OUTCOME OF ENDOMETRIOSIS TREATMENT IN INFERTILE PATIENTS IN A TERTIARY LEVEL HOSPITAL

RAHMAN F[1], SULTANA N[2], RAHMAN F[3], PAUL R[4], SALMA U[5], YEASMIN F[6], JESMIN N[7]

Abstract:

Introduction: *Prevalence of endometriosis is 6-10% in reproductive-age females. Around 25-35% of infertile women may be affected by endometriosis. Modalities of treatment for infertile patients depends on the stage of the disease. It starts from ovulation inducing drug to advanced ART. The objective of this study was to assess the outcome of surgical treatment in infertile, endometriosis patients.*

Materials and Methods: *It was an observational study, which was conducted at Reproductive Endocrinology and infertility Unit, Dhaka Medical College. Total 144 patients were included during July 2018 to July 2021, aged 20-40 yrs. All the demographic variables, clinical and sonographic findings, and hormonal assessment were done. Then, staging was done by clinical pelvic assessment, and ultrasonographic findings. Patients who had ovarian endometrioma, more than 4 cm, were selected for laparoscopic surgery. In patients whose endometrioma was less than 4 cm, or had no ovarian endometrioma, were selected for ovulation induction with or without prior GnRH agonist therapy. Further infertility management were planned according to ovarian reserve, tubal patency, and male factor.*

Result: *Mean age of the patients were 28.30±4.95 yrs. 75.0% patients had primary infertility. Dysmenorrhea was the most common symptom (86.96%), followed by chronic pelvic pain (81.16%). Bilaterality of endometrioma was associated with decreased serum AMH.*

Laparoscopic surgery was the mainstay of treatment, Cystectomy was done in 58% patients. Conservative treatment was done in remaining patients. Fertility enhancing treatment was done by ovulation inducing drug -letrozole, GnRH agonist, followed by controlled ovarian stimulation and followed by IUI. IVF was advised for fertility management in 26 patients (18.06%).

Conclusion: *Endometriosis is not only associated with decreased ovarian reserve but also responsible for diminished response to ovarian stimulation. So, it is a great challenge to obtain successful fertility treatment for this group of patients.*

Keywords: *Endometriosis, infertile.*

DOI: https://doi.org/10.3329/jdmc.v32i1.76403
J Dhaka Med Coll. 2023; 32(1) : 9-15

Introduction

Endometriosis is characterized by the presence of functional endometrial glands and stroma in ectopic locations like pelvic peritoneum, ovaries recto-cervical septum or pouch of douglas. The Prevalence of endometriosis in reproductive age women is 6-10%[1]. Around 25-50% of infertile women may be affected by endometriosis. Mean age of diagnosis is 25-35 years.

50-60% of women with chronic pelvic pain or unexplained infertility may have undiagnosed endometriosis.[2] It is more prevalent in women with Obstructive Müllerian anomalies.[3]

1. Dr. Florida Rahman, Associate Professor, Reproductive Endocrinology and Infertility, DMCH
2. Prof. Nilufar Sultana, Ex. Head of The Dept. and Head of Reproductive Endocrinology and Infertility, DMCH
3. Prof. Fatema Rahman, Head of Reproductive Endocrinology and Infertility Unit, DMCH
4. Dr. Ratna Paul, Asst. Prof. Reproductive Endocrinology and Infertility, DMCH
5. Dr. Umma Salma, Register, Reproductive Endocrinology and Infertility, DMCH
6. Dr. Farida Yeasmin, Student (FCPS) Reproductive Endocrinology and Infertility, DMCH
7. Dr. Nafisa Jesmin, Student, Reproductive Endocrinology and Infertility, DMCH

Correspondence: Dr. Florida Rahman, Associate Professor, Reproductive Endocrinology and Infertility, DMCH, E-mail: florida_rahman@yahoo.com Cell: 01711153656

Received: *04.09.2023* ***Revision:*** *17.11.2023* ***Accepted:*** *12.02.2024*

Retrograde menstruation, coelomic metaplasia, lymph vascular dissemination, direct transplantation, altered immunity, and more recently a genetic basis are the possible etiology of the disease.[5] Recent evidence shows that bone marrow derived stem cells migrate to utopic and ectopic endometrium and differentiate into endometrial cells. CXCR4/CXCL-12 play a key role. They induce stem cell recruitment, angiogenesis and tissue growth.[5] Activated macrophages at the ectopic endometrium secretes IL-1, IL-6, IL-8, TNF, Rantes, VEGF, and stimulate the proliferation of ectopic endometrium. Endometriosis is 6-8 times more prevalent among 1st degree relatives of affected women.[6] Both estrogen production and metabolism are altered in endometriosis, and promote the disease. Excess production of prostaglandin, metalloproteinase, and chemokines results in chronic inflammation that interferes with ovarian, tubal, or endometrial function and results disordered folliculogenesis and implantation failure. 30-50% of women with endometriosis have infertility. Monthly fecundity of women with minimal and mild endometriosis, receiving gonadotropin and IUI is lower, compared with women without the disease. Endometrioma negatively hampers the ovarian reserve. Surgical management also decreases the ovarian reserve. Several types of classification and staging systems have been developed to give guidelines for treatment. Current version of the revised American Society of Reproductive Medicine (ASRM) classification system based on surgical findings at laparoscopy or laparotomy was the mostly accepted system for fertility management but it has got some limitations.[7] In 2005 Enzian classification was developed to understand deep infiltrating lesions. In 2009, a new staging system was proposed after analyzing surgical and clinical outcome of 697 patients, called the endometriosis fertility index (EFI), combining the factors that best predict pregnancy without IVF.[8]

According to European Society of Human Reproduction and Embryology (ESHRE) 2021-GDG (Guideline Group) recommends that fertility treatment of infertile patients with endometriosis and decision to perform surgery should be guided by the –Size of tumour (>4 cm), Presence or absence of pain symptoms, Patient's age and preference, history of previous surgery, Other infertility factors, Ovarian reserve and Estimated EFI score [10]Objective of Study

Prevalence of endometriosis is high in Bangladesh, especially among infertile patients. This study was performed to evaluate the outcome of surgical management of endometriosis patients in a tertiary level government hospital where IVF facilities are not well established.

Materials and Methods

It was an observational study conducted at Reproductive Endocrinology and infertility Unit, Dhaka Medical College. Total 144 patients were included during July 2018 to July 2021, aged 20-40 yrs. All the demographic variables, clinical features, sonographic features, and hormonal assessment were done. Then, staging was done depending on clinical pelvic assessment, and ultra-sonographic and laparoscopic findings. Paine scoring was assessed by verbal scale which was correlated with visual analog scale (VAS). Where 0 corresponds to worst pain. But in verbal scale this was no pain, moderate pain, severe pain, unbearable pain.

Patients who had ovarian endometrioma by USG, >4 cm, were selected for laparoscopic surgery. In patients whose endometrioma was less than 4 cm, or had no ovarian endometrioma, were selected for ovulation induction with or without prior GnRH agonist. Further infertility management were planned according to ovarian reserve, tubal patency, male factor and other associated comorbidities.

Results

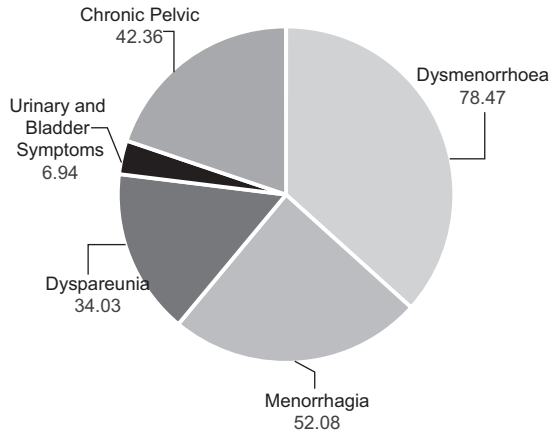
144 patients were selected by pelvic assessment and USG evaluation S. FSH, S. TSH, and S. AMH were measured. Those who had >4 cm endometrioma were selected for surgery S. FSH and S. AMH were measured 3 months post-surgery. Results were analyzed by SPSS v26.0.

Table-I

Demographic Variables (N=144)

Age (Mean ± SD)	28.45±5.02
Type of Infertility (%)	
Primary	72.92%
Secondary	27.08%
Duration of Marriage (Mean ± SD)	7.23±4.42
Parity (%)	
Nullipara	77.78%
Multipara	22.22%
BMI (Mean ± SD)	25.55±4.06

Most of the patients were >30 years & 72.92% had primary infertility



Fiture 1: *Clinical Presentation of Patients*

Dysmenorrhea was the most important clinical symptom followed by Menorrhagia.

Table-II

Pain Score by Verbal Scale (N=144)

	Number of Patients	
No Pain	29	20%
Moderate Pain	58	40%
Severe Pain	43	30%
Unbearable Pain	14	10%
Total	144	100%

Most of the patients who had endometrioma was suffering from moderate to severe pain 70% and there was no chronic pelvic pain in 20% patients.

Among 144 patients there was no associated pathology in 107 (74.31%). Only adenomyosis was present in 15 (10.42%), fibroid uterus in 4.17%, hypothyroidism in 2.78%. Only fibroid uterus was present in 5 (3.47%) patients (Figure-2).

Patients who had ovarian endometrioma <4cm with good ovarian reserve, Ovulation induction was done by letrozole or clomiphene citrate at least for six cycles. In some patient gonadotrophin also added with or without IUI. GnRH agonist was also added in some patients (Table V).

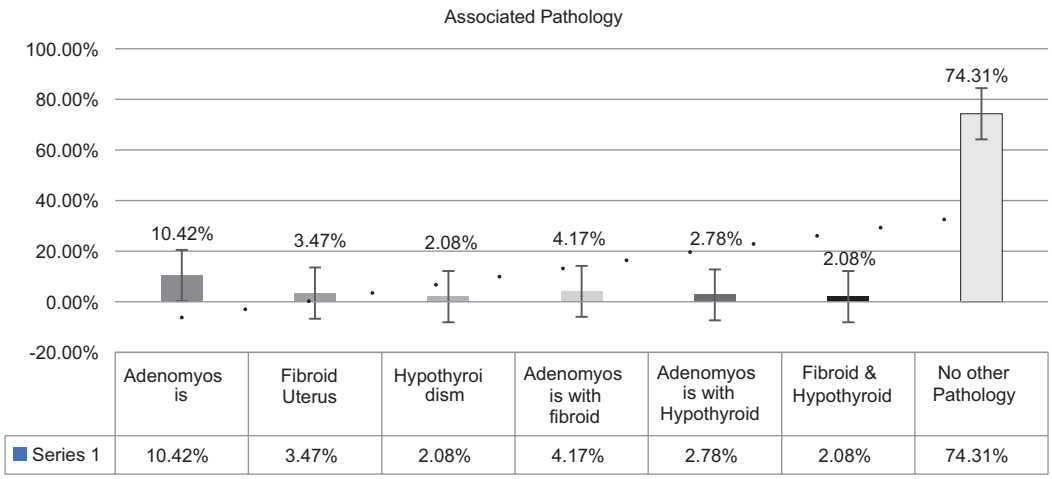
Table-III

Ultrasonographic Findings

Size of tumour (%)	2-4 cm	4-6 cm	>6 cm	No tumour	
	19.44%	49.31%	26.39%	4.86%	100.00%
Laterality	Unilateral	Bilateral	no tumour		
	91	46	7		
	63.19%	31.94%	4 .86 %		
Adhesion with	Superficial	Deep	Pouch of Douglas-Obliteration	No tumour	surroundings
	86	44	7	7	
	59.72%	30.56%	4.86%	4.86%	100.00%

63.19% endometrioma were unilateral and 31.94% were bilateral.

Difference between pre- and post-surgery is highly significant. It‘s not sure, if surgery decreases AMH increases FSH (Table-VII).



Fiture 2:

Table-IV

Baseline Hormone Levels

Hormone levels Mean + SD	AMH (ng/ml)	FSH (IU/ml)	TSH (mIU/l)	Prolactin (ng/ml)
Mean	2.45	5.99	3.10	17.94
SD	±1.46	±2.83	±1.96	±7.37

Mean serum AMH level was 2.45 ±1.46 and serum FSH was 5.99 ±2.83

Table-V

Fertility Management without Surgery

Fertility Management without surgery	n = 56	Percentage
OID	10	17.86%
OID & Gonadotrophins	10	17.86%
OID, Gonadotrophins & IUI	1	1.79%
GnRHa Gonadotrophins	7	12.50%
GnRHa, Gonadotrophins & IUI	12	21.43%
Planned for IVF	16	28.57%

Table-VI

Fertility Management with Surgery

Types of Surgery	n= 88	Percentage
Coagulation and Adhesiolysis	50	56.82%
Excision of Endometrioma	23	26.14%
Aspiration of Cyst	6	6.82%
Laparotomy	9	10.23%

IUI was performed on 17 patients post surgically
IVF was planned for 10 patients after surgery

Table-VII

Paired correlation between pre- and post-surgery AMH

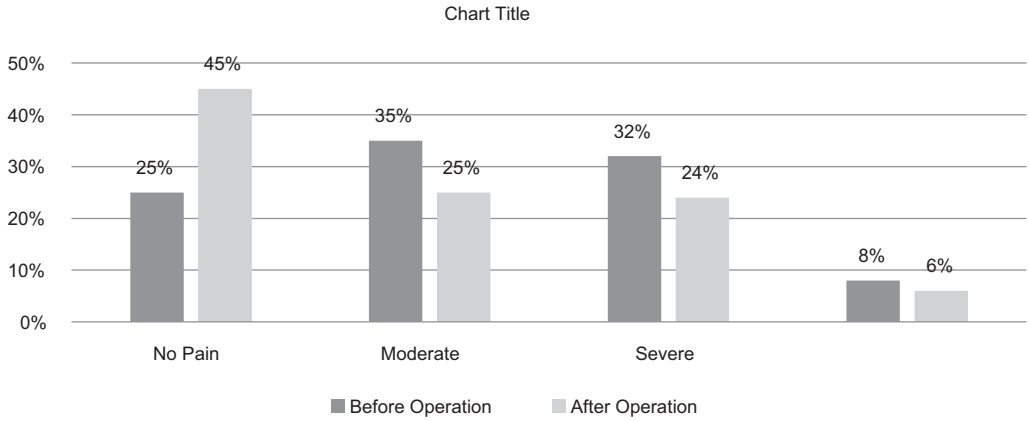
n=94	Mean	SD	t value	p value
Pre-surgery	2.5863	1.2961	6.7848	<0.001
Post-surgery	1.898	1.3572		

Table-VIII

Pearson's R test between Post Surgery AMH and FSH

n=94	Mean	SD	R value	p value
Post AMH	1.90	1.36	-0.0252	0.81
Post FSH	6.20	2.88		

Pearson's R test is not significant between post-surgery AMH and FSH



Fiture 3: *Comparison of pain before and after surgery (n=88)*

Reduction of pain in patients with chronic pelvic pain and endometrioma were not significantly improved after surgery. At 95% confidence interval the two-tailed P value equals 1.0000 considered to be not statistically significant.

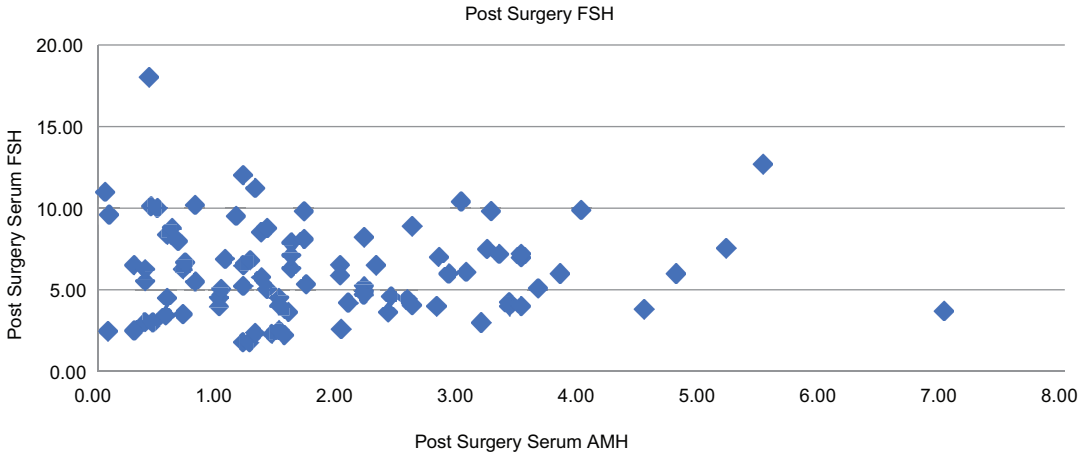


Figure-4: *Correlation between Post surgery AMH and FSH,*

There was no correlation of post-surgery (3 months) serum AMH and serum FSH level.

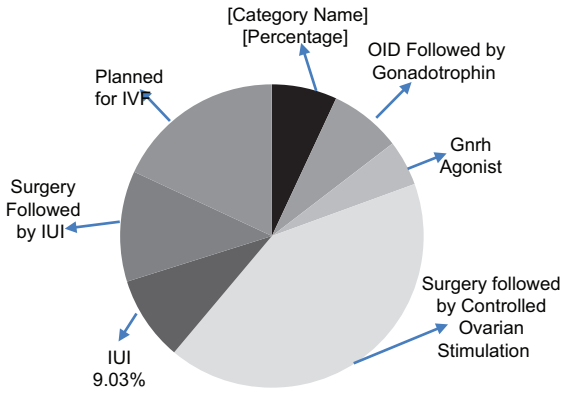


Figure 5: *Modalities of Treatment (n=144)*

In Our Hospital most of the patients were admitted with endometrioma (unilateral, bilateral or Recurrent endometrioma) in stage III & IV of the disease. So, surgery was the main stay of treatment (Surgery followed by controlled ovarian stimulation in 41.67% and Surgery followed by IUI 11.81%. Without prior surgery IUI was done in 9.03%. GnRH analogue was used in 4.86% before or after IUI. IVF planned for 18.06% patients.

Table-IX

Outcome of Fertility Treatment

Outcome of Treatment	n=144	Percentage
Pregnancy Positive	28	19.44%
Take Home Baby	6	4.1%
Drop-Out (due to COVID-19)	46	31.94%
Continuing Management	38	26.38%
Waiting for IVF	26	18.06%

Only 4.1% patients were successful with live birth and pregnancy positive was 28 patients but complicated with miscarriage.

Table-X

Outcome of medical management (without surgery) n=38

Management	Number of Patients	Successful Patients
OID	10	-
OID f/b Gn	13	1
OID + Gn + IUI	12	1
GnRh a f/b Gn	2	-
GnRh a + Gn + IUI	1	-
	38	2 (5%)

Among the different modalities of medical management OID & Gonadotropin followed by IUI have shown same as OID & Gonadotropin.

Discussion

In this series, mainstay of treatment was surgery in 61% of patients, which is very high in comparison to other similar studies. However, a study by a Canadian collaborative group, who studied 341 infertile women with minimal to mild endometriosis with laparoscopy, found a significantly high pregnancy in the treatment group (30.7% vs 17.7%, p=0.006) suggesting enhanced fecundity with surgical treatment.[11]

As our center is a government level tertiary care hospital, most of the patients came from different parts of the country at an advanced stage of their disease, with large endometrioma, severe adhesion or severe symptoms. So, these patients require surgery for their symptom relief and also for fertility management.

In this series pre-surgery Serum AMH 2.5863 ± 1.2 and post-surgery serum AMH 1.898 ± 1.35 and P value was <.001 which is highly significant. It's not sure, if surgery decreases serum AMH, increases serum FSH. Whether surgery should be deferred as far as possible.

Patients who had good ovarian reserve - Ovulation Induction was done by letrozole or clomiphene citrate at least for 6 cycles. Then, gonadotropin was added for 3 more cycles if OID not responded. In some patients with endometrioma <4 cm, GnRH agonist was used before ovulation induction for 1-3 cycles. IUI was done in 30 patients. Due to COVID 19 situation, large number of patients were dropped out from the study, and appropriate management was not possible to be given to those patients. So, fertility management in our study was hampered in every step.

Although we have established a new IVF lab in our hospital, IVF procedure has been started and 3rd batch was completed. 3 patients of recurrent endometrioma were included who had very low AMH. There embryos are cryopreserved and waiting for embryo transfer. So, result can not be assumed. However we have tried our best to give the optimum treatment to these patients.

Women with endometriosis are confronted with one or both of two major problems: endometriosis associated pain, infertility or both.

According to ESHRE 2021[10] Recommendations for hormone treatment are

- In infertile women with endometriosis, ovarian suppression treatment should not be prescribed to improve fertility.

- Women seeking pregnancy should not be prescribed postoperative hormonal suppression with (GnRh analogue) the sole purpose to enhance future pregnancy rates.

-Those women who cannot attempt or decide not to conceive immediately after surgery should be offered hormonal therapy as it does not negatively impact their fertility and improves the immediate outcome of surgery for pain.[10]

Regarding surgery ESHRE[10] Recommendations are- Operative laparoscopy could be offered as a treatment option for endometriosis-associated infertility in rASRM stage I/II endometriosis as it improves the rate of ongoing pregnancy.

Clinicians may consider operative laparoscopy for the treatment of endometrioma-associated infertility as it may increase their chance of natural pregnancy, although no data from comparative studies exist.[10]

Although no compelling evidence exists that operative laparoscopy for Deep infiltrating endometriosis improves fertility, operative laparoscopy may represent a treatment option in symptomatic patients wishing to conceive.

Conclusion

Endometriosis is not only associated with decreased ovarian reserve but also responsible for diminished response to ovarian stimulation. So, it is a great challenge to obtain successful fertility treatment for this group of patients. By raising the awareness and diagnosing the patients at an early stage, improving operative techniques, optimizing ART facilities, we are hopeful to overcome our difficulties for treatment and obtain optimum result.

Reference:

1. Macer ML, Taylor HS. Endometriosis and infertility: review of the pathogenesis and treatment of endometriosis associated infertility. *Obstet Gynecol Clin North Am*; 39:535-49. 2012
2. Giudice IC. Clinical Practice. Endometriosis, *N England J Med* 362(25):2389. 2010.
3. Olive DI, Henderson DY. Endometriosis and Müllerian Anomalies. *Obstet Gynecol* 69:412. 1987.
4. Burney RO, Giudice IC. Pathogenesis and Pathophysiology of Endometriosis. *Fertil Steril* 98(3):511. 2012.
5. Moridi I, Mamillapalli R, Cosar E et al. Bone Marrow Stem Cell Chemotactic Activity is induced by elevated CXCI12 in endometriosis. *Reprod Sci* 24(4):526. 2017.
6. Bruner-Tran KI, Herington JL, Duleba AJ et al. Medical Management of Endometriosis: Emerging Evidence Linkning Inflammation to Disease Pathophysiology. *Minerva Ginecol* 65(2): 199. 2013.
7. Guzick DS, Silliman NP, Adamson GD et al. Prediction of Pregnancy in infertile women based on the American Society for Reproductive Medicine's revised classification of endometriosis. *Fertil Steril* 67:822. 1997.
8. Tuttlies F, Keckstein J, Ulrich U et al. ENZIAN score, a classification of Deep infiltrating endometriosis (in German). *Zentralbl Gynakol* 127:275. 2005
9. Adamson GD, Pasta DJ. Endometriosis fertility index: the new, validated endometriosis staging system. *Fertil Steril* 94(5): 1609-1615. 2010
10. ESHRE. ESHRE Guidelines Endometriosis: Draft for Review. . Accessed in Oct 2021. Accessed from https://www.eshre.eu/-/media/sitecore-files/Guidelines/Endometriosis/ESHRE-GUIDELINE-ENDOMETRIOSIS-2021_DRAFT-FOR-REVIEW. pdf ?la=en & hash= 76E6C1C4A0A24 FE67F3853 E8EEA37C0D611DB251
11. Society of ART. *National Data Summary.* 2009. (Accessed Oct 2021). From https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?ClinicPKID=0