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Original Research Article

Surgical versus non-surgical intervention in endometriosis with infertility: a patient preference trial

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ABSTRACT

Background: Hormonal suppression decrease pain and reduce endometrioma size in women with endometriosis. There are medications like cabergoline which reduce inflammation associated with endometriosis but do not prevent ovulation. Hormonal suppression followed by cabergoline may allow pregnancy in women with endometriosis. The objective of the study was to assess and compare the efficacy of medical versus surgical management in infertile women with endometriosis.
Methods: A patient preference clinical trial was carried out on 20 women who wish pregnancy and has sonographic evidence of endometrioma and pain. They were counseled adequately about the advantages and disadvantages of surgical and medical management of endometriosis with infertility and were asked to make a choice. The interventions were applied according to patient preference. The interventions were i) dienogest for 3 months when cyst size ≤5 cm and letrozole plus norethisterone for 6 months when cyst size > 5 cm followed by cabergoline 0.5 mg twice weekly for 6 months, plus timed intercourse and ii) laparoscopic surgery followed by expectant management or ovarian stimulation with or without intrauterine insemination. The women were followed up for results.
Results: A total of 18 participants opted for medical management and only 2 participants for surgery. All participants given medical management had reduction of pain, and all except one had reduction of cyst size. Pregnancy occurred in 2 out of 14 (14.3%) participants given medication. One woman with surgery had persistence of pain and recurrence of cyst. No one having surgery got pregnant during the study period.
Conclusions: The infertile women with endometriosis prefer medical management over surgery. The medical management may be a better option for infertile women with endometriosis who do not plan in vitro fertilization in near future.

Keywords: Cabergoline, Dienogest, Dydrogesterone, Endometrioma, Endometriosis, laparoscopy

INTRODUCTION

Endometriosis is a chronic recurrent inflammatory disease characterized by the presence of abnormal, functioning endometrial tissue outside uterus, causing pain and infertility.[1] There is so far no established evidence based management of endometriosis with infertility.[2] Clinical guidelines recommend expectant management or fertility treatment with ovarian stimulation with or without intrauterine insemination in mild and minimal endometriosis and in vitro fertilization in moderate to severe endometriosis.[3] The grading of endometriosis into minimal, mild and moderate endometriosis can be done with laparoscopy only. Diagnostic laparoscopy is accompanied by ablations of lesions in minimal and mild endometriosis and cystectomy and adhesiolysis in more advanced endometriosis. So the traditional management in infertile women with endometriosis is laparoscopic cystectomy and adhesiolysis. The surgical diagnosis and

management is followed by expectant management or ovarian stimulation with or without intrauterine insemination if the women are young and has good tubal function or tubo ovarian relationship. When the tubes are not functional, the women are older and there are associated factors like male factor or diminished ovarian reserve, in vitro fertilization is advised.[4]

A woman with endometriosis and infertility usually presents to us with a sonogram suggestive of chocolate cyst with or without associated dysmenorrhea. The woman is likely to have advanced endometriosis when there is a chocolate cyst. Transvaginal ultrasound has fairly good (>85%) sensitivity and specificity in diagnosing endometriosis and adenomyosis.[5]

Laparoscopy is the gold standard method of diagnosis of endometriosis, but imaging modalities like ultrasonogram is increasingly used in diagnosis of chocolate cyst and deep infiltrative endometriosis. Clinicians can begin medical treatment without surgical confirmation when endometriosis is suspected by clinical symptoms combined with radiologic diagnosis.[6] Medical management with hormones (norethisterone, dienogest, letrozole) administered over a variable period of 6-9 months reduce pain and size of endometrioma.[7] Some drugs like cabergoline and dydrogesterone which do not suppress ovulation can also be given.[8]

The patient population in Bangabandhu Sheikh Mujib Medical University are mostly from low economic background. Most of the time women with advanced endometriosis do not pursue expensive fertility procedures like intrauterine inseminations or in vitro fertilizations.[9] The reasons are cost and psychosocial inhibition against intrauterine insemination and in vitro fertilization. The women often end up with persistence and recurrence of symptoms such as pain, chocolate cyst and infertility.

Preference clinical trial is one where two or more health care interventions are compared among several groups of patients, who purposefully choose the intervention to be administered to them.[10] This preference clinical trial assessed whether non-surgical interventions improved pregnancy rate, taking into account the patient centered care.

METHODS

This was a patient preference trial carried out in the department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University, (BSMMU), Shahbag, Dhaka, Bangladesh over one year from July 2021 to June 2022. Study participants were clinically diagnosed cases of women with endometriosis who are infertile or wants to conceive and who would like to express preference.

Inclusion criteria

Inclusion criteria were women of reproductive age 18-35 years, infertile or wants to conceive, staying with her husband and having sonographic diagnosis of chocolate cyst with or without dysmenorrhea.

Exclusion criteria

Exclusion criteria were palpable abdominal mass, endometrioma recurrent after previous surgery, BMI at or more than 30 kg/m^2, significant abnormalities in renal and liver function, known male factor, use of investigational drugs or hormones, concomitant or in last 30 days. The couples who cannot decide what treatment to prefer were also excluded.

There was no similar previous study to provide the data to generate sample size. Meeting the exclusion criteria like recurrent endometriosis, abdominal mass, failure to express preference etc., 20 couples were recruited. After evaluating for eligibility criteria, adequate counseling was done with appropriate patient education materials and counseling checklists so that they could make free and informed choice of treatment modality. The women were assigned to either medical management group or to laparoscopic surgery group according to the preference of the couples. Women assigned to medical management group were to receive hormonal suppression for 3-6 months (dienogest for 3 months if cyst size ≤5 cm, and combination of letrozole and norethisterone for 6 months if cyst size > 5 cm). Once the cyst size was less than 4 cm, the woman had 0.5 mg cabergoline twice weekly (fridays and tuesdays), after meal at night for 6 months. The couple was to have intercourse timed with LH kit or intercourse on alternate days from day 10 to day 15 of the cycle if the LH kit was not available. The patient had option to convert to surgery whenever she wanted or whenever there was inadequate reduction in pain or cyst size. The surgical management group underwent laparoscopic cystectomy, adhesiolysis and dye test and was to be followed by expectant treatment or ovarian stimulation with or without intrauterine stimulation, or in vitro fertilization depending on functional status of tubes and ovaries and affordability of the patient.

Study outcomes

The primary outcome measures included pregnancy, biochemical (serum beta hCG >40 IU/mL) or clinical (sonographic appearance of gestational sac), pain reduction (Visual Analog Scale score reduced to less than 3) and reduction in size (maximum diameter) of chocolate cyst, the larger one when bilateral, to less than 4 cm assessed by transvaginal ultrasound. She was followed up every 3 months up to 1 year to check for compliance or any side effects. At each follow up visit, she was assessed for pregnancy, visual analog scale for pain and transvaginal sonogram to measure the chocolate cyst.

Statistical analysis

SPSS version 26 was used for analysis**.** Socio-demographic, clinical and sonographic characteristics was summarized as frequency for categorical variables, mean±SD for continuous variables. Both 'intention to treat' analysis and per protocol analysis was done.

RESULTS

A total of 20 patients, diagnosed with sonography as having endometriosis were approached. After counseling 18 opted for non-surgical and 2 opted for surgical intervention. The baseline characteristics of the study participants are described in Table 1.

Table 1: The baseline characteristics of the study participants.

Baseline characteristics	Surgical (n=2)	Non surgical (n=18)	P value
Age (years) mean±SD	26.00±2.828	27.00±3.835	0.727
Residence (%)			
Rural	50.0	66.7	0.589
Urban	50.0	33.3	
Occupation (%)			
Housewife	100.0	83.3	1.000
Service	0	5.6	
Student	0	11.1	
Husband's occupation (%)			
Service	100.0	44.4	0.684
Business	0.0	33.3	
Farmer	0.0	5.6	
Student	0.0	5.6	
Unemployed	0.0	11.1	
Monthly income (%)			
<10,000 Tk	0.0	16.7	1.000
10,000-<20,000 Tk	50	33.3	
20,000-<30,000 Tk	50	50.0	
>30,000 Tk	0.0	0.0	
Type of infertility (%)			
Primary	50.0	77.8	0.447
Secondary	0.0	11.1	
Pre-conception counseling	50.0	11.1	
Duration of infertility (yrs.) mean±SD	7.75±4.59	4.92±2.03	0.109

Of the 18 participants who opted for medical management, 3 patients were lost from follow up. One participant left the study after 3 months of cabergoline and had controlled ovarian stimulation with IUI. Of the remaining 14 participants who completed the study, two participants (14.3%) got pregnant. They had LH kit positive for ovulation from 4th month onwards. One patient whose cyst size did not decrease was advised surgery, but she preferred to continue medication. Intention to treat analysis reveals pregnancy rate (2/18) 11.1%.

Of the two patients who opted for surgery, no one got pregnant. One patient who had surgery continued hormonal suppression with dienogest and norethisterone because she had relationship problems with her husband. Another woman was advised in vitro fertilization following surgery, but this was a treatment she could not afford. There is persistence of pain and recurrence of cyst larger than that before surgery on a sonogram done after 6 months. Now she is on continuous active estrogen progesterone pills. Table 2 compares the clinical outcome in two groups.

Table 2: Clinical outcome of surgical versus non-surgical interventions.

Clinical outcome	Surgical (n=2)	Non-surgical (n=14)
Pregnancy (%)	nil	14.3
Pain reduction (%)	50	100
Endometrioma size reduction (%)	50	93

DISCUSSION

The patient preference trial was undertaken to see if non-surgical interventions allowed pregnancy in infertile women with endometriosis. More couples preferred treatment strategy with medications. There was pregnancy in 14.3% of the couples while no pregnancy in those who had surgery.

Different combination of hormonal suppression can be used to reduce pain and size of cyst in women having clinical and sonographic diagnosis of endometriosis.

There is increased aromatase activity and estrogen production in ectopic endometrial tissue. Estrogen stimulates synthesis of prostaglandin E2 which in turn potentiates the ectopic endometrial aromatase activity. Letrozole is an aromatase inhibitor that can break the vicious cycle responsible for the new growth of ectopic endometrial tissue.[11] There were studies on women with endometriosis given letrozole daily for 3-6 months; all of them had reduction in pain.[12-15] There are other studies which added norethisterone to letrozole.[16-19] Norethisterone is distinct from other progestins in having estrogenic metabolites and a possible favorable effect on bone density.[20] Agarwal et al showed that mean endometrioma volume reduction of 75% at the end of three months.[19] One prospective observational study by Ansary et al, revealed that cyst volume reduction greater than 50% can be achieved in 90% of the women given letrozole, norethisterone for 6 months.[21] The percentage reduction in size of endometrioma by combination of letrozole and norethisterone over six months is positively correlated to the baseline size. In this study there were three pregnancies (10%) in the follow up period after completion of 6 months

treatment. Pregnancy after successful completion of treatment with aromatase inhibitor were also observed by Verma et al, Seal et al and Abushahin et al.[12-14]

Dopamine agonists target angiogenesis, a mechanism in the pathogenesis of endometriosis. They modulate pro and anti-angiogenetic pathways, impair VEGF (vascular endothelial growth factor) secretion and VEGF receptor activity, blocks cellular, endothelial and endometrial proliferation and ultimately reduce endometrial lesion size and pain. In contrast to the traditional hormonal agents used in endometriosis, they do no suppress ovulation or create hypoestrogenic environment.[22] There was a prospective, randomized study by Hamid et al which found that cabergoline is better in decreasing the size of endometrioma, compared to LHRH-agonist and it is cheaper, easier to administer, and safer.[23] Mukhopadhyay et al conducted a randomized controlled trial showing that cabergoline is as effective as medroxyprogesterone acetate in decreasing chronic pelvic pain in women with endometriosis.[24] Cabergoline had a better compliance than medroxyprogesterone acetate due to less side effects and less frequent dosing. The prospective comparative study carried out by Shume et al on women with endometrioma (diagnosed by ultrasound) to see the effect of cabergoline versus dienogest given for 3 months.[25] They concluded that cabergoline has better results in decreasing pelvic pain but less reduction in the size of endometrioma when compared to dienogest. DiVasta et al carried out a randomized, double-blind, placebo-controlled pilot study on women with surgically confirmed endometriosis, comparing cabergoline to norethisterone (NETA).[26] The study showed similar or more improvements in pain scores in women given cabergoline and it was well tolerated. There was a randomized controlled study with cabergoline and dydrogesterone given to women with endometriosis who wish pregnancy.[27] The pain was reduced and there were cases of spontaneous pregnancies and live births.

Surgery in advanced endometriosis by itself does not improve pregnancy rate beyond that achieved by watchful waiting if not followed by in vitro fertilization.[28] There is risk of decreasing ovarian reserve in infertile women by cystectomy. Repeat surgery is discouraged in women with recurrent cyst and pain endometriosis because second surgery does not improve fertility and there in pain reduction in only 53% cases.[6] In some cases of women with deep infiltrative endometriosis the surgery may not be complete without multidisciplinary involvement. So there is persistent of symptoms. Since surgery is not the complete answer to the problems of these women with endometriosis and infertility, these medical management options can be an alternative. Management of these couples need adequate counseling and follow up and be tailored to the need of women as well as to the cost and affordability.[29]

According to WHO, patient centeredness is one of the six dimensions of quality of care beyond the efficacy and safety of treatment modalities. Endometriosis specific quality of life is influenced by patient centered care experience. Patients satisfaction with endometriosis care is dependent on the information that match the patients' needs, being handled with empathy and respect and technical competence.[30] A survey conducted on women with endometriosis revealed that patient preference trial is the option most frequently chosen if they are to participate in any research on associated pelvic pain.[31]

Surgery was not preferred by most of the couples in our study. There are many arguments arising now against surgery even if the women are infertile or nulliparous. Endometriosis is not cancer like that all lesions should have surgical removal as soon as suspected. There may be irreversible reduction in ovarian reserve because of surgery but less so with medical suppression. Since medical management has to be taken for prolonged period, tolerability and cost is as significant as safety and efficacy.[32] Even the woman in need of a child will prefer pain relief over the treatment of infertility.[33] To be preferred as the first line treatment, surgery will have to ensure more than 83% of success in improving pain or fertility which is not the actual scenario.[34]

CONCLUSION

The infertile women with endometriosis prefer medical management over surgery. The medical management with hormonal suppression to reduce cyst size and pain followed by cabergoline and timed intercourse result in a higher pregnancy rate than surgery alone. So medical management can be a better option for infertile women with endometriosis who do not opt for in vitro fertilization in near future.

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REFERENCES

1. Giudice LC. Clinical practice. Endometriosis. N Engl J Medi. 2010;362(25):2389-98.
2. Heather R, Quinivan A. Let's not forget endometriosis and infertility amid the Covid 19 crisis. J Psychos Obstetr Gynecol. 2020;41(2):83-5.
3. Dunselman GA, Vermeulen N, Becker C, Calhaz-Georg C, D'Hoogie T, De Bie B, et al. ESHRE guideline management of women with endometriosis. Human Reproduct. 2014;29(3):400-12.
4. Khine YM, Taniguchi F, Harada T. Clinical management of Endometriosis associated infertility. Reproduct Medi Biol. 2016;15:217-25.
5. Keckstein J, Saridogan E, Ulrich UA, Sillem M, Oppelt P, Schweppe KW, et al. The Enzian Classification: a comprehensive non-invasive and surgical description system for endometriosis. Acta Obstetr Gynecolog Scandin. 2021;100(7):1165-75.

6. Hwang H, Chung Y, Lee SR, Park H, Song J, Kim H et al. Clinical evaluation and management of endometriosis: guideline for Korean patients from Korean Society of Endometriosis. Obstetr Gynecol Sci. 2018;61(5):53-64.
7. Ferrero S, Evangelisti G, Barra F. Current and emerging treatment options for endometriosis. Expert Opi Pharmacother. 2018;19(10):1109-25.
8. Barra F, Scala C, Mais V, Guerriero S, Ferrero S. Investigational drugs for the treatment of endometriosis, an update on recent developments. Expert Opin Investigat Drugs. 2018;27(5):445-58.
9. Ishrat S, Deeba F, Anwary SA, Banu J, Fatima P. Treatment experiences of infertile women with endometriosis: a qualitative analysis. Ann Internat Med Dental Res. 2021;7(3):176-86.
10. Kowalski CJ and Mrdjenovich AJ. Patient preference clinical trials: why and when they will sometimes be preferred. Perspect Biol Medi. 2013;56(1):18-35.
11. Shi J, Tan X, Feng G, Zhuo Y, Jiang Z, Banda S, et al. Research advances in drug therapy of endometriosis. Front. Pharmacol. 2023;14:1199010.
12. Verma A and Konje JC. Successful treatment of refractory endometriosis-related chronic pelvic pain with aromatase inhibitors in premenopausal patients. Eur J Obstet Gynecol Reprod Biol. 2009;143(2):112-5.
13. Seal SL, Kamilya G, Mukherji J, De A, Ghosh D and Majhi AK. Aromatase inhibitors in recurrent ovarian endometriomas: report of five cases with literature review. Fertil Steril. 2011;95(1):291-315.
14. Abushahin F, Goldman KN, Barbieri E, Milad M, Rademaker A and Bulun SE. Aromatase inhibition for refractory endometriosis-related chronic pelvic pain. Fertil Steril. 2011;96(4):939-42.
15. Madny EH. Efficacy of letrozole in treatment of endometriosis-related pain. Middle East Fertil Soc J. 2014;19(1):64-8.
16. Ailawadi RK, Jobanputra S, Kataria M, Gurates B, Bulun SE. Treatment of endometriosis and chronic pelvic pain with letrozole and norethindrone acetate: a pilot study. Fertil Steril. 2004;81(2):290-6.
17. Remorgida V, Abbamonte HL, Ragni N, Fulcheri E and Ferrero S. Letrozole and norethisterone acetate in rectovaginal endometriosis. Fertil Steril. 2007;88(3):724-6.
18. Ferrero S, Remorgida V, Venturini PL, Maggiore ULR. Norethisterone acetate versus norethisterone acetate combined with letrozole for the treatment of ovarian endometriotic cysts: a patient preference study. Eur J Obstet Gynecol Reprod Biol. 2014;174:117-22.
19. Agarwal SK and Foster WG. Reduction in endometrioma size with three months of aromatase inhibition and progestin add-back. Bio Med Res Int. 2015;2015(1):878517.
20. Chwalisz K, Surrey E and Stanczyk FZ. The hormonal profile of norethindrone acetate: rationale for add back therapy with gonadotropin-releasing hormone agonists in women with endometriosis. Reprod Sci. 2012;19(6):563-71.
21. Ansary SA, Ishrat S, Banu J, Fatima P, Nasreen F, Jahan I, et al. Evaluation of the effect of aromatase inhibitor in reducing the size of endometrioma. Int J Reproduct Contracept Obstetr Gynecol. 2021;10(4):1295-302.
22. Brichant G, Laraki I, Henry L, Munaut C and Nisolle M. New therapeutics in endometriosis: a review of hormonal, non-hormonal, and non-coding RNA treatments. Int J Mol Sci. 2021;22(19):10498.
23. Hamid AM, Madkour WA, Moawad A, Elzaher MA and Roberts MP. Does cabergoline help in decreasing endometrioma size compared to LHRH agonist? A prospective randomized study. Arch Gynecol Obstetr. 2014;290:677-82.
24. Mukhopadhyay P, Kyal A, Mukhopadhyay A. Does cabergoline help in decreasing chronic pelvic pain due to endometriosis compared to medroxyprogesterone acetate? A prospective randomized study. J South As Federat Obstetr Gynaecol. 2015;10:167-9.
25. Shume MM, Banu J, Ishrat S, Munira S, Uddin MJ and Sultana S. The effects of cabergoline compared to dienogest in women with symptomatic endometrioma. Fertil Reproduct. 2021;3(2):49-54.
26. DiVasta AD, Stamoulis C, Gallagher JS, Laufer MR, and Hornstein MD. Nonhormonal therapy for endometriosis: a randomized, placebo-controlled, pilot study of cabergoline versus norethindrone acetate. Fertil Steril Rep. 2021;2(4):2666-3341.
27. Ishrat S, Deeba F, Anwary SA, Begum N, Banu J. Cabergoline versus dydrogesterone in infertile women with endometriosis: a parallel-design randomized clinical trial. Gynecol Obstetr. 2021;11(8):565.
28. Johnson NP, Hummelshoj L. Consensus on current management of endometriosis. Human Reproduct. 2013;28(6):1552-68.
29. Vitali SG, La Rossa VL, Rapisarda AMC and Lagana AS. Endometriosis and Infertility: the impact on quality of life and mental health. J Endometri Pelvic Pain Disord. 2017;9(2):112-5.
30. Dancet EAF, Ameye L, Sermeu W, Welkenhuysen M, Nelen WLDM, Tully L. The ENDOCARE questionnaire (ECQ): a valid and reliable instrument to measure the patient-centeredness of endometriosis care in Europe. Human Reproduct. 2011;26(11):2988-99.
31. Vercellini P. Introduction: Management of endometriosis: moving toward a problem-oriented and patient-centered approach. Fertil Steril. 2015;104(4):0015-0282.
32. Vercellini P, Somigliana E, Cortinovis I, Bracco B, de Braud L, Dridi D, et al. " You can't always get what you want": from doctrine to practicability of study designs for clinical investigation in endometriosis. BMC Wom Health. 2015;15:1-9.
33. Metzemaekers J, van den Akker-van Marle ME, Sampat J, Smeets MJGH, English J, Thijs E, et al. Treatment preferences for medication or surgery in patients with deep endometriosis and bowel

involvement-a discrete choice experiment. BJOG. 2022;129(8):1376-85.
34. Bohn JA, Bullard KA, Rodriguez MI, Ecker AM. Stepwise approach to the management of endometriosis related dysmenorrhea, a cost effective analysis. Obstetr Gynecol. 2021;138(4):557-64.

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