International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Shah H et al. Int J Reprod Contracept Obstet Gynecol. 2025 Jul;14(7):2298-2304
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20251982

Original Research Article

Effect of metformin plus statin combination therapy compared to metformin alone in infertile woman with symptomatic endometrioma

Hritu Shah[1]*, Fawzia Hossain[2], M. Ariful Islam[1], Rebeka Sultana[3], Mostafa M. Al Tarique[1], Chowdhury Faisal Alamgir[4], Maliha Darmini[5], Nur-Wa-Bushra Jahan[6], Jesmine Banu[1]

[1]Department of Reproductive Endocrinology and Infertility, Bangladesh Medical University, Dhaka, Bangladesh
[2]Department of Gynaecological Oncology, Bangladesh Medical University, Dhaka, Bangladesh
[3]Department of Reproductive Endocrinology and Infertility (OSD), Directorate General of Health Services (DGHS), Dhaka, Bangladesh
[4]Department of Urology, New Cross Hospital, The Royal Wolverhampton NHS Trust, United Kingdom
[5]Department of Gynecology, Mymensingh Medical College and Hospital, Mymensingh, Bangladesh
[6]Department of Obstetrics and Gynaecology (OSD), Directorate General of Health Services (DGHS), Dhaka, Bangladesh

Received: 21 May 2025
Accepted: 18 June 2025

***Correspondence:**
Dr. Hritu Shah,
E-mail: hritushah873@gmail.com

ABSTRACT

Background: Endometriosis is an estrogen-dependent inflammatory condition characterized by endometrial tissue growth outside the uterus. Metformin suppresses estrogen production and has anti-inflammatory, anti-proliferative, and anti-angiogenic effects. Statins inhibit cholesterol synthesis and offer anti-inflammatory actions, reducing angiogenesis, invasion, adhesion, and lowering MCP-1 and MMP-3 levels. This study compares metformin plus statin versus metformin alone in infertile women with symptomatic endometrioma.
Methods: A randomized controlled trial was conducted in the department of reproductive endocrinology and infertility, BSMMU. Forty women with symptomatic endometrioma diagnosed via transvaginal ultrasound (TVS) were randomized into two groups. The experimental group received metformin 500 mg thrice daily plus atorvastatin 40 mg once daily; the control group received only metformin. Treatment lasted 3 months. Outcomes-endometrioma size (TVS), pain [visual analog scale (VAS)], and complement C3 level (Nephelometry)-were measured pre-and post-treatment. Data were analyzed using SPSS v.26.
Results: After treatment, the experimental group showed significant reductions in endometrioma size (3.50±0.82 vs 2.41±0.52 cm) and pain score (6.80±1.67 vs 3.13±2.32) from baseline ($p<0.05$). The control group showed significant reductions in endometrioma size (3.40±0.96 vs 2.92±0.80 cm) and pain score (6.65±2.10 vs 3.47±2.09) from baseline ($p<0.05$). Serum complements levels increased in both groups insignificantly. Endometrioma size reduction was significantly higher in the experimental group (1.06±0.53 vs 0.45±0.44 cm), but pain score and complement level reductions showed no significant difference between groups.
Conclusions: Metformin plus statin shows significantly better reduction in endometrioma size compared to Metformin alone in treating symptomatic endometrioma in infertile women.

Keywords: Endometrioma, Statin, Metformin, Complement

INTRODUCTION

Endometrioma develops when endometriosis occurs in the ovaries and leads to cyst production. Endometriosis is when tissue similar to the uterine lining grows outside the ovaries. This tissue can cause complications, including infertility.[1] This proliferation leads to inflammation, scarring, infertility, irregular menstrual cycles, and pelvic pain. Incontinence is another possible outcome.[2,3] While statins and metformin are both medications, they work

differently and treat different conditions.[4]

The growth of endometrial glands and stroma beyond the uterine cavity is a hallmark of endometriosis, an estrogen-dependent inflammatory condition.[5] About 10% of women of reproductive age have endometriosis.[6] The prevalence of endometriosis in infertile women is 25% to 40%.[7] These women may be asymptomatic, but most present with chronic pelvic pain, dysmenorrhea, dyspareunia, infertility, adnexal mass, or endometrioma. Endometriomas were found in 17% to 44% of patients with endometriosis.[1] One theory about endometriosis development is retrograde menstruation, where menstrual blood flows backward through the fallopian tubes into the abdominal area. Implantation and angiogenesis must occur for this tissue to grow outside the uterus. Ectopic fixation and endometrial stromal and gland growth are necessary to create endometrial implants. The invasive insertion of endometriotic tissues involves extracellular matrix degradation and altered expression of matrix metalloproteinases (MMPs) in the eutopic and ectopic endometrium.[8] Interleukin-6 in peritoneal fluid may initiate an inflammatory response in endometriosis pathogenesis.[9]

Treatment options for management include medication and surgery, depending on ovarian reserve, lesion size, symptoms, and desire to have children. Laparoscopic excision of ovarian endometrioma is a common surgical procedure, though expensive, invasive, and reduces ovarian reserve. Medical therapy aims to lower estrogenic and inflammatory status. Progesterone, danazol, oral contraceptives, Dienogest, GnRH-analogs help with pain symptoms and lesion regression, but inhibit ovulation. Their side effects limit long-term use, and recurrence rates after stopping are high. Therefore, non-hormonal medications like statins and metformin are well tolerated and may not inhibit ovulation. This treatment should be as effective as hormonal treatment.

Complement involves both the innate and adaptive immune systems. C3 is a component of the alternative pathway. "The pathophysiology of endometriosis (EM) is an excellent example of immune dysfunction." Complement participation has been linked to disease activity and damage. Attempts have been made to correlate endometriosis with various laboratory measures, including complements. The disruption of complement system activation regulation may significantly influence the pathophysiology of endometriosis and infertility.[10]

Metformin is an oral prescription used primarily to lower blood sugar levels in people with type 2 diabetes.[11] It has been examined as a treatment for reproductive problems, including polycystic ovarian syndrome (PCOS), which is related to endometriosis. Metformin can increase insulin sensitivity and address hormonal abnormalities, reducing symptom intensity.[12]

Statins are drugs commonly used to lower blood cholesterol levels by inhibiting a liver enzyme required for cholesterol production.[13] Statins have shown therapeutic effects in lowering cholesterol, reducing inflammation, and potentially preventing cancer.[14] Metformin improves insulin sensitivity and treats polycystic ovary syndrome.[15] It is active against endometriosis through anti-inflammatory and anti-proliferative effects, reducing pro-inflammatory cytokines.[16] Metformin causes regression of endometriotic implants and suppresses angiogenesis. In rats treated with metformin, superoxide dismutase and MMP-2 increased while VEGF and MMP-9 decreased in endometrial lesions.[17]

Metformin may help endometriosis patients who don't respond to hormones and desire pregnancy. It could combine with hormonal treatment, allowing dose reduction. Both metformin and statin are effective, cost friendly and may not delay fertility. This study was performed to determine the impact of metformin and statins in treating symptomatic endometrioma. These non-hormonal drugs may be effective in treating symptomatic endometrioma.

Objectives

The objective of this study was to evaluate the clinical and biochemical response of symptomatic endometrioma with metformin plus statin compared to metformin alone.

METHODS

This study was a randomized controlled trial conducted in the department of reproductive endocrinology and infertility, Bangabandhu Sheikh Mujib medical university (BSMMU), Shahbag, Dhaka, Bangladesh, from July 2023 to December 2024. A total of 40 infertile women with symptomatic endometrioma were enrolled and allocated into two treatment groups. The study population consisted of women attending the outpatient department, diagnosed with endometrioma both clinically and by transvaginal sonography. The sample size was 17 participants per group, with an additional buffer for a 15% dropout rate, resulting in 20 participants in each group (n=40).

Inclusion criteria

Women aged 18-40 years, diagnosed case of endometrioma by transvaginal sonography, with a mean diameter of <5 cm, experiencing dysmenorrhea and diagnosed with primary or secondary infertility were included.

Exclusion criteria

Known contraindication to metformin or statin, history of pulmonary, cardiac, renal, or hepatic disease, presence of other types of ovarian cysts, diagnosed with a psychological disorder and history of hormonal treatment, including contraceptives, in the last 3 months were excluded.

Study procedure

Eligible patients who met the inclusion criteria were enrolled after informed consent. Participants were randomly assigned into two groups: Group A received metformin 500 mg daily and Atorvastatin 40 mg once daily for three months. Group B received metformin 500 mg three times daily for the same duration. Baseline data were collected via interview and chart review, including demographic profile, clinical history, and previous treatment records. Endometrioma size was assessed using transvaginal ultrasonography by trained clinicians, recording the mean of the largest two transverse diameters. Pelvic pain, including dysmenorrhea and dyspareunia, was quantified using the VAS. Nephelometry measured complement level (C3). Monthly telephone follow-ups ensured compliance and captured side effects. After three months, final assessments of pain score, endometrioma size, and complement level were repeated. All data were recorded in structured data collection sheets and securely stored.

Ethical considerations

The institutional review board (IRB) of Bangladesh medical university approved the study. Ethical principles outlined in the Helsinki declaration (1964) were strictly followed. Participants were informed about the study objectives, procedures, risks, and their right to withdraw at any time. Written informed consent was obtained from each participant before enrollment. Only the principal investigator had access to identifiable data, ensuring confidentiality. No investigational or unapproved drug was used, and no placebo control was involved. Participants did not face any additional risk from the research process. The study was conducted purely as an academic research initiative with no conflict of interest.

Statistical analysis

Data were analyzed using SPSS version 26.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means and standard deviations, while categorical data were presented as frequencies and percentages. Categorical variables were compared using the Chi-square or Fisher's exact test. Paired t-tests were used to compare pre- and post-treatment values within groups, and independent t-tests were used to compare outcomes between the two groups. A $p<0.05$ was considered statistically significant.

RESULTS

This randomized controlled trial study was conducted in the department of reproductive endocrinology and infertility, BMU. A total of forty patients with symptomatic endometrioma, diagnosed by ultrasound, fulfilling the inclusion and exclusion criteria, were randomly assigned into 2 groups by sequentially numbered sealed opaque envelopes. In the experimental group, 20 patients received tab. metformin (500 mg) three times daily orally plus tab. atorvastatin (40 mg) once daily for 3 months. At the third month of follow-up, four patients became pregnant, and 1 patient was lost to follow-up in the experimental group. In the control group, 20 patients received tab. metformin (500 mg) three times daily orally for 3 months. At the third month of follow-up, one patient became pregnant, and 2 patients were lost to follow-up in the control group. Analyses of the data obtained from both groups were done. All the results are shown in the tables below.

Table 1 shows that the mean age was 27.4±6.5 years in the experimental group (Metformin plus atorvastatin) and 28.4±5.2 years in the control group (Metformin alone). The majority of the patients were housewives in both groups. Half (50.0%) of the patients came from rural areas in the experimental group, and 13 (65.0%) in the control group. The two groups had no significant differences regarding age, occupational status, residence, monthly household income, and BMI.

Table 2 shows that most of the patients had primary subfertility in both groups, with a duration of infertility ≤5 years.

Table 3 shows that there were no statistically significant ($p>0.05$) differences between the two groups at baseline mean size of endometrioma, VAS score for pain and serum complement level.

Table 4 shows that in the experimental group, after 3 months of treatment, the mean size of endometrioma and VAS score reduced significantly from baseline ($p<0.05$). However, serum complement level increased after treatment compared to pretreatment, but the difference was insignificant ($p>0.05$).

Table 5 shows that after 3 months of treatment in the control group, the mean size of endometrioma and the VAS score reduced significantly from baseline ($p<0.05$). However, serum complement level increased after treatment compared to pretreatment, but the difference was insignificant ($p>0.05$).

Table 6 shows that after 3 months of treatment, the mean size of endometrioma was statistically significant between the two groups ($p<0.05$). However, the VAS score and serum complement level were not significant ($p>0.05$) between the two groups.

Table 7 shows that after 3 months of treatment, the mean reduction in size of endometrioma was significantly higher in the experimental group than in the control group. Mean reduction visual analogue scale score was significantly higher in the experimental group than the control group, but the difference was not significant. The mean increase in serum complement level was not significant between the two groups.

Table 8 shows that the side effects were comparatively less in the control group than the experimental group, but the difference was not statistically significant between the two groups.

Table 1: Demographic characteristics of study populations, (n=40).

Demographic characteristics		Experimental group, (n=20)		Control group, (n=20)		P value
		N	%	N	%	
Age (in years)	≤20	4	20	2	10	
	21-30	10	50	11	55	
	31-40	6	30	7	35	
Mean±SD		27.4±6.5		28.4±5.2		0.595
Range (min-max)		18-39		19-37		
Occupational status	House wife	14	70	15	75	0.815
	Service holder	2	10	3	15	
	Student	1	5	1	5	
	Teacher	2	10	1	5	
	Business	1	5	0	0	
Residence	Rural	10	50	13	65	0.337
	Urban	10	50	7	35	
Household income (monthly)		22700±8000.7		21750±7745.1		0.705
Range (min-max)		10000-38000		10000-35000		
BMI (kg/m^2)	18.5-24.9	10	50	11	55	
	25.29.9	8	40	8	40	
	≥30	2	10	1	5	
Mean±SD		24.8±3.7		23.6±3.7		0.337

Table 2: Type and duration of infertility of study populations, (n=40).

Demographic characteristics		Experimental group, (n=20)		Control group, (n=20)		P value
		N	%	N	%	
Type of infertility	Primary	16	80	12	60	0.168
	Secondary	4	20	8	40	
Duration of infertility (in years)	≤5.0	14	70	15	75	0.723
	>5.0	6	30	5	25	

Table 3: Baseline comparison of size of endometrioma, VAS score, and serum complement level between 2 groups.

Variables	Experimental group, (n=20)	Control group, (n=20)	P value
	Mean±SD	Mean±SD	
Size of endometrioma (cm)	3.5±0.82	3.4±0.96	0.732
VAS score	6.8±1.67	6.65±2.10	0.805
Serum complements level (g/l)	1.27±0.23	1.37±0.46	0.411

Table 4: Changes in size of endometrioma, VAS score and serum complement level in experimental group (Metformin plus atorvastatin).

Variables	Pre-treatment, (n=20)	Post-treatment, (n=15)	Mean difference (95% CI)	Effect size	P value
	Mean±SD	Mean±SD			
Size of endometrioma (cm)	3.5±0.82	2.41±0.52	1.06 (0.76 to 1.35)	2	0.001
VAS score	6.8±1.67	3.13±2.32	3.60 (2.71 to 4.48)	2.26	0.001
Serum complements level (g/l)	1.27±0.23	1.29±0.21	-0.01 (-0.21 to 0.19)	0.03	0.897

Table 5: Changes in size of endometrioma, VAS score and serum complement level in control group (Metformin).

Variables	Pre-treatment, (n=20)	Post-treatment, (n=17)	Mean difference (95% CI)	Effect size	P value
	Mean±SD	Mean±SD			
Size of endometrioma (cm)	3.4±0.96	2.92±0.80	0.45 (0.22 to 0.67)	1.02	0.001
VAS score	6.65±2.10	3.47±2.09	3.23 (2.54 to 3.92)	2.41	0.001
Serum complements level (g/l)	1.37±0.46	1.45±0.40	-0.03 (-0.22 to 0.15)	0.08	0.691

Table 6: Post-treatment comparison of the size of endometrioma, VAS score and serum complement level between two groups.

Variables	Experimental group, (n=15)	Control group, (n=17)	Mean difference (95% CI)	Effect size	P value
	Mean±SD	Mean±SD			
Size of endometrioma (cm)	2.41±0.52	2.92±0.80	-0.51 (-1.01 to -0.01)	0.75	0.042
VAS score	3.13±2.32	3.47±2.09	-0.33 (-1.93 to 1.25)	0.15	0.699
Serum complements level (g/l)	1.29±0.21	1.45±0.40	-0.15 (-0.39 to 0.08)	0.5	0.194

Table 7: Reduction of size of endometrioma, VAS score and serum complement level between two groups.

Variables	Experimental group, (n=15)	Control group, (n=17)	P value
	Mean±SD	Mean±SD	
Size of endometrioma (cm)	1.06±0.53	0.45±0.44	0.001
VAS score	3.6±1.59	3.23±1.34	0.489
Serum complements level (g/l)	-0.01±0.36	-0.03±0.36	0.86

Table 8: Side effects of the study population.

Variables	Experimental group, (n=15)		Control group, (n=17)		P value
	N	%	N	%	
Nausea	2	13.3	1	6.7	0.588
Vomiting	1	6.7	0	0	0.469
Dry mouth	1	6.7	0	0	0.469

DISCUSSION

Endometriosis is a common, chronic gynecological disorder characterized by the presence of endometrial-like tissue outside the uterus. This ectopic tissue growth results in a range of symptoms including pelvic pain, dysmenorrhea, dyspareunia, and infertility. According to Zhang et al approximately 10% of women of reproductive age are affected.[18] Endometriosis is often resistant to conventional treatment, prompting the investigation of new pharmacologic approaches.

Metformin, widely used in managing type 2 diabetes, has demonstrated anti-inflammatory, anti-oxidative, and anti-tumor properties. Preclinical studies suggest metformin reduces endometriotic lesion growth, inhibits proliferation and invasion of endometrial cells, and relieves pain in animal models.[19] Statins, particularly atorvastatin, are potent inhibitors of cholesterol biosynthesis via HMG-CoA reductase inhibition and have shown promise in reducing angiogenesis and cell proliferation in endometriosis models.[20] Despite these findings, combination therapy involving metformin and statins not yet been adequately studied in humans with endometriosis.

This study was designed to compare therapeutic efficacy of metformin alone and in combination with statins in infertile women suffering from symptomatic endometrioma. Parameters assessed included pelvic pain (using VAS), endometrioma size and serum complement levels.

In this prospective comparative study, the experimental group received metformin plus Statin, while the control group received metformin alone. Mean age was 27.4±6.5 years in the experimental group and 28.4±5.2 years in the control group, with no statistically significant difference.

Primary infertility was present in 80% of women in the experimental group and 60% in the control group. Most participants in both groups had experienced infertility for fewer than five years. No significant difference was found regarding the type or duration of infertility, supporting previous findings by Lasker et al who also observed no meaningful differences in infertility type or duration between treatment groups.[21]

A significant reduction in endometrioma size was noted in the experimental group after three months of treatment, from a baseline of 3.50±0.82 cm to 2.41±0.52 cm (mean difference 1.06 cm). Animal studies have supported this outcome; for instance, Oktem et al reported that oral atorvastatin at 2.5 mg/kg/day significantly reduced the size of endometriotic implants in rat models.[22] Salam et al in a human study using DNZ plus atorvastatin for 3 months, observed reduction in endometrioma size from 4.86±0.77 cm to 4.77±0.91 cm.[23] Bruner-Tran et al also demonstrated a dose-dependent decrease in endometrial implant size and number in mice treated with simvastatin.[24]

Regarding pain relief, the VAS score in the experimental group significantly decreased from 6.80±1.67 to 3.13±2.32, showing a mean reduction of 3.60. Almassinokiani et al conducted the first randomized clinical trial using simvastatin (20 mg/day) after laparoscopic surgery and found pain reduction comparable to that seen with GnRHa therapy.[20] Salam et al reported a similar decline in pain score with DNZ plus statin from

6.76±1.26 to 2.81±0.93.[23] Lasker et al also documented a significant VAS score decrease with pentoxifylline plus metformin therapy (2.73±1.21, p<0.001).[21]

Regarding immune markers, a slight but statistically insignificant increase in serum complement C3 levels was observed in experimental group (mean difference -0.01 g/L). Hasan et al found elevated complement levels in endometriosis patients following laparoscopic diagnosis.[25] However, no substantial change was noted in either group in current study.

In the control group treated with metformin alone, endometrioma size decreased significantly from 3.40±0.96 cm to 2.92±0.80 cm (mean difference 0.45 cm). Lasker et al reported a similar decrease (3.12±1.42 cm, p=0.003).[21] Metformin also significantly reduced the VAS score from 6.65±2.10 to 3.47±2.09 (mean difference 3.23). These findings align with earlier work by Omer et al and Foda et al which demonstrated notable reductions in dysmenorrhea, pelvic pain, and dyspareunia with metformin treatment.[11,26]

Post-treatment serum complements levels in the control group slightly increased (from 1.37±0.46 g/l to 1.45±0.40 g/l), though this change was not statistically significant. Previous studies have suggested that metformin might affect complement pathways in conditions like PCOS, but findings in endometriosis remain inconclusive.[27,28]

Statistical comparisons between groups after three months showed a significantly greater reduction in endometrioma size in experimental group (p=0.042). However, changes in VAS score and complement levels were not statistically different between the two groups. Salam et al also reported no significant post-treatment differences regarding pain or lesion size between DNZ+statin and DNZ alone.[23]

Though not a primary outcome, pregnancy occurred in 4 (21.1%) patients in the experimental group and 1 (5.6%) in the control group during the study period. The difference was not statistically significant. Similar pregnancy rates have been documented in trials involving simvastatin and pentoxifylline, suggesting potential but inconclusive fertility benefits.

Side effects were relatively minor and did not differ significantly between groups. In the experimental group, 13.3% reported nausea, while 6.7% experienced it in the control group. One patient in the experimental group also reported vomiting and dry mouth. Lasker et al confirmed similar tolerability between treatment regimens.[21] Given that endometriosis often requires long-term management, these safety findings support the viability of both metformin and statin-based therapies for chronic use.

Limitations

This study has several limitations. Due to time constraints, it was conducted with a small sample size and over a short duration, which may affect the generalizability and strength of the conclusions. Additionally, neither participants nor investigators were blinded to treatment after randomization, potentially introducing bias. All participants were recruited from a single department of one tertiary-level hospital, which may limit the applicability of the findings to the broader population, especially given possible genetic, racial, and geographical variations.

CONCLUSION

This study found that metformin combined with a statin significantly reduced endometrioma size compared to metformin alone over three months. While pain scores and serum complement levels also improved, the differences between groups were not statistically significant. Both regimens were well tolerated with minimal side effects. These findings suggest that metformin plus statin therapy may offer a promising treatment option for symptomatic endometriosis in infertile women.

Recommendations

To build on these findings, future studies should include larger, community-based or multi-centre trials involving patients from diverse ethnic backgrounds. Well-designed, double-blind randomized controlled trials with extended follow-up periods are essential to more accurately assess the long-term efficacy and safety of combined metformin and statin therapy. While the current results suggest potential advantages of this combination in reducing endometrioma size and pelvic pain, additional research is necessary to fully evaluate its impact on fertility outcomes in women with endometriosis. Moreover, exploring newer pharmacologic agents could lead to more effective non-surgical treatment options, particularly benefiting patients who cannot afford or access advanced reproductive technologies like *in vitro* fertilization (IVF).

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Shah H, Hossain F, Islam MA, Sultana R, Al Tarique MM, Alamgir CF, et al. Effect of metformin plus statin combination therapy compared to metformin alone in infertile woman with symptomatic endometrioma. Int J Reprod Contracept Obstet Gynecol 2025;14:2298-304.