

# **An investigation into the relationship between endometriosis and the outcomes experienced by infertile patients**

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## **Abstract:**

### **Introduction:**

Females of reproductive age have a 6–10% prevalence of endometriosis. About 25–35% of women who are infertile may have endometriosis. Treatment options for infertile patients vary according to the disease's stage. It begins with an ovulation-inducing medication and progresses to sophisticated ART. This study was out to evaluate the results of surgical treatment for patients with endometriosis who were infertile.

### **Materials and Methods:**

The study was carried out in selected government hospitals at Haryana. A total of 150 patients between the ages of 20 and 40 were included in this study. Every demographic factor, clinical and sonographic result, and hormonal evaluation was completed. Following that, staging was completed using ultrasonographic results and a clinical pelvic evaluation. For laparoscopic surgery, patients with ovarian endometriomas larger than 4 cm were chosen. Patients were chosen for ovulation induction with or without prior GnRH agonist therapy if their endometrioma measured less than 4 cm or if they did not have an ovarian endometrioma.

**Results:** The patients' mean age was 29.64 years & 70.52% had primary infertility. Dysmenorrhea (76.24%) was the most important clinical symptom followed by Menorrhagia (54.61%) and chronic pelvic (40.51%). Decreased serum AMH was linked to bilateral endometrioma. The primary treatment was laparoscopic surgery. The remaining patients received conservative care. In order to increase fertility, ovulation-inducing medications such as letrozole and GnRH agonists were used, followed by controlled ovarian stimulation and IUI. In 25 patients (33.33%), IVF was recommended for fertility management. In conclusion, endometriosis causes a reduced response to ovarian stimulation in addition to being linked to a decreased ovarian reserve. Therefore, obtaining effective reproductive treatment for this patient population is quite difficult.

## **1. Introduction**

Endometriosis as a risk factor for natural conception The existence of endometrial glands outside the uterus is a hallmark of endometriosis, a persistent inflammatory illness. About 5–10% of women who are of reproductive age are affected, and it frequently results in pelvic discomfort, decreased fertility, or

both (Giudice, 2010). Up to 30–50% of women with endometriosis are infertile, which is a serious worry (Somigliana et al., 2017). Furthermore, up to 25–50% of infertile individuals have endometriosis, which is ten times more common than in the general population (Ozkan et al., 2008; Koch et al., 2012); additionally, endometriosis accounts for 10% of referrals for IVF treatments (Somigliana et al., 2017). The connection between endometriosis and infertility has been explained by a number of theories.

These include endometrioma-induced damage to the ovarian parenchyma, pelvic anatomy distortion due to adhesion formation, chronic inflammation in the pelvis and peritoneal fluid linked to superficial and deep peritoneal lesions, any associated adenomyosis, altered hormone and cell-mediated functions in the endometrium, dyspareunia (and consequently difficulty having intercourse), and potential iatrogenic damage during ovarian parenchyma surgery (Somigliana et al., 2017; Llarena et al., 2019). Reduced tubal function, poor folliculogenesis and/or oocyte quality, and/or changes to the uterine milieu that hinder sperm motility and embryo implantation are all possible outcomes of these issues (Somigliana et al., 2017; Llarena et al., 2019).

In 17–44% of cases, endometriosis manifests as an ovarian endometrioma. The relationship between endometrioma and altered ovarian endocrine function has received special attention in the scientific literature. Massive concentrations of free iron, reactive oxygen species, proteolytic enzymes, and inflammatory molecules are found in the fluid of endometriomas. These substances eventually cause fibrous tissue to replace normal ovarian cortical tissue, which in turn reduces the pool of primordial follicles (Sanchez et al., 2014; Llarena et al., 2019). According to a recent systematic review, endometriosis considerably lowers anti-Müllerian hormone (AMH) levels as compared to controls.

Additionally, a subgroup analysis that looked at the antral follicle count (AFC) of ovaries with endometriomas discovered that the affected ovary's AFC was considerably lower than the contralateral ovary's prior to surgery. This confirms that the majority of ovarian reserve loss happens before surgery (Tian et al., 2021). Additionally, the ovary may be subjected to mechanical stress due to large endometriomas (Llarena et al., 2019). In comparison to age-matched non-endometriosis controls, women with endometriomas have lower AMH levels and a faster loss in ovarian reserve (Sanchez et al., 2014). Furthermore, endometriosis is frequently associated with a higher risk of premature ovarian failure and less ovulation in the afflicted ovary relative to the normal ovary.

Although these findings are still debatable, it has also been proposed that women with endometriomas have lower-quality oocytes. Women with endometriosis had oocytes with decreased in-vitro fertilization and in-vitro maturation rates, according to data from IVF operations (Harb et al., 2013; Sanchez et al., 2017). To determine whether endometriosis affects embryo quality, a number of studies have examined the quality of embryos derived from the oocytes of women who have the condition. In a study with 235 human embryos, scientists discovered that embryos derived from the oocytes of women with endometriosis were more likely to exhibit cytoplasmic fragmentation, uneven cleavage, and nuclear and cytoplasmic abnormalities than those from patients with other forms of infertility.

However, patients with endometriosis appear to have similar rates of embryo aneuploidy compared to unaffected age-matched controls, and those who have undergone IVF for other reasons appear to have comparable rates of pregnancy, live birth, and miscarriage (Gonzalez-Comadran et al., 2017). Even though there is strong evidence linking endometriosis to infertility, only 30 to 50% of endometriosis-affected women are infertile, and many of them are able to conceive naturally (Somigliana et al., 2017).

**The role of surgery in improving fertility**

A contentious issue is the surgical management of infertility brought on by endometriosis. Specifically, there is disagreement on whether surgery or IVF should be used as the initial treatment for these patients (Calagna et al., 2020). The decision-making process is complicated because the likelihood of enhancing natural fertility through surgical intervention can depend on a number of variables, including the patient's age, preferences, history of previous surgeries, presence of other infertility factors, ovarian reserve, estimated endometriosis fertility index (EFI), and the presence and severity of pain symptoms. This staging technique predicts the rates of non-IVF pregnancies following surgical staging and treatment for endometriosis.

The identification of deep infiltrated endometriosis (DIE) prior to surgery can potentially be a useful indicator of the severity of the procedure. Furthermore, in the context of infertility, DIE is a significant factor in deciding whether to use ARTs or move on with a surgical intervention, especially when paired with predictive tools such as the EFI (Condous et al., 2024). For individuals with endometriosis, the initial indication for surgery is the presence of symptoms that are not adequately controlled with medication (Dunselman et al., 2014).

In ASRM stage III and IV endometriosis, it is less evident whether surgical treatment improves fertility (Koch et al., 2012; Dunselman et al., 2014).

The 3-year projected cumulative pregnancy rate following laparoscopic surgery was 62%, according to a prospective cohort study conducted by Adamson and Pasta (1994). According to other research, patients who had surgery to correct DIE prior to IVF operations had higher post-IVF conception rates than patients who did not have surgery (Ferrero et al., 2009). According to Liang et al. (2024), surgery, whether total or partial, increased the likelihood of getting pregnant. This emphasizes how important surgical procedures are as a treatment for DIE; even if they don't completely eradicate the condition, they can still have a significant positive impact on fertility outcomes. Nevertheless, patients should always carefully consider the risks associated with surgery before deciding to have it done.

However, according to some other research, surgery has no effect on fertility outcomes (Vercellini et al., 2006). In order to restore normal pelvic architecture in women with DIE, laparoscopic intervention may be suggested; nevertheless, the indication should be thoroughly reviewed with the patient (Dunselman et al., 2014). For women with DIE who primarily want to have children, some experts recommend IVF as the first line of treatment instead of surgery (Falcone and Flyckt, 2018).

Effects of surgical methods on fertility preservation and ovarian reserve in the treatment of endometriosis The potential benefit of removing an endometrioma to boost fertility must be weighed against the possibility of harming the ovarian reserve, which has been discussed by a number of authors (Dunselman et al., 2014).

AMH levels really drop following the removal of an endometrioma, according to numerous studies and meta-analyses (Raffi et al., 2012; Somigliana et al., 2012; Seyhan et al., 2015; Goodman et al., 2016).

Furthermore, in the post-operative period, ovarian cystectomy has been linked to a 2.4–13% risk of premature ovarian failure (Busacca et al., 2006).

Prior to therapy, people with bilateral ovarian cysts, advanced surgical staging, a fully contained Douglas pouch, advanced age, elevated BMI, and shorter menstrual cycles all had considerably lower AMH levels than people without these problems.

Furthermore, within a year after laparoscopic cystectomy, AMH levels continued to drop (Zhang et al., 2024). Numerous factors have been suggested as causes of surgery-induced damage to the ovarian parenchyma, such as the overremoval of healthy ovarian tissue (Muzii et al., 2002), electrocoagulation-induced vascular damage, and autoimmune reactions brought on by severe local inflammation (Li et al., 2009). Conservative surgical management of ovarian endometriomas usually includes a number of alternatives, such as ethanol-based sclerotherapy, ablative procedures (such as laser, plasma energy, or bipolar diathermy), and cystectomy by stripping, as well as a combination of these methods.

In India, endometriosis is very common, particularly in infertile individuals. The purpose of this study was to assess the results of surgical treatment for endometriosis patients in a government tertiary hospital with underdeveloped IVF facilities.

## **2. Methodology**

### **Study Design**

In order to assess the effects of surgical intervention on uterine receptivity and pregnancy outcomes in women with endometriosis, this study is planned as an experimental investigation. There will be two groups in the study:

#### **Intervention Group (Group A):**

Endometriotic lesions and adhesions are being removed in women undergoing laparoscopic surgery for endometriosis.

#### **Group B, the control group:**

women undergoing conservative medical treatment, such hormone therapy or painkillers.

### **Area of Study**

The study will be carried out at several government hospitals in Delhi, guaranteeing access to a range of patient demographics and making use of the cutting-edge surgical and diagnostic capabilities offered by these establishments. In order to guarantee that participants receive top-notch care, these facilities were chosen for their proficiency in gynecology and reproductive health.

### **Sample Size**

There will be 150 participants in total, split equally between two groups (75 in Group A and 75 in Group B). The sample size was established through statistical power calculations to guarantee sufficient representation and validity of the results.

Every demographic factor, clinical characteristic, sonographic characteristic, and hormonal evaluation was completed. Following that, staging was carried out based on the results of the laparoscopic and ultrasonographic procedures as well as the clinical pelvic assessment. A verbal scale that was associated with the visual analog scale (VAS) was used to score pain. where the worst discomfort is represented by 0. However, this was classified as no discomfort, moderate pain, severe pain, and intolerable pain on a verbal scale. Patients were chosen for laparoscopic surgery if their ovarian endometrioma measured more than 4 cm by USG. Patients who had no ovarian endometrioma or whose endometrioma measured less than 4 cm were chosen for ovulation induction, whether or not they had previously taken a GnRH agonist. Ovarian reserve, tubal patency, male factor, and other related comorbidities were taken into consideration while planning further infertility treatment.

### 3. Results

Through pelvic assessment and USG evaluation, 150 individuals were chosen. Measurements were made of S. FSH, S. TSH, and S. AMH. Surgery was chosen for those with endometriomas larger than 4 cm. Three months after surgery, S. FSH and S. AMH levels were assessed. SPSS v20.0 was used to analyze the results.

Table1. shows the demographic variables of the study participants.

Most of the patients were >30 years and mean age was 29.64 years & 70.52% had primary infertility.

#### Demographic variables (n=150)

Age (mean+-)	29.64+-6.22
Type of inferility	70.52%
Primary	29.48%
Secondary	6.54+-3.98
DURATION of marriage	
PARITY(%)	
NULLIPARA	75.64%
MULTIPARRA	24.36%
BMI	24.76+-3.98

Table1. shows the pain score by verbal scale.

Most of the patients who had endometrioma was suffering from moderate to severe pain 68% and there was no chronic pelvic pain in 21% patients.

Pain score by verbal scale (n=150)	No of patients	Percentage
No pain	32	21.33333
Moderate pain	58	38.66667
Severe pain	46	30.66667
Unbearable pain	14	9.333333

Fig 1: Clinical Presentation of Patients.

Dysmenorrhea (76.24%) was the most important clinical symptom followed by Menorrhagia (54.61%) and chronic pelvic (40.51%).

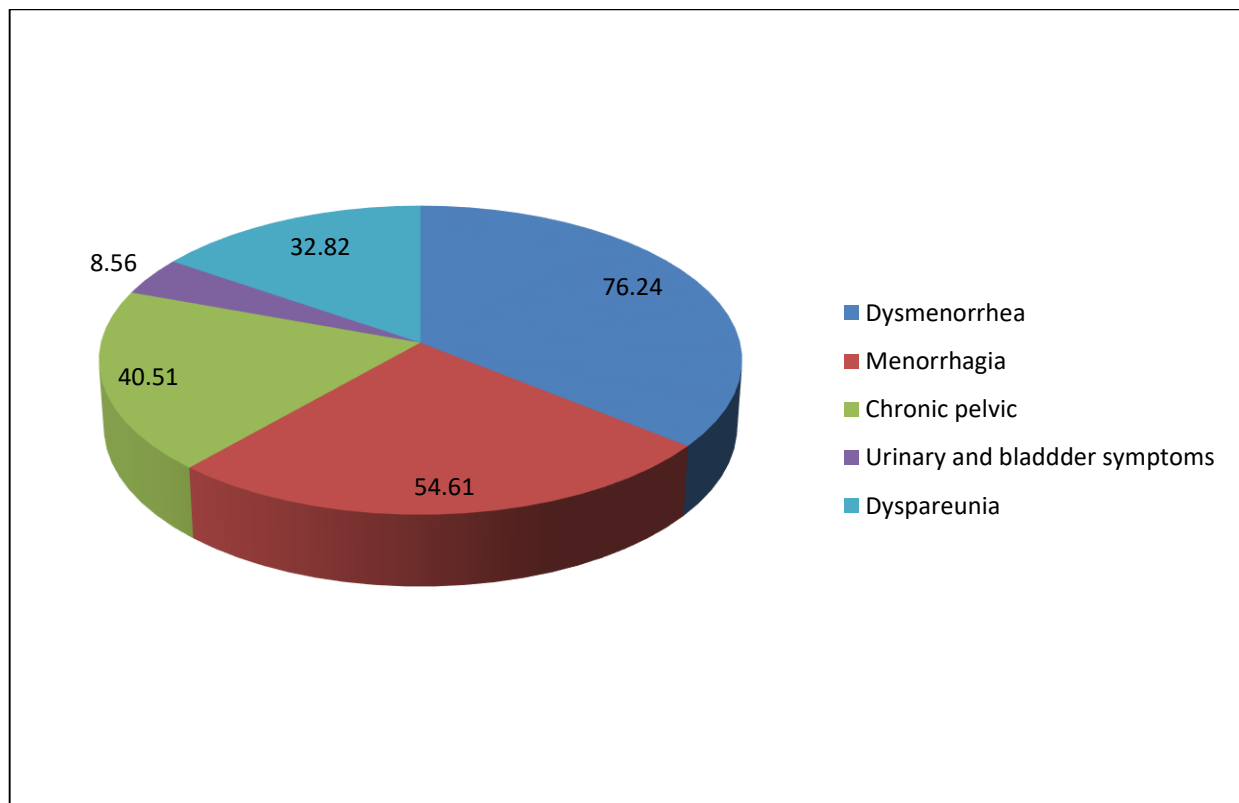


Fig. 2. shows the data on associated pathology of the patients

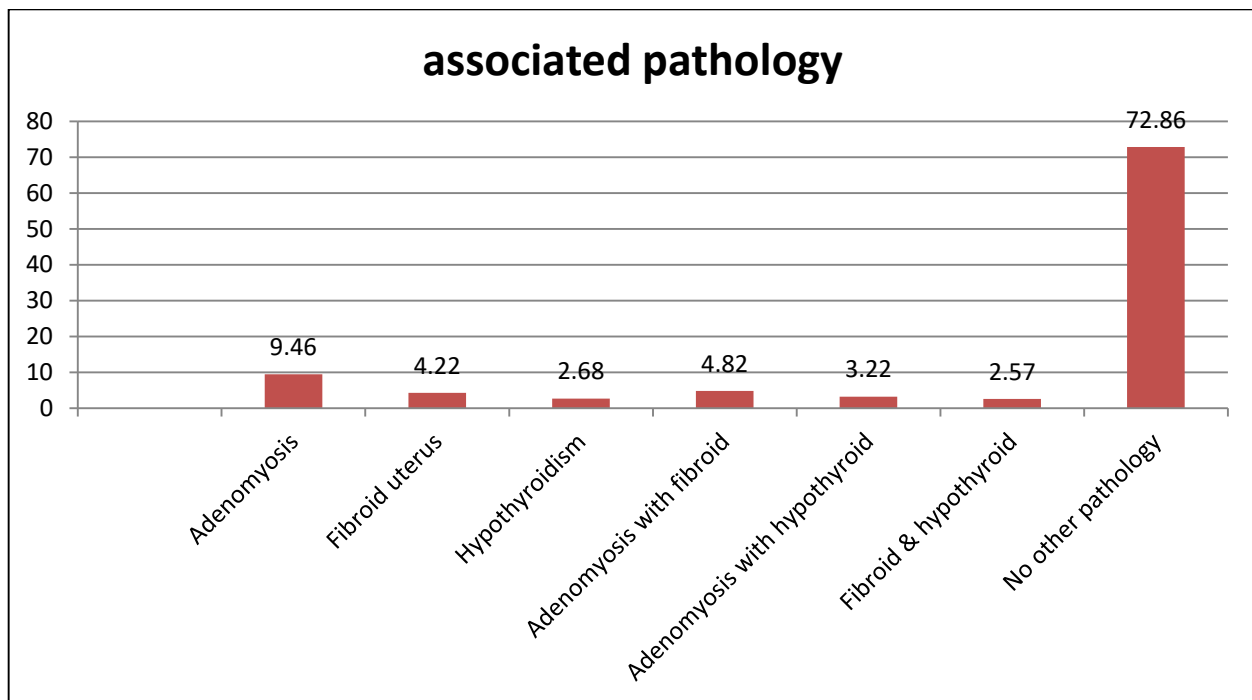
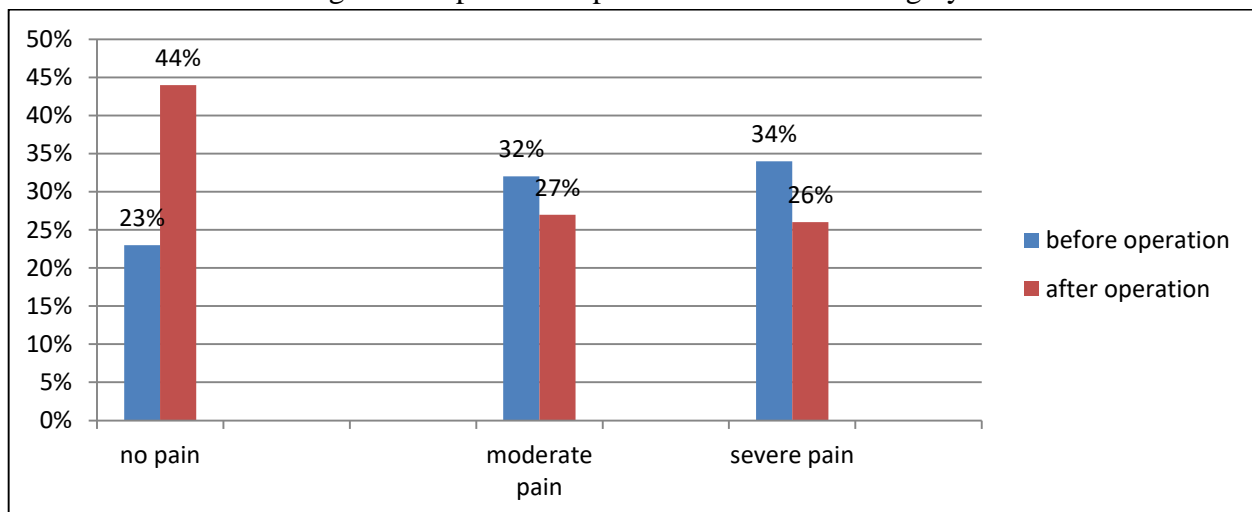


Fig. 3: Comparison of pain before and after surgery



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 1.000 considered to be not statistically significant

Table 3. shows the data of USG findings.

62.66% endometrioma were unilateral and 28% were bilateral.

Size of tumour(%)	2-4cm	4-6cm	>6cm	No tumour

laterality	18.36%	51.24%	24.48%	3.82%	100%
	Unilateral	Bilateral	No tumour		
	94	42	14		
	62.66%	28%	9.33%		
Adhesion with	Superficial	Deep	Pouch of douglass	No tumor	surroundings
	90	42	obliteration	10	
	60%	28%	8	6.66%	
			5.33%		

Table 4. shows the data on baseline hormone levels.

The mean serum AMH level was  $2.72 \pm 1.23$ , FSH was  $5.49 \pm 1.76$ , TSH was  $3.52 \pm 1.49$  and prolactin was  $18.29 \pm 6.57$ , respectively.

Hormone levels	Mean+-SD
AMH(ng/ml)	$2.72 \pm 1.23$
FSH(IU/ml)	$5.49 \pm 1.76$
TSH(mIU/l)	$3.52 \pm 1.49$
Prolactin(ng/ml)	$18.29 \pm 6.57$

Table 5. fertility management without surgery

Fertility management without surgery	n=75	Percentage
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GnRHa Gonadotrophins	9	12%
GnRHa, Gonadotrophins & IUI	14	18.66%
OID	12	16%
OID & Gonadotrophins	13	17.33%
OID, Gonadotrophins & IUI	2	2.66%
Planned for IVF	25	33.33%

Table 6. fertility management without surgery

Types of surgery	N=75	percentage
Coagulation and adhesiolysis	41	54.66%
Excision of endometrioma	19	25.33%
Aspiration of cyst	5	3.33%
lapraomy	10	6.66%

Table 7. show outcome of fertility treatment.

Only 5.33% patients were successful with live birth and pregnancy positive were 20% of patients bit with complicated msdicarriage.

Outcome of fertility treatment	N=150	percentage
Pregnancy positive	30	20%
Take home baby	8	5.33%
Continuing management	46	30.66%
Waiting for IVF	24	16%
Drop out due to various reasons	42	28%

#### 4. Discussion

Functional endometrial glands and stroma in ectopic sites such as the pelvic peritoneum, ovaries, recto-cervical septum, or pouch of Douglas are characteristics of endometriosis. Endometriosis affects 6–10% of women in their reproductive years. About 25–50% of women who are infertile may have endometriosis. The average age at diagnosis is between 25 and 35. Undiagnosed endometriosis may be present in 50–60% of women who experience persistent pelvic pain or infertility (Giudice IC., 2010). Women with obstructive Müllerian abnormalities are more likely to have it (Burney RO, Giudice IC., 2012). The disease's potential causes include direct transplantation, lymphatic vascular spread, coelomic metaplasia, retrograde menstruation, weakened immunity, and, most recently, a genetic foundation (Moridi I et al., 2017). According to recent data, stem cells produced from bone marrow move to the ectopic and utopic endometrium and develop into endometrial cells. CXCR4 and CXCL-12 are important. They promote tissue development, angiogenesis, and the recruitment of stem cells (Moridi I et al., 2017). In addition to stimulating the growth of the ectopic endometrium, activated macrophages at the site release IL-1, IL-6, IL-8, TNF, Rantes, and VEGF.

First-degree relatives of affected women are 6–8 times more likely to have endometriosis (Bruner-Tran KI, et al., 2013). Endometriosis is exacerbated by changes in estrogen metabolism and synthesis. Chronic inflammation caused by excessive prostaglandin, metalloproteinase, and chemokine production disrupts ovarian, tubal, or endometrial function and leads to disrupted folliculogenesis and implantation failure. Infertility affects 30 to 50% of women with endometriosis. Compared to women without endometriosis, women with minimal and mild endometriosis who receive gonadotropin and IUI had reduced monthly fecundity. The ovarian reserve is adversely affected by endometrioma.

The ovarian reserve is also reduced by surgical treatment. In order to provide therapeutic guidelines, many classification and staging systems have been created. Although it has several drawbacks, the most widely used classification system for managing fertility is the most recent iteration of the American Society of Reproductive Medicine's (ASRM) updated classification system, which is based on surgical findings at laparoscopy or laparotomy (Guzick DS, et al., 2005). In order to comprehend deeply infiltrating lesions, the Enzian classification was created in 2005. A new staging method, known as the endometriosis fertility index (EFI), which combines the parameters that best predict conception without IVF, was proposed in 2009 following an analysis of the surgical and clinical outcomes of 697 patients (Adamson GD, Pasta DJ. 2010). The European Society of Human Reproduction and Embryology (ESHRE) 2021-GDG (Guideline Group) suggests that infertile patients with endometriosis should receive fertility treatment before deciding to have surgery. This should be determined by the following factors: tumor size (>4 cm), presence or lack of pain complaints, patient age and preference, prior surgical history, other causes of infertility, Ovarian reserve as well as EFI score estimate of 10.

The present study included 150 patients from different backgrounds. Most of the patients were >30 years and mean age was 29.64 years & 70.52% had primary infertility. Surgery was the primary treatment for 50% of patients in this series, which is much higher than in other comparable studies. However, a study conducted by a collaborative group in Canada that examined 341 infertile women with mild to minor endometriosis using laparoscopy revealed that the treatment group had a considerably higher pregnancy rate (30.7% vs. 17.7%,  $p=0.006$ ), indicating that surgical therapy improved fecundity. 11. Since our facility is a government-run tertiary care facility, the majority of the patients arrived from all over the

nation at an advanced stage of their illness, exhibiting severe symptoms, a huge endometrioma, or a severe adhesion.

Therefore, these people need surgery to regulate their fertility as well as to relieve their symptoms. The mean serum AMH level was  $2.72 \pm 1.23$ , FSH was  $5.49 \pm 1.76$ , TSH was  $3.52 \pm 1.49$  and prolactin was  $18.29 \pm 6.57$ , respectively.

It's unclear if surgery raises serum FSH or lowers serum AMH. If surgery should be postponed as long as feasible. For patients with a healthy ovarian reserve, letrozole or clomiphene citrate was used to induce ovulation for at least six cycles. If OID did not respond, gonadotropin was then added for three additional cycles. GnRH agonist was utilized prior to ovulation induction for one to three cycles in certain patients with endometrioma  $<4$  cm. 16% of patients had IUI. Therefore, every stage of fertility management in our study was hindered. Three recurring endometrioma patients with extremely low AMH were included. They are awaiting embryo transfer and have their embryos cryopreserved. Therefore, the outcome cannot be presumed. Nonetheless, we have made every effort to provide these individuals with the finest care possible.

Endometriosis-related discomfort, infertility, or both are the two main issues that women with endometriosis face. ESHRE 202110 Recommendations for hormone treatment state that ovarian suppression therapy should not be recommended to increase fertility in endometriosis-affected infertile women. In order to increase future pregnancy rates, postoperative hormone suppression with a GnRh analogue should not be recommended to women who are trying to conceive.

Hormonal therapy should be made available to women who are unable or choose not to become pregnant right after surgery because it does not impair fertility and enhances the immediate results of pain management surgery. 10. According to ESHRE10 recommendations, since it increases the likelihood of continuing pregnancy, surgical laparoscopy may be recommended as a treatment option for endometriosis-associated infertility in rASRM stage I/II endometriosis. Despite the lack of comparison study data, clinicians may think about using operational laparoscopy to treat endometrioma-associated infertility because it may improve the patient's chances of a spontaneous conception. 10. Operative laparoscopy for deep infiltrating endometriosis may be a therapy option for symptomatic people who wish to become pregnant, even if there is no strong evidence that it increases fertility.

## 5. Conclusion

In addition to being linked to a reduced ovarian reserve, endometriosis is also the cause of a decreased ovarian stimulation response. Therefore, obtaining effective reproductive treatment for this patient population is quite difficult. We intend to overcome our treatment challenges and get the best outcome by increasing awareness, detecting patients early, enhancing surgical procedures, and maximizing ART facilities.

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