with a BMI >30, Table 3 shows summary of with a success rate of 81% and significant improvements in pain scores (VAS mean reduction from 6.7 to 2.1, $p<0.05$). While the treatment was well-tolerated, mild side effects such as headache (15%), breast discomfort (10%), and weight gain (8%) were reported.

Irregular bleeding led to discontinuation in 3% of cases. Notably, 30% of women required the higher dose beyond 8 weeks due to poor adherence to lifestyle modifications, emphasizing the importance of dietary and exercise compliance. The absence of severe adverse events, including thromboembolic complications, highlights the safety and tolerability of the regimen. These findings suggest that short-term use of 4mg Dienogest is a viable option for symptom relief in this population, particularly when combined with lifestyle interventions.

The study highlights the importance of personalized treatment strategies for obese women with adenomyosis. Regular follow-ups, dietary counselling, and physical activity are essential components of management.

CONCLUSION

Higher doses of dienogest (4 mg daily) are effective and well-tolerated in obese women with adenomyosis who do not respond to standard dosing. However, individualized treatment plans, emphasizing lifestyle modifications and regular monitoring, are critical for sustained symptom relief and improved quality of life.

While the standard 2mg dose of dienogest is generally sufficient for most individuals, a higher dose of 4 mg can provide significant benefits for women with adenomyosis and a BMI >30. The study demonstrated that short-term use of 4 mg dienogest for 8-12 weeks effectively alleviated symptoms in this population, particularly when combined with lifestyle interventions. However, higher doses are not routinely recommended, and treatment should be individualized, with regular follow-up to monitor efficacy and potential side effects. Personalized medical advice is essential to ensure optimal outcomes and safety.

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