
Cabergoline, metformin and Clomiphene citrate therapy in infertile female with mild endometriosis: A Randomized Clinical Trial

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Ethical statement

Authors declare that there is no interest

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Written informed consent was taken from the participants

Introduction

an urgent need for new medication without impeding the patient's fertility. cabergoline, Metformin, and Clomiphene citrate have been studied in experimental model in cases of endometriosis. however, there was still no evidence of its use with mild endometriosis. Our study's goal was to see if use these medications could help women with minimal to mild endometriosis.

Methods

Between November 2021 to November 2022, 150 Infertile women with minimal to mild endometriosis were recruited from outpatient Gynecology clinic for this study a prospective, randomized trial.

The cases will be randomly assigned to receive one of the four treatment modalities by using computer generate random table and sealed envelop

- Group A: they got cabergoline (0.25 mg twice weekly) for three months.
- Group B: they received metformin 500 mg three times daily for three months
- Group C: they received Clomiphene citrate (50mg twice daily for 5days) from second day of menstrual cycle for three months
- Group D: they got placebo once per day during the three months follow up period Serum prolactin (PRL), basal follicular stimulating hormone (FSH), basal

luteinizing hormone (LH), basal serum estradiol (E2) and midluteal serum progesterone (P) were measured before the start of the treatment.

After the three months, a clinical evaluation was conducted, which comprised clinical examination with assessment of dysmenorrhea, dyspareunia and pelvic pain, menorrhagia, and pregnancy. A second hormonal assessment was performed.

Results

For group A; 20 cases, for group B 22 cases, for group C 20 cases, and for group D 17 cases were analyzed. The mean prolactin level, mean FSH level, and mean estradiol level after treatment statistically significant difference between studied group and placebo. The pregnancy in studied groups were 8 out of 20 in Group A, 10 out of 22 in Group B, 8 out 20 in Group C, however, 2 out of 17.

Conclusion

We had encouraging results from the use of cabergoline, metformin, and clomiphene citrate in patient with mild to moderate endometriosis.

Introduction

Despite being one of the most prevalent gynecological disorders, endometriosis pathogenesis is still poorly understood. There is a pressing need for new medication without impeding the patient's fertility because the traditional medical treatments have this effect (1). Dopamine agonists as a molecule with antiangiogenic activity, have been studied in experimental model in cases of endometriosis with good results (2). Metformin, as an insulin sensitizer, studied in vitro and animal models and proved to be associated with the recession of endometriotic implants (3). However, the clinical data are insufficient to recommend

the use of both (2,3). Clomiphene citrate, as antiestrogen for ovulation induction, had tried in infertile patients with endometriosis, however, still had no evidence of its use with mild endometriosis after laparoscopy (4). The aim of our study to try to use these drugs in the treatment of women with minimal to mild endometriosis.

Patients & Methods

This study a prospective randomized study conducted on a total of 150 Infertile women with endometriosis. Patients were collected from outpatient Gynecology clinic within the period from November 2021 to November 2022 after obtaining the approval our Institutional Research Board (MS.21.12.1763). Informed consent obtained from participants in study.

Our study included infertile woman aged between 25 and 35 years who had minimal to mild endometriosis according to the revised American fertility society classification diagnosed by previous laparoscopy (5). These patients should have normal tubal patency, within normal luteal phase progesterone levels, and normal seminal analysis of her husband.

All patients with any other causes of infertility and those with any renal, hepatic dearrangement, apparent endocrinopathy (hypothalamopituitary, diabetes mellitus and thyroid disorders), cardiac disorders, hypertension, or any medical condition were excluded from the study.

The cases will be randomly assigned to receive one of the four treatment modalities by using computer generate random table and sealed envelop

- Group A: they received cabergoline (0.25 mg twice weekly) for three months.
- Group B: they received metformin 500 mg three times daily for three months
- Group C: they received Clomiphene citrate (50mg twice daily for 5days) from

second day of menstrual cycle for three months

- Group D: they got placebo once per day throughout the three months follow up period

Before the treatment cases, full history taking, and physical examination were done. Ultrasound scan was done and laboratory Investigations: serum prolactin (PRL), basal follicular stimulating hormone (FSH), basal luteinizing hormone (LH), basal serum estradiol (E2) and midluteal serum progesterone (P) were done.

Clinical assessment was done after three months, this included clinical examination with assessment of dysmenorrhea, dyspareunia and pelvic pain, menorrhagia and pregnancy. Hormonal assessment was also repeated.

Statistical analysis:

Using the SPSS application (version 22) for windows, the gathered data were recorded, processed, and analyzed. When necessary, the relevant statistical tests will be applied. P values under 0.05(5%) were regarded as statistically significant.

Results

Consort flow chart showing study design in Figure 1. The number of cases finally remain for analysis were: For group A; 20 cases, for group B 22 cases, for group C 20 cases, and for group D 17 cases. Table 1 demonstrates that there is no statistically significant difference between studied groups as regard age, sex, weight, height and body mass index, duration of symptoms, infertility type, and Mean duration of infertility. Table 2 demonstrates that the mean prolactin level, mean FSH level, and mean estradiol level after treatment statistically significant difference between studied group and placebo. Table 3 shows that there is no statistically significant difference between studied groups as regard symptoms before nor after treatment

except for menorrhagia after treatment. The pregnancy in studied groups were 8 out of 20 in Group A, 10 out of 22 in Group B, 8 out of 20 in Group C, however, 2 out of 17 in placebo as shown in Table (3)

Discussion

the new era in the medical treatment of infertile patients with endometriosis is to target the pathogenesis of this lesion either Targeting Angiogenesis, Neuroangiogenesis, Apoptotic, or Estrogens (6).

The dopamine agonist cabergoline acts as an anti-angiogenic drug interaction with dopamine receptors, causing general and local prolactin decreases and subsequent decrease in Vascular endothelial growth factor (VEGF) level (2). Metformin seems to regress endometriotic implants as anti-inflammatory and anti-proliferative agent by decreasing the levels of the VEGF through the activation of AMP-activated protein kinase (3). Clomiphene citrate can be used in the treatment of mild to moderate endometriosis because it may correct the ovarian dysfunction that is considered one of the reasons that endometriosis causes infertility (4).

Mean prolactin level that is decreased in the three drugs support the concept of their mechanism of action on prolactin and subsequent effect on VEGF. the decreased of FSH level and increase estradiol level may be explained by increase ovarian follicular activity and correction of ovarian dysfunction.

Our result showed symptomatic relief of heavy menstrual bleeding only with variable degree of relief of dyspareunia, dysmenorrhea, or pelvic pain for each drug without any firm conclusion which can be explained by the drugs did not inhibit the ovulation in contrast with Yarmolinskaya et al who studied 227 patients of reproductive age with endometriosis I—III and found that Patients receiving cabergoline combined with

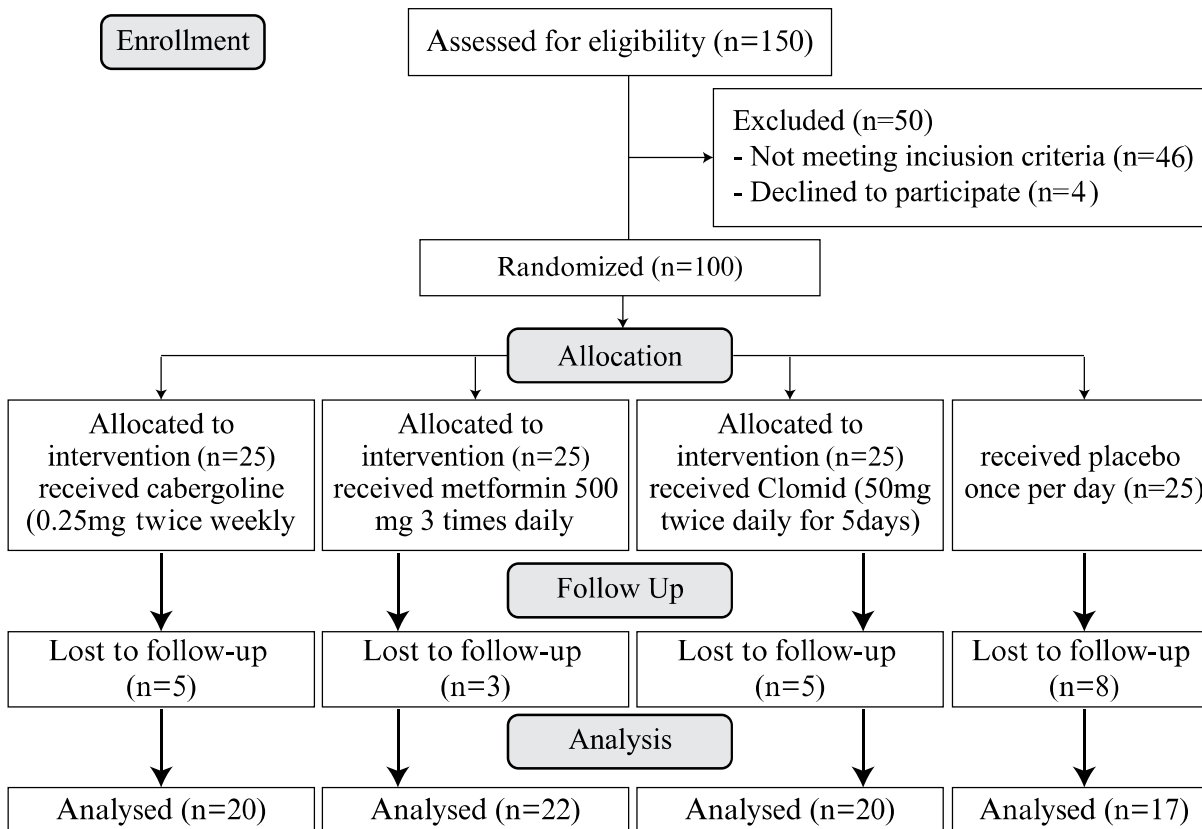
hormone therapy standard show considerable pain relief (7).

The pregnancy rate in our trial is promising and give a good hope for these patients in contrast with Zhou et al who studied ovulation induction with clomiphene citrate after laparoscopy for infertile women with minimal to mild endometriosis and showed significantly increases ovulation rate without a significant improving pregnancy rate when compared to laparoscopy alone (4).

To the best of our knowledge, all the experimental data of using these medications are positive and encouraging however, limited number of clinical trials aren't enough to confirm or reject this hypothesis. Limitation of our study is the bounded number of cases and limited duration of follow up. The promising results may motivate us more for further prospective multicenter trials. We concluded that we had promising results on the use of cabergoline, metformin, and clomiphene citrate in patient with mild to moderate endometriosis.

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Figure (1): consort flow chart showing study design**Table 1: Demographic characteristics of the studied groups:**

	Group A (n=20)	Group B (n= 22)	Group C (n= 20)	Group D (n= 17)	P-value
Age (years)	29.65±3.27	30.36±3.67	28.40±3.03	29.88±3.35	0.288
Weight (kg)	73.03±9.08	74.97±11.58	70.57±9.73	77.66±11.68	0.220
Height (m)	1.65±0.06	1.64±0.06	1.62±0.06	1.66±0.054	0.212
BMI (kg/m²)	26.96±2.84	27.74±3.83	26.84±3.14	28.15±3.82	0.595
Duration of symptoms (months)	45.60±12.68	41.45±12.68	39.60±12.37	44.47±11.03	0.515
Infertility type	9(45.0)	14(63.6)	7(35)	9(52.9)	0.298
Primary					
Secondary	11(55.0)	8(36.4)	13(65)	8(47.1)	
Infertility duration (months)	23.40±7.26	24.55±9.25	21.30±6.59	24.71±7.31	0.490
Data is expressed as mean and standard deviation P is significant					

Table 2 Laboratory assessment of the studied groups before treatment:

		Group A (n= 20)	Group A (n= 20)	Group C (n=20)	Group D (n= 17)	P-value
Prolactin	before	22.48±1.16	22.07±1.30	23.23± 1.39	22.74±1.53	0.053
	After	18.64±1.22 ^a	18.23±1.29 ^{bc}	19.16±1.91 ^{bd}	22.81±1.49 ^{acd}	<0.001*
FSH	before	8.02±1.42	8.18±1.46	8.32± 1.98	8.29±1.65	0.936
	After	6.29±1.27 ^a	6.26±1.33 ^b	6.47± 1.55 ^c	8.30±1.70 ^{abc}	<0.001*
LH	before	3.14±1.31	3.63±1.79	2.61±1.17	2.59±1.82	0.135
	After	4.74±1.54	5.40±2.24 ^{ab}	4.25±1.47 ^a	3.61±1.84 ^b	0.02*
Estradiol	before	144.13±75.21	182.96±62.23	182.35±56.44	159.90±93.05	0.253
	After	189.19±95.84 ^a	238.94±81.74 ^b	244.76±78.22 ^{ac}	164.38±95.50 ^{bc}	0.015*
Progester- one	before	9.16±3.69	8.19±3.51	8.06±3.75	9.06±5.48	0.766
	After	12.35±5.20	12.03±4.33	12.15±4.79	9.24±5.59	0.220

Data is expressed as mean and standard deviation. P is significant when < 0.05.

Similar superscripted letters denote significant difference between groups within same row by Post Hoc Tukey test

Table 3 Symptoms of endometriosis after treatment of the studied groups:

		Group A (n=20)	Group B (n= 22)	Group C (n= 20)	Group D (n= 17)	P value
Dysmenor- rhea	before	11(55)	13(59.1)	14(70)	9(52.9)	0.708
	After	9(45)	8(36.4)	10(50)	9(52.9)	0.733
p-value		0.157	0.025*	0.046*	1.0	
Pelvic pain	before	12(60)	15(68.2)	15(75.0)	10(58.8)	0.688
	After	10(50)	13(59.1)	12(60)	10(58.8)	0.911
p-value		0.157	0.157	0.083	1.0	
Dyspareu- nia	before	9(45)	11(50)	12(60)	10(58.8)	0.749
	After	6(30)	7(31.8)	9(45)	10(58.8)	0.247
p-value		0.083	0.046*	0.083	1.0	
Menorrh- gia	before	13(65)	13(59.1)	13(65.0)	15(88.2)	0.242
	After	8(40) ^c	5(22.7) ^{bd}	11(55.0) ^{ad}	15(88.2) ^{abc}	0.001*
p-value		0.025*	0.005*	0.157	1.0	

Data is expressed as percentage and frequency. P is significant when < 0.05. Similar superscripted letters denote significant difference between groups within same row by Post Hoc Tukey test.

Table 4 Pregnancy rate of the studied groups:

	Group A (n= 20)	Group B (n= 22)	Group C (n= 20)	Group D (n= 17)	P value
Pregnancy	8(40) ^a	10 (45.5) ^b	8(40) ^c	2 (11.8) ^{abc}	0.139

Data is expressed as percentage and frequency. P is significant when < 0.05.

Similar superscripted letters denote significant difference between groups within same row by Post Hoc Tukey test