

## Cabergoline versus Dydrogesterone in Infertile Women with Endometriosis: A Parallel-Design Randomized Clinical Trial

Shakeela Ishrat<sup>\*</sup>, Farzana Deeba, Shaheen Ara Anwary, Nurjahan Begum, Jesmine Banu

Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University, Bangladesh

## ABSTRACT

**Background:** The management of infertile women with advanced endometriosis is difficult and controversial. Medications like cabergoline and dydrogesterone which reduce endometriosis-associated pelvic inflammation but do not prevent ovulation can be an alternative to surgery in these women.

**Objective:** To assess and compare the efficacy of cabergoline and dydrogesterone in infertile women with endometriosis.

**Methods:** A parallel design randomized clinical trial was carried out on 18 infertile women with clinically diagnosed endometriosis. They were randomly allocated either to cabergoline (0.5 mg twice weekly for 6 months, plus timed intercourse) or dydrogesteron (20 mg daily from day 5 to day 25 of menstrual cycle for 6 months, plus timed intercourse). The woman was assessed by telephone interview, face-to-face consultation, and transvaginal sonogram at 3 months and 6 months.

Results: Four women receiving cabergoline (36.4%) had a pregnancies from the 3<sup>rd</sup> month onwards. Fourteen women,7 in each group were available for final analysis. The reduction in visual analog scale score of pain in those given cabergoline was 3 times that in those given dydrogesterone. Adequate reduction in the size of endometrioma was achieved in 28.6% of women given dydrogesterone, but not in those given cabergoline.

Conclusion: Cabergoline, compared to dydrogesterone has significant pain reduction over a short period of time in infertile women with endometriosis, and in addition promotes pregnancys.

Keywords: Endometriosis; Endometrioma; Cabergoline; Dydrogesterone

### INTRODUCTION

Endometriosis is a chronic recurrent inflammatory disease characterized by the presence of abnormal functioning endometrial tissue outside the uterus, causing pain and infertility [1]. An infertile young woman is likely to have advanced endometriosis at laparoscopy when she presents with the sonographic diagnosis of a chocolate cyst with or without pain [2]. If the cyst size is small and the woman is young, fertility treatment is advised without surgery. If the size of the chocolate cyst is large or the woman is older, diagnostic laparoscopy and laparoscopic cystectomy are done [3] Following surgery, she is advised to go for *in vitro* fertilization. Moderate to severe endometriosis in infertile women, according to clinical guidelines, is best managed by a combination of laparoscopic surgery for removal of disease and assisted reproductive techniques such as *invitro* fertilization [4]. When couples cannot afford *In Vitro* Fertilization (IVF), Intrauterine Insemination (IUI) is advised provided the fallopian tubes are patent and tuboovarian relationships are normal [5]. This is because spontaneous pregnancy is not likely to occur as the monthly fecundity is 0.02%-0.1% in women with endometriosis, about 100 times less than that of the normal couple [6]. There may be tubal block or altered tubo-ovarian relationship due to the formation of new adhesions following surgery, necessitating IVF [7]. Assisted reproductive techniques are not acceptable to most couples because of financial disability or psychosocial inhibitions. Most of the time surgery for endometriosis is followed by no fertility treatment or inadequate fertility treatment and women end up with a recurrence of endometriosis and pain [6].

Non-surgical measures in practice to treat endometriosis include hormonal medications like progestins, estrogen-progestin pills, or GnRH analogs that suppress endometriosis by inhibiting

**Correspondence to:** Shakeela Ishrat, Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University, Bangladesh; Phone: +8801729897221; E-mail: shakeelaishrat@bsmmu.edu.bd.

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ovulation. They can reduce the cyst size and pain but delay fertility. This chronic condition frequently needs long-term or intermittent repetitive medication [4]. Ideal medical treatment should be relatively well tolerated, inexpensive, and should not inhibit ovulation in infertile women. Newer drugs that have been tried include Vascular Endothelial Growth Factor (VEGF) inhibitors like pazopanib, sunitinib [8], sorafenib [9], dopamine agonists [10], and progestin like dydrogesterone [11] that do not inhibit ovulation. Dopamine agonist like cabergoline has a VEGF inhibiting property.

Neoangiogenesis is essential for the onset and progress of endometriosis. Endometrial stem progenitor cells produce Vascular Endothelial Growth Factor (VEGF) to induce angiogenesis. The direct inhibitory effect on angiogenesis was demonstrated in a murine experimental endometriosis model. This anti-angiogenesis effect, combined with a relative safety profile supports the potential therapeutic role of dopamine agonists in the management of endometriosis [10]. Cabergoline is used in hyperprolactinemia, postpartum suppression of lactation, and for prevention of ovarian hyperstimulation syndrome in IVF [12]. Cabergoline may be useful in reducing peritoneal endometriosis [13]. Cabergoline and quinagolide, ergot and non-ergot derivative of dopamine agonists respectively can reduce angiogenesis and endometriosis lesion size [10]. A 69.7% decrease in peritoneal lesion size at second-look laparoscopy was observed in a proof of concept study to test the efficacy of quinagolide administered for 18-20 weeks [14].

Dydrogesterone, like other progestins, is effective in the symptomatic management of pain and bleeding disorders [15]. The mode of action may involve modulation of local immuno-activity, growth factors, and growth factor receptors, and anti-inflammatory reactions [16]. Cyclic administration of dydrogesterone induces regular menstruation with reduced blood flow and excellent symptomatic relief of dysmenorrhea [17]. It is preferable in infertile women because there are no androgenic side effects and no inhibition of ovulation [16]. A prospective multicenter study on women with endometriosis having 10 mg/day-20 mg/day dydrogesterone for 9 months showed significant improvement of pain. There was pregnancy in one-fifth of the women who wanted to conceive [11].

Endometriosis occurs in about 10% of women of reproductive age [1]. Infertility is prevalent in around 40% to 50% of women with endometriosis [4]. Pregnancy can occur spontaneously in many women with endometriosis. Medications that reduce endometriosis-associated pelvic inflammation but do not prevent ovulation can be an answer to the problems for these women. The management of infertile women with advanced endometriosis is difficult and controversial. Evidence-based best practice in fertility care of women with endometriosis is yet to develop. Conflicting advice and treatment options without acknowledging the uncertain prognosis are in practice [18]. The search now should be for less expensive, non-invasive, and acceptable measures that will reduce the endometriosis-associated inflammation, cyst size, and pain and at the same time will promote or at least will not inhibit or delay fertility.

Evaluating more than one new intervention concurrently increases the chance of finding an effective treatment, at a lower cost with better use of resources [19]. The parallel design randomized clinical trial was aimed to help us decide the best medical options for infertile women with endometriosis. It was hypothesized that cabergoline and dydrogesterone are equally effective in infertile women with endometrioma in terms of adequate pain reduction, reduction in the size of endometrioma, and pregnancy. The objective of the study was to assess and compare the efficacy of cabergoline and dydrogesterone in infertile women with endometriosis.

### METHODOLOGY

The parallel design randomized clinical trial was carried out in the Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. The protocol was approved by the Institutional Review Board (IRB), registration number BSMMU/2021/6. The women who were infertile or wished for pregnancy, with sonographically diagnosed endometrioma, with or without dysmenorrhea, and staying with their husbands were the study participants. Those with recurrence of endometrioma following previous surgery were excluded as a surgery-induced reduction in ovarian reserve and adhesions altering tubo-ovarian relation were likely to confound the outcome of pregnancy. Other exclusion criteria were Body Mass Index (BMI) at or more than  $30 \text{ kg/m}^2$ , significant abnormalities in renal and liver function, known male factor subfertility, and the use of investigational drugs or hormones, concomitant or in the last 30 days.

The eligible women who consented to participation were randomly allocated to one of the two arms: one receiving tab cabergoline 0.5 mg twice-weekly (Fridays and Tuesdays) for 6 months plus timed intercourse and the other arm receiving tab dydrogesterone 10 mg twice daily for 6 months plus timed intercourse. Random sequence generation was done by computer and allocation concealment was done by sequentially numbered opaque sealed envelopes. Timed intercourse was intercourse timed with urinary LH kit or if LH kit is not available, intercourse on alternate days from day 10 to day 15. Primary endpoints were an adequate reduction in pain (reduction of VAS score to less than 3) and reduction in the size of endometrioma (>50% reduction in maximum diameter of endometrioma, larger one if bilateral) as measured by sonography. The secondary endpoint was pregnancy (positive urinary pregnancy test and sonographic appearance of gestational sac). The outcome variables and adverse events were assessed at baseline and visits after 3 months and 6 months by face-to-face consultation and telephone interviews. Statistical analysis was done by SPSS version 26. The difference between the two arms was assessed by chi-square or Fishers Exact test for categorical variables and with independent sample t-test or Mann-Whitney U-test where appropriate for continuous variables.

### RESULTS

A total of 18 women (age mean  $26.0 \pm 3.2$  years, range 22-33 years) participated in the study. Before administering the drugs, a mean visual analog score of pain for dysmenorrhea was  $8.2 \pm 2.1$ , the mean size of endometrioma was  $5.0 \pm 1.3$  cm. Serum Ca-125 was median 31.90, range 20.5 U/mL-108.3 U/mL.

Eleven women completed 3 months; two women receiving dydrogesterone wanted a change of treatment because the pain did not decrease and three women receiving cabergoline wanted a change of treatment because the size of the cyst did not

Variables	Cabergoline (n=11)	Dydrogesterone (n=9)	p-value	
Age (years)	27.9 ± 3.5	24.1 ± 1.45	0.025	
Residence				
Urban	57.1%	28.6%	0.502	
Rural	42.9%	71.4%	0.592	
Occupation				
Housewife	42.9%	100.0%	0.070	
Others	57.1%	0.0%		
Household income (monthly)				
Less than	57.1%	85.7%	0.550	
30,000	42.9%	14.3%	0.559	
30,000 or more				
Type of infertility				
Primary	71.4%	100.0%	0 462	
Secondary	28.6%	0	0.402	
Years of infertility	4.0 ± 2.4	4.6 ± 3.3	0.692	
Visual analogue scale for Pain (dysmenorrhea)	7.1 ± 2.3	9.3 ± 0.8	0.053	
Serum CA 125 (U/mL)	55.5 ± 41.9	44.0 ± 25.4	0.586	
Maximum diameter (cm)	5.2 ± 1.6	4.9 ± 1.1	0.721	

 Table 2: Reduction of VAS score of pain achieved in cabergoline group compared to dydrogesterone group.

	Adequate reduction of VAS score in infertile women with endometriosis (n=14)		Relative risk	95% confidence interval
	no	yes	3.000	0.895- 10.058
	%(n)	%(n)		
Cabergoline (n=7)	14.3%	85.7%		
Dydrogesterone (n-7)	71.4%	28.6%		

decrease. Four women, one in cabergoline group and two in the dydrogesterone group completed 6 months. Four women receiving cabergoline were withdrawn from the study because they became pregnant. Fourteen women,7 in cabergoline group and 7 in the dydrogesterone group were available for final analysis.

Table 1 describes the baseline characteristics of the study participants (n=18). Table 2 compares the reduction of pain scores achieved in cabergoline and dydrogesterone groups.

The probability of reduction of VAS score in those receiving cabergoline is 3 times that in those receiving dydrogesterone. Adequate reduction in the size of endometrioma (more than 50% reduction) was achieved in 28.6% (2/7) patients given dydrogesterone, but not in those given cabergoline. However, 4/11 (36.4%) of the women given cabergoline got pregnant in 3<sup>rd</sup> month or onwards. Two of them had a live birth, two have ongoing pregnancies.

There was no adverse event or major side effect of the drugs during the study period.

### DISCUSSION

The study was undertaken to see if cabergoline and dydrogesterone

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given to infertile women with sonographically diagnosed endometriosis could reduce the pain and endometrioma size. According to this study, cabergoline has the probability of reducing pain three times more than dydrogesterone, while being less effective in reducing the size of endometrioma. In addition, cabergoline allowed four women to conceive during the treatment period.

# Cabergoline and dydrogesterone have both been used in endometriosis.

A prospective randomized study of 140 women with endometriosis conducted by Hamid, et al. [20] compared the effect of cabergoline 0.5 mg tablets twice per week for 12 weeks to that of monthly subcutaneous injection of Luteinizing Hormone-Releasing Hormone (LHRH) agonist decapeptyl 3.75 mg for 3 months. The outcome was a more than 25% reduction in the size of endometrioma. There was a reduction of the size of endometrioma in 64.1% of the women having cabergoline compared to 21% of those having LHRH agonists. The cabergoline and LHRH agonist were similar in reducing severe pain. Another randomized controlled trial conducted by Kyal, et al. [21] on 80 women with endometriosis compared cabergoline 0.5 mg twice weekly with medroxyprogesterone acetate 10 mg three times daily for 3 months. Cabergoline decreased the pain as effectively as medroxyprogesterone acetate. The findings are similar to our findings regarding the pain reduction function of cabergoline. We did not find a favorable effect of cabergoline on the reduction of the size of endometrioma. The reason may be the small sample size or that we defined more than 50% decrease in maximum diameter as a reduction in the size of endometrioma.

A prospective multicenter study was done on women with endometriosis who had 10 mg/day-20 mg/day dydrogesterone from day 5 to day 25 of the menstrual cycle following laparoscopic surgery for 9 months [11]. There was a significant improvement in pain. There was pregnancy in one-fifth of the women who wanted to conceive. A post-marketing multicenter observational study in Japan [22] observed the effect of dydrogesterone for four cycles on women with endometriosis who did not have surgery in the previous 2 months. The age range was 20-49 years. Dydrogesterone reduced pain and reduced the volume of endometrioma in 50% of the women. We found inadequate pain reduction in women given dydrogesterone probably because of a short duration of treatment. Moreover, there was an inadequate reduction in the size of endometrioma in most of the women having dydrogesterone. Probably dydrogesterone will be more appropriate to administer after laparoscopic surgery in infertile women with endometriosis to prevent recurrence when fertility treatment cannot be undertaken for financial reasons.

Laparoscopic surgery is the current gold standard for the diagnosis and management of endometriosis. Surgical removal of chocolate cyst and ablation of endometriotic lesions by laparoscopy has traditionally been done in infertile women in preference of medical management. In infertile women, laparoscopic surgery is combined with assisted reproductive techniques [23]. Surgery may not be able to remove all the lesions leading to persistence or early recurrence of pain. Despite adequate counseling, women and their husbands expect complete removal and cure after surgery; they are frustrated and angry when there is a recurrence. Surgery is likely to reduce

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ovarian reserve and result in postoperative adhesion, factors that adversely affect the fertility prospects of infertile women. The pregnancy rate after repeat surgery is lower, approximately half that after the first surgery. Recently the surgical management has been questioned because of its adverse effect on ovarian reserve. The pregnancy rate following surgery is not improved unless combined with assisted reproductive techniques [23]. Surgery, in current guidelines, is not advised unless there is pain with endometrioma in infertile women [23]. Assisted reproductive techniques are not financially and psychologically acceptable to most couples in Bangladesh. The facilities for laparoscopic surgery are now limited in COVID-19 crisis. This leaves us with an opportunity to explore the non-surgical interventions in infertile women with endometriosis. Medications like cabergoline and dydrogesterone may be given to infertile women with endometriosis hoping that they will reduce pain and the size of endometriosis and at the same time allow ovulation and pregnancy. Recurrence after medication may be psychologically more acceptable than that after surgery. Prior medication for 3-6 months to reduce the size of endometrioma and associated inflammation may be helpful in increasing fecundity with subsequent ovulation stimulation with or without IUI.

Recurrence of endometriosis after surgery is a problem that has not been resolved with certainty. The effectiveness of medical therapy before or after surgery in infertile women with endometriosis is controversial [24]. Our search was for medications that reduce pelvic inflammation apparent on reduction of pain, reduce the size of endometrioma, and at the same time do not inhibit ovulation. If the infertile women are not symptomatic with pain or do not agree to surgery we should try all means to get her pregnant with the endometrioma in place. That may be timed intercourse or ovarian stimulation with or without IUI, taking into consideration the couple's financial ability, preferences, and trade-offs. Cabergoline, in consideration of its favorable effect on endometriosis-associated pain and chance of pregnancy, can be offered to women who wish to be pregnant prior or as an alternative to surgery or other fertility treatments like ovarian stimulation or IUI. The compliance may be better with cabergoline due to less frequent dosing.

The limitations of the study include a small sample size and singlecenter recruitment. The study was open-label without any blinding. This may be considered a preliminary study the findings of which may guide further studies on the effect of cabergoline in infertile women with endometriosis.

### CONCLUSION

Cabergoline, compared to dydrogesterone has significant pain reduction over a short period of time in women with endometriosis and in addition, can promote pregnancy. This makes cabergoline a worthwhile option in infertile women with endometrioma of smaller size prior to surgery.

### SOURCE OF FUNDING

Nil.

## CONFLICT OF INTEREST

Nil.

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