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Original Research Article

Effect of cabergoline and metformin combination therapy in the treatment of infertile women with symptomatic endometrioma: comparison with cabergoline alone

Asma Akter[1]*, Jesmine Banu[2], Jahirul Islam[3], Shakeela Ishrat[2], Rafikunnahar Renu[1], Tanzina Iven Chowdhury[4], Rawnok Laila[2], Nastaran Lasker[5], Tahmida Islam[6]

[1]Department of Obstetrics & Gynaecology, Dhaka Medical College Hospital, Dhaka, Bangladesh
[2]Department of Reproductive Endocrinology and Infertility, Bangladesh Medical University, Dhaka, Bangladesh
[3]Department of Internal Audit, Bangladesh Bank, Dhaka, Bangladesh
[4]Department of Obstetrics & Gynaecology, Bangladesh Medical University, Dhaka, Bangladesh
[5]Department of Reproductive Endocrinology and Infertility, Dr. Sirajul Islam Medical College, Dhaka, Bangladesh
[6]Department of Obstetrics & Gynaecology, 250 Bedded Mohammad Ali Hospital, Bogura, Bangladesh

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***Correspondence:**
Dr. Asma Akter,
E-mail: dr.asmatania@gmail.com

ABSTRACT

Background: Endometrioma is a prevalent manifestation of endometriosis and a common cause of infertility in women of reproductive age. This study aimed to evaluate the effectiveness of cabergoline alone versus in combination with metformin in infertile women with symptomatic endometrioma.
Methods: This randomized controlled trial was conducted in the Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from July 2022 to June 2023. This study included 50 women with clinically and sonologically diagnosed cases of endometrioma and dysmenorrhea attending the Reproductive Endocrinology and Infertility outpatient Department. Participants were assigned to two treatment groups: Group A (Cabergoline with metformin) and Group B (Cabergoline alone).
Results: Baseline demographic and clinical characteristics were comparable between the groups. At 3 months, both groups showed significant reductions in pain scores (Group A: 5.38±2.52; Group B: 4.86±1.52) and endometrioma size (Group A: 1.11±0.75 cm; Group B: 0.72±1.10 cm), with slightly higher reductions in Group A. However, the differences were not statistically significant ($p>0.05$). Endometrioma size reduction was more pronounced in Group A (mean difference: 1.11 cm vs. 0.72 cm; effect size 1.26 vs. 0.75). Side effects were mild and comparable in both groups, with no statistically significant differences.
Conclusions: This study showed that both treatment regimens significantly improved pain and reduced endometrioma size, with no significant difference in outcomes between the groups. The combination of cabergoline and metformin may offer a slight advantage in reducing endometrioma size and improving fertility outcomes.

Keywords: Cabergoline, Endometrioma, Infertility, Metformin, Pain score

INTRODUCTION

Endometriosis is a chronic condition where tissue similar to the endometrial lining of the uterus grows outside the uterus. It affects around 10% of women of reproductive age, with a notably higher prevalence, about 25-40%, in those experiencing infertility.[1,2] This progressive disease often leads to significant pelvic pain, the development of

ovarian cysts known as endometriomas, infertility, and an overall reduced quality of life. Endometriomas are ovarian cysts lined with ectopic endometrial tissue and are found in approximately 17-44% of women with endometriosis.[3]

Despite being widely studied; the exact cause of endometriosis remains unclear. The most accepted theory is Sampson's hypothesis of retrograde menstruation, where menstrual blood flows backward through the fallopian tubes into the pelvic cavity, implanting endometrial tissue on peritoneal surfaces.[4] Other contributing factors may include immune system dysfunction, genetic predisposition, hormonal imbalances, oxidative stress, angiogenesis, and environmental influences.[5] Endometriosis creates a pro-inflammatory and immunologically altered environment. Cytokines play a key role in the inflammatory process, and angiogenesis, the formation of new blood vessels, is crucial for the establishment and persistence of endometriotic lesions.[6] Elevated levels of vascular endothelial growth factor (VEGF) have been found in endometriotic lesions and peritoneal fluid, supporting angiogenesis and lesion progression.[7] Histological studies further highlight the importance of angiogenesis in sustaining endometriosis.[4]

Treatment for endometriomas typically includes both medical and surgical options. Laparoscopic excision is the standard surgical approach, but it is costly, invasive, and can reduce ovarian reserve. Hormonal treatments such as progestins, oral contraceptives, dienogest, danazol, and GnRH analogs are commonly used to alleviate pain and reduce lesion size. However, they often inhibit ovulation and are associated with side effects like hormonal suppression, progesterone resistance, and high recurrence rates once treatment is stopped. Due to these limitations, interest has grown in non-hormonal therapies such as cabergoline and metformin, which may offer effective symptom control without suppressing ovulation. These drugs are generally well-tolerated, affordable, and more accessible compared to conventional hormonal therapies.

Research suggests that dopamine agonists like cabergoline inhibit VEGF-induced angiogenesis without toxic effects.[8] Cabergoline promotes the internalization of VEGF receptor-2 (VEGFR-2) in endothelial cells, thereby disrupting angiogenesis. This mechanism contributes to the regression of endometriotic lesions by reducing cell proliferation and angiogenic activity.[2] Clinical studies have shown significant improvement in pain and reduced VEGF receptor levels in patients treated with cabergoline, with few reported adverse effects.[9] One study even found that cabergoline was more effective than GnRH agonists in shrinking endometriomas, with added benefits such as lower cost, ease of use, and fewer side effects.[2]

Metformin, a well-established antidiabetic drug, also shows promise in treating endometriosis due to its anti-inflammatory and anti-proliferative properties.[10,11] It has been shown to reduce serum levels of inflammatory cytokines such as IL-6, IL-8, and VEGF, alleviate symptoms, and improve fertility outcomes.[12] In animal models, metformin improved endometrial receptivity by upregulating genes like LIF and HOXA10, while downregulating proangiogenic and matrix-remodeling genes such as VEGF and MMP-9.[13] Additionally, it may inhibit vascular cell adhesion molecule-1 expression, which plays a role in lesion implantation.[14] Metformin also promotes apoptosis in endometrial cells by lowering p53 expression, thereby contributing to disease control.[15]

Both cabergoline and metformin independently show improvements as non-hormonal treatments for endometriosis, targeting inflammation, angiogenesis, and lesion proliferation without compromising fertility. Given their complementary mechanisms, combining the two may offer improved therapeutic benefits. Therefore, this study aimed to compare the effectiveness of combination therapy with cabergoline and metformin versus cabergoline alone in infertile women suffering from symptomatic endometrioma.

METHODS

This randomized controlled trial was conducted in the Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from July 2022 to June 2023. In this study, we included 50 women with clinically and sonologically diagnosed cases of endometrioma and dysmenorrhea attending the outpatient Department of Reproductive Endocrinology and Infertility. Participants were assigned to two treatment groups: Group A received cabergoline with metformin, and Group B received cabergoline alone.

These are the following criteria to be eligible for enrollment as our study participants:

Inclusion criteria

Diagnosed case of endometrioma by transvaginal sonography, mean diameter <5cm; patients presented with dysmenorrhea; infertile women aged 18 to 40 years were included in the study.

Exclusion criteria

Any contraindications to cabergoline or metformin; known case of pulmonary, cardiac, renal, or hepatic disease; known case of psychiatric disturbance; patients having other types of ovarian cyst and bilateral tubal block; patients with severe male factor abnormalities; patients with a history of any hormonal treatment, including contraceptives, in the last 90 days were excluded from the study.

Intervention

The study was conducted on infertile women with symptomatic endometrioma who met the inclusion

criteria. Randomization was done using computer-generated permuted block random numbers with allocation concealment through serially numbered opaque envelopes. Treatment began on the first day of menstruation after baseline evaluation. There were two groups of women, Group A and Group B. In this study, Group A was the Experimental Group and Group B was the Control Group.

Group A: Tab. Cabergoline 0.5 mg (tab. Cabolin of Renata Pharmaceuticals) twice weekly orally after a meal before going to bed, and tab. metformin (tab.Comet of Square Pharmaceuticals) 500mg three times daily orally after a meal was given for three months. They stored these drugs at room temperature.

Group B: Only tab. Cabergoline 0.5 mg (tab. Cabolin of Renata pharmaceuticals) was given twice weekly after a meal before going to bed for three months.

Data collection procedure

All participants were thoroughly informed about the study's objectives, rationale, potential benefits, and possible side effects. Written informed consent was obtained. Data collection included interviews, physical examinations, and laboratory investigations, documented in a structured datasheet. Baseline assessments covered demographics, endometrioma size, pelvic pain characteristics, and prior treatments.

Endometrioma size was measured pre- and post-treatment using the same transvaginal ultrasound machine (Mindray DP-2200 Plus, 6.5 MHz transducer), with the mean of the largest two perpendicular diameters of each endometrioma. Pain intensity, including dysmenorrhea, was assessed using a 10 cm Visual Analog Scale (VAS), where patients marked their pain on a line ranging from 0 ("no pain") to 10 ("worst pain imaginable"). Patients were followed monthly for compliance and adverse effects. At the end of the third month, a second assessment was conducted, recording endometrioma size and VAS scores.

Statistical analysis

All data were recorded systematically in a pre-formatted data collection form. Quantitative data was expressed as mean and standard deviation, and qualitative data was expressed as frequency distribution and percentage. Student's t-test was used for continuous variables, while the chi-square test was used for categorical variables. Paired sample t-test was used for comparing measurements before and after treatment, and an independent samples t-test (Unpaired t-test) for comparing between 2 groups of treatment arms. A p-value <0.05 was considered significant. Statistical analysis was performed by using SPSS 19 (Statistical Package for Social Sciences) for Windows version 26. This study was ethically approved by the Institutional Review Committee of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

RESULTS

This randomized controlled trial included 50 women diagnosed with endometrioma who were selected for treatment as part of the study. The participants were randomly divided into two groups: Group A (25 patients) received a combination of cabergoline and metformin, while Group B (25 patients) received cabergoline alone. By the third month of follow-up, one patient from each group was lost to follow-up. Additionally, three patients in Group A and two in Group B became pregnant during the study period. The data collected from both groups were analyzed, and the results are presented in the following tables.

Table 1: Baseline demographic characteristics of study patients (n=50).

Variables	Group A (n=25)	Group B (n=25)	P value
Age (in years)	**N (%)**	**N (%)**	
<20	1 (4.0)	2 (8)	
20-30	17 (68.0)	14 (56.0)	
31-40	7 (28.0)	9 (36.0)	
Total	25 (100.0)	25 (100.0)	
Mean age (years±SD)	28.29±4.79	28.41±6.85	0.845
BMI (kg/m²)			
18.5-24.9	14 (56%)	13 (52)	
25-29.9	11 (44%)	12 (48)	
Mean BMI	24.25±2.58	24.95±1.86	0.3007
Household income			
<30,000	11 (44.0)	12 (48.0)	0.552
≥30,000	14 (56.0)	13 (52.0)	
Occupation			
Housewife	21 (84.0)	20 (80.0)	
Service	4 (16.0)	4 (16.0)	0.300
Others	0 (0.0)	1 (4.0)	
Residence			
Urban	21 (84.0)	19 (76.0)	0.440
Rural	4 (16.0)	6 (24.0)	
Duration of infertility (year)			
≤5	12 (48)	10 (40.0)	0.462
>5	13 (52.0)	15 (60.0)	
Type of infertility			
Primary infertility	20 (80.0)	21 (84.0)	0.507
Secondary infertility	5 (20.0)	4 (16.0)	

Group A=Cabergoline and Metformin, Group B =Cabergoline

Table 1 shows that the mean age of participants was comparable between the two groups (28.29±4.79 years in Group A vs. 28.41±6.85 years in Group B; p=0.845). Most patients in both groups were aged 20-30 years. The mean BMI was also similar between the groups (24.25±2.58 kg/m² in Group A vs. 24.95±1.86 kg/m² in Group B; p=0.3007). The majority of participants had a household

income ≥30,000, were housewives, and resided in urban areas. Duration and type of infertility were also comparable, with most women experiencing infertility for more than five years and a higher prevalence of primary infertility in both groups. There were no statistically significant differences between the groups for any baseline variables (p>0.05).

Table 2: Baseline comparison of visual analog score and endometrioma size between the two groups (n=50).

Variables	Group A (n=25)	Group B (n=25)	P value
	Mean±SD	Mean±SD	
Visual analog scale score	8.32±2.12	7.6±2.10	0.239
Size of endometrioma (cm)	3.64±0.82	3.35±0.69	0.227

Group A=Cabergoline and Metformin, Group B =Cabergoline

Table 2 shows that the mean VAS score was slightly higher in Group A (cabergoline + metformin) at 8.32±2.12 compared to 7.6±2.10 in Group B (cabergoline alone), although this difference was not statistically significant (p=0.239). Similarly, the mean size of endometriomas was 3.64±0.82 cm in Group A and 3.35±0.69 cm in Group B, also showing no significant difference (p=0.227).

Table 3: Distribution of the study population by pregnancy at the 3rd month follow-up (n=48).

Pregnancy	Group A (n=24)		Group B (n=24)		RR
	N	%	N	%	
Yes	3	12.5	2	8.33	1.5
No	21	87.5	22	91.67	

Group A=Cabergoline and Metformin, Group B =Cabergoline

Table 4: Pre-treatment and post-treatment comparison of the size of endometrioma and pain score in Group A and Group B (N=43).

Variables	Group A (n=21)	Group B (n=22)
Visual analog scale score		
At baseline	8.62±2.01	7.77±2.14
After 3 months	3.24±2.72	2.91±2.49
Mean difference	5.38±2.52	4.86±1.52
Effect size	1.98	1.95
P-value	0.000	0.000
Size of endometrioma (cm)		
At baseline	3.79±0.77	3.46±0.63
After 3 months	2.68±0.88	2.74±0.96
Mean difference	1.11±0.75	0.72±1.10
Effect size	1.26	0.75
P value	0.000	0.006

Group A=Cabergoline and Metformin, Group B =Cabergoline

Table 3 displays the distribution of pregnancy outcomes at the 3-month follow-up among participants in both groups (n=48). In Group A, 3 out of 24 participants (12.5%) achieved pregnancy, compared to 2 out of 24 (8.33%) in Group B. The relative risk (RR) of pregnancy in Group A compared to Group B was 1.5. Although Group A showed a higher pregnancy rate, the difference was not substantial within this short follow-up period.

Table 4 shows the pre- and post-treatment comparison of pain scores and the size of endometrioma in both treatment groups over 3 months. In Group A, the mean pain score significantly decreased from 8.62±2.01 at baseline to 3.24±2.72 after treatment, with a mean reduction of 5.38±2.52 and a large effect size of 1.98 (p=0.000). Similarly, Group B showed a significant reduction in pain score from 7.77±2.14 to 2.91±2.49, with a mean difference of 4.86±1.52 and an effect size of 1.95 (p=0.000). Regarding endometrioma size, Group A showed a decrease from 3.79±0.77 cm to 2.68±0.88 cm, with a mean reduction of 1.11±0.75 cm and an effect size of 1.26 (p=0.000). Group B also experienced a reduction from 3.46±0.63 cm to 2.74±0.96 cm, with a smaller mean difference of 0.72±1.10 cm and an effect size of 0.75 (p=0.006).

Table 5: Post-treatment comparison of the size of endometrioma and pain score between the two groups (n=43).

Variables	Group A (n=21)	Group B (n=22)	P value
	Mean±SD	Mean±SD	
Visual analog scale score	3.24±2.72	2.91±2.49	0.739
Size of endometrioma (cm)	2.68±0.88	2.74±0.96	0.715

Group A=Cabergoline and Metformin, Group B =Cabergoline

Table 5 compares post-treatment outcomes between the two groups in terms of pain severity (measured by the Visual Analog Scale) and endometrioma size after 3 months of therapy. The mean pain score was slightly lower in Group B at 2.91±2.49 compared to 3.24±2.72 in Group A, but the difference was not statistically significant (p=0.739). Similarly, the average size of endometrioma after treatment was 2.68±0.88 cm in Group A and 2.74±0.96 cm in Group B, with no significant difference between the two groups (p=0.715).

Table 6 shows the side effects among participants in both treatment groups. In Group A, side effects included nausea or vomiting in 10% of patients, bowel syndrome in 10%, headache in 5%, dizziness in 10%, and irregular bleeding in 5%. Group B showed fewer side effects overall, with nausea or vomiting, headache, dizziness, and irregular bleeding each reported in 5-10% of cases, and postural hypotension reported in one participant (5%). None of the differences in side effect incidence between the groups were statistically significant (p>0.05).

Table 6: Side effects of the study population (n=43).

Side effects	Group A (n=21)		Group B (n=22)		P value
	N	%	N	%	
Nausea or vomiting	2	10	1	5	0.432
Bowel syndrome	2	10	0	0	0.623
Headache	1	5	1	5	0.231
Dizziness	2	10	1	5	0.395
Postural hypotension	0	0	1	5	0.412
Irregular bleeding	1	5	2	10	0.276

Group A=Cabergoline and Metformin, Group B =Cabergoline

DISCUSSION

In this study, we compared the effectiveness of combination therapy with cabergoline and metformin versus cabergoline alone in infertile women with symptomatic endometrioma. Fifty patients were enrolled and equally divided into two groups. During the three-month follow-up, one patient from each group was lost to follow-up, and pregnancy was achieved in three patients from the combination group and two from the cabergoline-only group.

Most participants in both groups were aged between 20 and 30 years-68% in the combination group and 56% in the cabergoline group. The mean age was similar between the groups: 28.29±4.79 years in Group A (cabergoline and metformin) and 28.41±6.85 years in Group B (cabergoline only). These values are slightly lower than those reported by Hamid et al (2014), who found mean ages of 31.10±2 and 29.06±3 in their study groups, and by Chandra et al., who reported a higher mean age of 34.1±7.2 years.[2] Foda et al (2012) found comparable mean ages to ours, particularly in the metformin group (27.12±3.48 years).[12]

Primary infertility was the predominant diagnosis in both groups-80% in the combination group and 84% in the cabergoline group. No significant differences were observed in demographic characteristics between the two groups ($p>0.05$). These findings align with those of Hamid et al (2014), who also reported a higher prevalence of primary infertility in their study population.[2]

More than half of the participants in both groups had experienced infertility for more than five years, highlighting the significant role endometriosis plays in infertility. The average BMI was within the normal range for both groups: 24.25±2.58 kg/m² in the combination group and 24.95±1.86 kg/m² in the cabergoline group. These values are lower than those reported by Foda et al (2012), who found higher average BMIs in both study groups.[12]

Pain, measured by the Visual Analog Scale (VAS), also improved in both groups. While Group B had a slightly lower mean post-treatment score (2.91±2.49) compared to Group A (3.24±2.72), the difference was not statistically significant ($p=0.739$). Similar findings were reported by Foda et al (2012), who noted a significant reduction in dysmenorrhea and pelvic pain in patients treated with metformin.[12] Hamid et al (2014) also demonstrated that cabergoline significantly reduced endometriosis-related pain. Kyal et al (2019) and DiVasta et al (2021) further supported cabergoline's efficacy in reducing pain when compared to other agents like medroxyprogesterone acetate and NETA, respectively.[9,16] Additionally, Shume et al (2021) found cabergoline to be more effective than dienogest in lowering VAS scores.[17]

Following three months of treatment, the mean size of endometrioma decreased in both groups, with no statistically significant difference between them (2.68±0.88 cm in Group A vs. 2.74±0.96 cm in Group B, $p=0.715$). A study by Hamid et al (2014) found cabergoline to be significantly more effective than LHRH agonists (64.1% vs. 21.7%).[2] This supports the use of cabergoline as a potential first-line treatment for smaller endometriomas (<5cm) before opting for surgical intervention.

In terms of pregnancy outcomes, our study observed a slightly higher pregnancy rate in the combination group (12.5%) compared to the cabergoline-only group (8.3%), though this difference was not statistically significant. Foda and Aal (2012) reported a notable improvement in pregnancy rates with metformin treatment, rising from 0% at baseline to 25.7% after six months, which was statistically significant ($p<0.001$).[12] Their results reinforce the potential role of metformin in enhancing fertility among women with endometriosis.

Adverse effects reported in our study were mild and comparable between the two groups. The most common side effects included nausea, vomiting, dizziness, headache, irregular bleeding, and postural hypotension in group A, while group B experienced nausea, vomiting, headache, irregular bleeding, dizziness, and postural hypotension. No statistically significant differences were found in the frequency of side effects between the groups. These findings are consistent with those of Kyal et al (2019), who reported fewer side effects in the cabergoline group compared to medroxyprogesterone acetate,[16] and Hamid et al (2014), who found minimal adverse events across both treatment groups in their study.[2]

The first in vitro study to explore metformin's role in endometriosis was published in 2007 by Takemura et al, who reported that metformin could be effective in treating endometriosis by examining its impact on inflammatory responses, estradiol production, and the proliferation of endometriotic stromal cells. The researchers found that endometriotic cells released interleukin-1 beta (IL-1β), which in turn stimulated the secretion of interleukin-8 (IL-

8), promoting further cell proliferation. Metformin was shown to suppress both IL-1β and IL-8 production, effectively inhibiting the proliferation of endometriotic cells.[18]

A subsequent in vitro study by Zhou et al (2015) provided additional insight into metformin's anti-inflammatory effects. The study demonstrated that metformin could reduce the production of prostaglandin E2 (PGE2) in endometriotic cells by downregulating the expression of CYP19A1 and decreasing aromatase activity.[19] Another investigation, also published in 2015 by Zhang et al, found that ectopic endometriotic stromal cells (ESCs) expressed and secreted significantly higher levels of Wnt2 protein compared to normal endometrial stromal cells (NSCs). In these ESCs, metformin was able to reduce both the expression and secretion of Wnt2. Since Wnt2/β-catenin signaling is involved in stromal-epithelial cell interaction and contributes to cellular expansion in endometriosis, the study suggested that metformin may help regulate this communication pathway.[20]

These findings, including our study, highlight metformin's therapeutic potential in treating endometriosis among infertile women by targeting inflammatory pathways, hormonal activity, and intercellular signaling.

This study has few limitations. Our study was a single-center study, so it does not represent the whole community. We took a small sample size due to the short study period. After evaluating those patients, we did not follow up with them for the long term and did not know other possible interference that may happen in the long term with these patients.

CONCLUSION

In our study, we found that the size of endometrioma and pain decreased significantly in women with endometriosis having combined (cabergoline and metformin) therapy as well as cabergoline alone. Although the comparison between the two groups was not statistically significant ($p>0.05$), the group receiving metformin in addition to cabergoline showed a comparatively greater reduction in endometrioma size and pain.

Recommendations

Further study with a prospective and longitudinal study design, including a larger sample size, needs to be done to validate the findings of our study and to demonstrate the efficacy of metformin in the management of endometriosis.

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