



## SIG Newsletter

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### SIG Endoscopy



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### Adenomyosis and Infertility: A critical Review

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#### SIG Endoscopy:

Special Interest Group, Endoscopy is a focused and targeted group which is centred towards Endoscopy practices in the Infertile population. Our SIG boasts of a dynamic and motivated team mentored by Dr. (Prof) Kuldeep Jain, Convenor Dr. Parul kotadwala and Co convenors Dr. Desh deepak and Dr. Maansi Jain all of whom share a common passion and love for Endoscopic surgery.

Our aim is to promote and popularize the correct use of Endoscopy amongst the general Gynae practioners with emphasis on fertility enhancing surgery in the Infertile population. Also we aim to sensitize the masses to promote good practice guidelines in Endoscopy. We want to penetrate deep at the grass root level and work towards standardization of the Endoscopy practice in infertility. We aim at a pan India involvement through various online and offline activities in the form of webinars, CMEs and workshop.

Apart from this we look forward to some strong international collaborations with the aim of promoting IFS, SIG Endoscopy on the international platform and getting acknowledgement for the brilliant work that the Indian Endoscopy surgeons are doing.

Also we will start a teaching programme for the young and budding Endoscopy surgeons which will focus on the theoretical and technical aspect of basic and advanced endoscopy skills.

We will work towards encouraging maximum attendance in all our activities.

We will also be focusing on our digital presence as it will spread our message even in the remote areas.

And finally in the process we aim to add more members to our SIG as well as IFS.

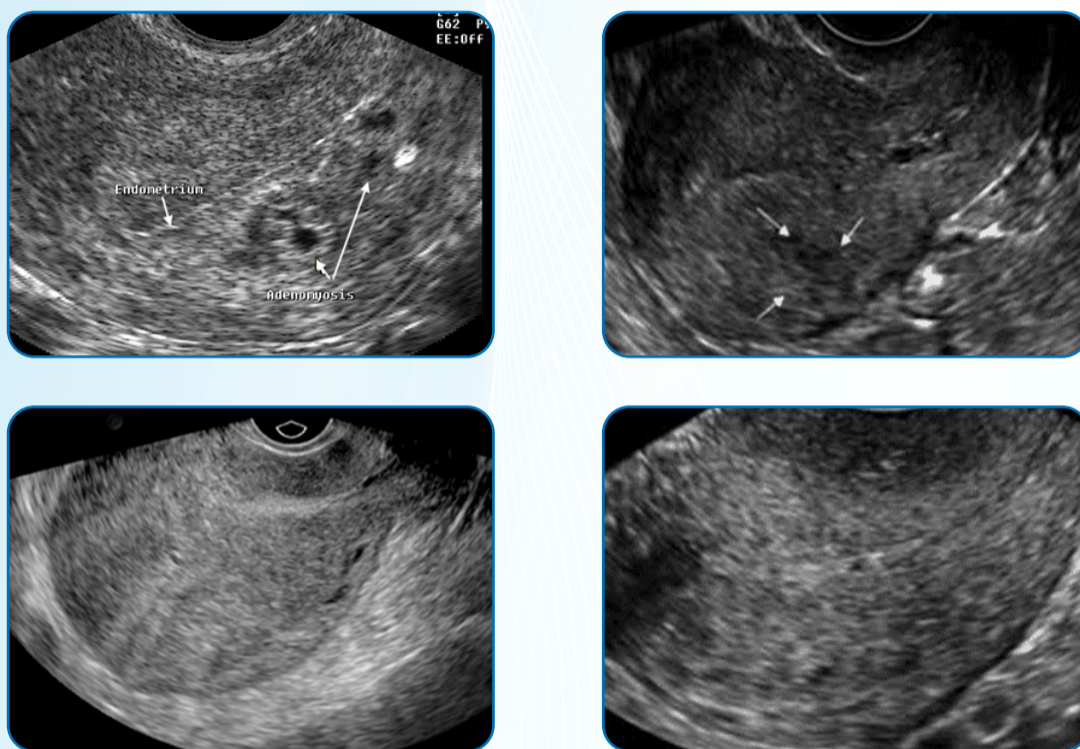
And so we invite anyone who shares a passion and love for Endoscopy surgery to become active members of our SIG.

Adenomyosis is infiltration of the myometrium (2.5 mm below the basal layer of the endometrium) by the endometrium with ensuing reactive myohyperplasia.<sup>[1]</sup> Additionally there is permeation of lymphatic and vascular channels in the myometrium. Literature reports a significant confounding effect of adenomyosis on ART outcomes.<sup>[5]</sup> But it is surrounded by conflicting controversies specially when associated with infertility. The areas of concern are-diagnostic criteria's and modalities, grading the disease, treatment options and the outcomes. This review article is to present data, and studies regarding diagnosing, grading the disease, reviewing the treatment options, and reproductive outcomes in infertile adenomyosis patients. The data would allow for appropriate counselling in these patients and the use of specific protocols in medically assisted reproduction.

### Diagnosis and Classification:

Conventional gold standard diagnostic modality is histopathological examination of hysterectomy specimens. And based on the depth of invasion many classification systems are in vogue. Not only this system lacks uniformity both in staging and diagnosing, there is no correlation of severity with the symptoms.<sup>[3,4]</sup> Also it lacks applicability in the infertile group planning for ART.<sup>[6,8,9,10,11]</sup> A review of some of the classification systems is as under:

**FIG-1: Ultrasound features in adenomyosis**



#### **Bird et al graded, 1972<sup>[8]</sup>**

Grade 1-sub basal lesion  
Grade 2-upto mid myometrium  
Grade 3-beyond mid myometrium

#### **In 2000-Leygur<sup>[6]</sup> graded adenomyosis as**

Superficial < 40%  
Intermediate between 40-80 %  
Deep >> 80% wall involvement

#### **In 2006 Vercellini et<sup>[11]</sup> al classified adenomyosis as**

Mild - one third of wall involvement  
Moderate -two thirds of wall involvement  
Severe -more than two thirds of involmnet

It is imperative that for clinical application the diagnostic modality should be non invasive but have a reasonable sensitivity and specificity. In current ART practice, TVS-USG is highly advocated as the first line of investigation to diagnose and grade adenomyosis with reasonable degree of confidence. Meticulous morphological uter-us sonographic assessment MUSA has been proposed based on grey scale parameters for a standard reporting format .

#### **The diagnosing features are direct features consequent to presence of ectopic endometrium in the myometrium-**

- A. Myometrial cysts
- B. Hyperechoic islands and echogenic subendometrial lines
- C. Buds

#### **Indirect features because of rective myohyperplasia include**

- A. Globular uterus,
- B. Asymmetrical thickening of the uterine walls
- C. Trans-lesional vascularity, and an irregular or interrupted junctional zone (JZ).

So the reporting format should mention

- Presence of normal or abnormal myometrium with signs of adenomyosis, myoma or sarcoma
- Location anterior, posterior, lateral or fundal
- Focal or diffuse or mixed type-focal if >25% of circumference is surrounded by normal myometrium
- Cystic or noncystic
- Uterine layer involvement junctional zone, middle or outer myometrium, serosa
- Extent-mild [<25% involvement], moderate [25-50% involvement] and severe [>50% involvement]
- Size of lesion

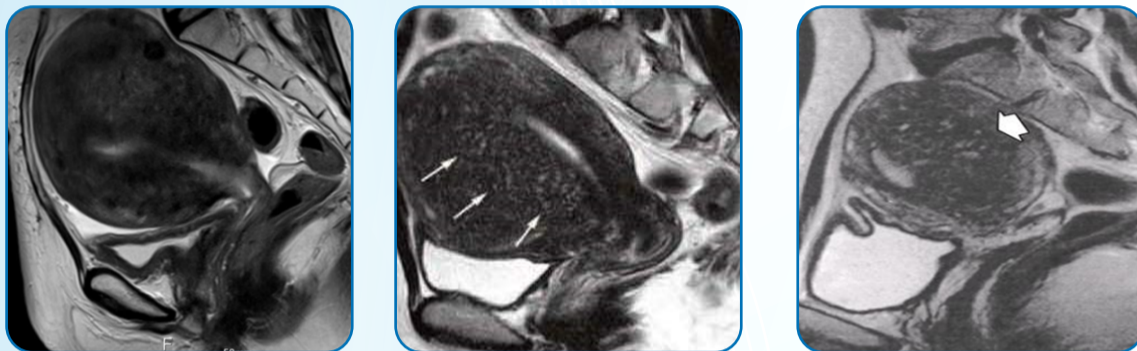
Three-dimensional (3D) TVUS supplements as the coronal view can better characterize the junctional zone with a specificity of 81% and sensitivity of 85%.<sup>[12]</sup> with the imaging features irregular, interrupted junctional zone, a junctional zone thickness > 8 mm, and a significant difference between maximum and minimum thickness measurements of the junctional zone > 4 mm.<sup>[13]</sup> In a recent meta-analysis, 2D two-dimensional TVUS had a sensitivity and specificity of 83.8% and 56.0%, respectively which increased to 88.9% and 63.9%, respectively on 3D scans.<sup>[4]</sup> However the diagnostic accuracy and sensitivity of USG dipped to 33% in the presence of co existing fibroids especially large .

MRI is recommended when USG is inconclusive and/or in the presence of fibroid with a reported sensitivity of 77% and a specificity of 89% which drops to a sensitivity of 67% and a specificity of 82% in the presence of fibroids.<sup>[3]</sup>

### MRI features of Adenomyosis

- Myometrial mass with indistinct margins of primarily low intensity,
- Diffuse or local widening of junctional zones on t2 weighted images,
- Junctional zone thickness >15 mm, I-defined low intensity lesion,
- Ill-defined low intensity lesion,
- Small hypo intense myometrial spots.

**FIG-2**



More non biased studies with classification of adenomyosis, correlation with symptoms, clinical details are required. Over the years, different classification systems have been proposed based on MRI or TVUS findings of adenomyosis in relation to histological and clinical findings of the disease.<sup>[14,15,16,17,18,19,20]</sup>

### Effect of Adenomyosis on Fertility

The effect and mechanism that impairs fecundity and effect on ART in adenomyosis is controversial

Literature review shows evidence of impaired fecundity in adenomyosis , implantation rate, clinical pregnancy rate and live birth rate in ART were all compromised<sup>[21,23,24, 25,26 ,27]</sup>

Corroborating meta-analyses stated an increased risk for miscarriages, 31% in women with adenomyosis vs 14.1% in non-affected women.<sup>[21]</sup> A multicenter prospective study states presence of numerous morphological features of adenomyosis on ultrasound worsens the reproductive outcome. CPR was 42.7% in the absence of adenomyosis but dropped to 22.9% and 13.0% when associated with 4 and 7 ultrasound features of adenomyosis,<sup>[21]</sup> respectively .

Another recent systematic review and meta-analysis revealed that adenomyosis is associated with a significantly lower clinical pregnancy rate (OR 0.69; 95% CI 0.51–0.94) and higher miscarriage (OR 2.17; 95% CI 1.24–3.80) rate after ART.

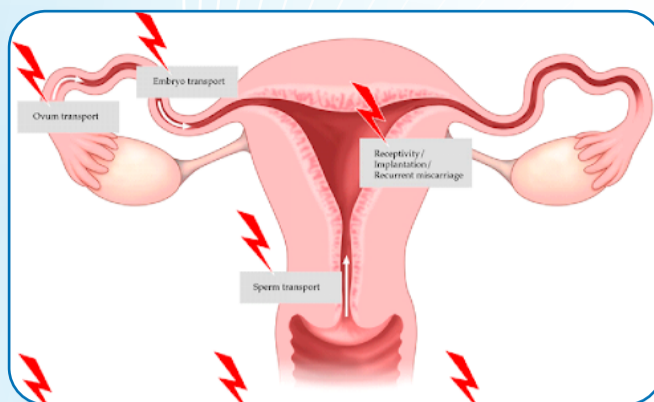
There was no significant difference in the live birth rate (OR 0.58; 95% CI 0.29–1.17) and type of adenomyosis<sup>[24]</sup> (focal or diffuse) did not effect the fecundity. Some studies speculate that focal adenomyosis is more detrimental but more RCTs are needed in this aspect

### Confounding facts

Many studies had associated endometriosis [seen in 6 -22 % of patients], fibroids [35-55%]. Also there was variation in size, type, localization, and severity of the adenomyosis was not accounted. Studies were heterogeneous in terms of age , duration of infertility, coexistence of endometriosis and leiomyoma, protocol of IVF/ICSI, number and stage of transferred embryos, and number of IVF/ICSI cycles. Diagnostic criterias also varied and type and severity of adenomyosis was not quantified mechanism

Adenomyosis disrupts the normal myometrial architecture, junctional zone, anatomical distortion of cavity causing abnormal contractility, negatively affecting implantation. Also disturbed uterine peristalsis and sperm transport, dysfunctional hyperperistalsis of the inner myometrium, increased intrauterine pressure, a disturbance in normal myocyte contractility with a subsequent loss of normal rhythmic contraction, local hyperestrogenism, increased inflammatory markers and oxidative stress, the reduced expression of implantation markers, a lack of expression of adhesion molecules, and altered function of the gene for embryonic development (the HOXA 10 gene) are other postulated explanations.

On the molecular level observed aberrations of P450 (P450arom) and mRNA expression, Leukemia inhibitory factor (LIF) in adenomyosis are other speculated explanations in literature that adenomyosis indeed has a negative impact on fertility.

**Figure 3. Negative impact of adenomyosis on the individual steps of reproduction.**

### Treatment and Reproductive Outcomes

Treatment options (Table 1) are highly dependent upon a woman's age, other fertility factors, and symptomatology. The small number of existing studies with limited sample sizes make it difficult to issue clear recommendations for adenomyosis and the success of reproduction.

The definite treatment in adenomyosis i.e hysterectomy is of no avail in infertile population Also palliative medical treatment - oral contraceptive pills, high-dose progestins, the levonorgestrel-releasing intrauterine device (LNG-IUD), danazol, aromatase inhibitors, selective progesterone receptor modulators, and gonadotropin-releasing hormone agonist (GnRH-a) cannot be used in treatment cycle and delays the treatment and reserved for pain and in patients not planning conception .

Coservative treatment options medical vs surgical in infertile patients needs review based on robust data. There is some data available in favor of medical therapy prior to ART.

GnRH-a treatment with add-back estrogen therapy positive effect on implantation markers with improved implantation rates.

GnRH-a therapy for 2 to 4 months, before frozen embryo transfer significantly improves clinical pregnancy implantation, and ongoing pregnancy rates.

Also speculated improved fecundity in IVF by pre-treatment with the LNG-IUD for 3 months before embryo transfer (41.8% versus 29.5%).

Surgery is not the first line treatment in infertile adenomyotic patients and is usually reserved for recurrent failures and recurrent pregnancy loss . Fertility enhancing surgical treatment of adenomyosis also is associated with controversies with no definitive consensus . Electrocoagulation , adenomyomectomy, with or without myomectomy by laparoscopy, hysteroscopy, or laparotomy is being done currently depending on the case and surgical expertise. Post surgical evaluation requires assessment of degree of removal of lesion and the amount of residual lesion left and the reconstruction of uterus with a view to reduce placenta accrete / percreta . The aim of any surgery should be debulking without leaving a defect in the uterine wall The wound healing and ensuing myometrial integrity result will depend on the extent of excision of the myometrial defect, the reconstruction technique, postoperative infection use of electrodiathermy or cold knife.

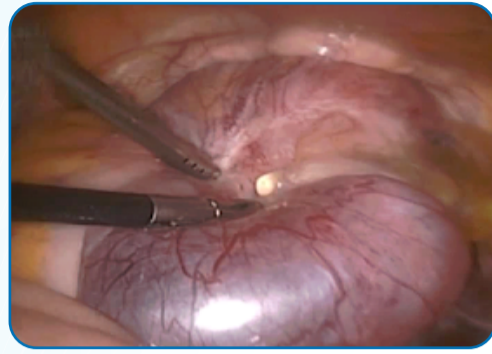
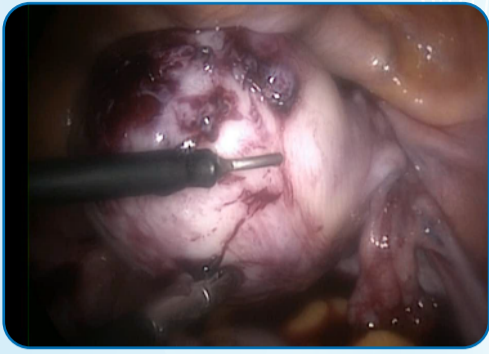
There is no optimum conservative surgical technique for adenomyosis include operative options (open or laparoscopic), surgical techniques (complete or partial adenomyomectomy), and modified surgical techniques (U-shaped suturing, overlapping flaps, the triple-flap method, and transverse H-incisions).

Regarding safety and the future risk of uterine rupture, for 113 women treated by the triple-flap technique, 81.4% had normal blood flow, as demonstrated by Doppler, with a 31.4% pregnancy rate and no cases of uterine rupture.

**Table-1: Treatment options of adenomyosis in infertility patients**

Pharmacological Treatment	Recommendations
Nonsteroidal anti-inflammatory drugs (NSAIDs)	First-line treatment for women with pain
Oral contraceptive	Treatment of pain and menstrual bleeding. No data on the impact on the subsequent fertility improvement.
GnRH analogue	Positive effect on implantation rates.
LNG-IUD	Positive effect on implantation rates.
Progestins, danazol, aromatase inhibitors, selective progesterone receptor modulators	Improvement of symptoms and induction of adenomyosis No clear data on the success of reproduction.
Electrocoagulation of adenomyosis foci	Positive effect on reproduction.
Adenomyomectomy with or without myomectomy	Positive effect on reproduction.

Three case series evaluated the effect of conservative surgery alone in women with adenomyosis. Two studies reported live birth rates (Tadjerouni et al., 1995; Takeuchi et al., 2006) and one reported pregnancy rate (Strizhakov and Davydov, 1995). The conservative surgical techniques described in all studies involve excision of the adenomyotic tissue or adenomyoma and hysteroplasty either laparoscopically or via laparotomy. An overall live birth rate of 36.2% (21 of 58) was achieved following the conservative surgery.



A study analyzing result of conservative surgeries on ART outcome showed a pregnancy rate of 25.0% to 61.5% and the miscarriage rates ranged from 11.1% to 25.0%. In another large study analyzed 2365 infertile women with adenomyosis the postoperative pregnancy rate varied from 17.5% to 72.7%. A review from 2014 concluded that the complete excision of localized adenomyosis in younger women is associated with a 50% delivery rate. Risk of uterine rupture due to pregnancy following conservative surgical treatment for uterine adenomyosis is associated is >1.0% compared to 0.26% in pregnancies following fibroid surgery. Again heterogeneity of studies assessing surgical approach hinders any definitive conclusion

### **Conservative Surgery with GnRH Agonist/Danazol**

Eight studies evaluating conservative surgery with or without GnRH agonist were analysed. Four of these were case series, and four were case reports. The pooled live birth rate after this mode of treatment was 88.2% (15 of 17). Six of these studies used GnRH agonist post-operatively and the other two used danazol. Considerable heterogeneity in the type of GnRH agonist, the duration and timing of use as well as the mode of diagnosis of adenomyosis before treatment was offered.

### **Surgery along with GnRH A vs GnRH Alone**

Only one retrospective study by Wang et al., 2009 comparing conservative surgery with GnRH agonist versus GnRH agonist alone (A total of 28 women with adenomyosis underwent conservative adenomyomectomy with or without post-operative Leuprolide every 4 weeks for 24 weeks, while 37 patients only received Leuprolide every 4 weeks for 24 weeks. The comparative live birth rates following conservative surgery with GnRH versus GnRH agonist alone were 32.14 versus 8%, respectively. The odds of having a live birth with conservative surgery ± agonist was 3.91 (95% CI, 1.06, 14.43) compared with that with GnRH agonist alone.

### **Conclusion**

The current literature on adenomyosis, infertility, and reproductive outcomes has conflicting reports, controversies and limitations. Most studies show a negative affect of adenomyosis on fecundity in in vitro fertilization, low pregnancy and live birth rate with an increased risk of miscarriage. There is a need for standard diagnostic criteria, uniform classification system. Despite variations TVS USG possibly supplemented by 3D is the primary investigation, MRI to be used when associated with myomas or in doubt. Most studies corroborate negative reproductive outcome in ART with altered receptivity and expression of adhesion molecules conducive for implantation postulated mechanism. GnRH-a pre-treatment has shown improved implantation rates. Role of conservative surgeries in infertile women with adenomyosis is controversial at present, as only small serial studies have shown improved reproductive outcomes. Minimally invasive procedures and ablation techniques or uterine artery embolization show no clear evidence for their role on fertility outcomes. Establishing an optimum conservative surgical technique for adenomyosis is difficult, and several operative options and surgical techniques have been proposed. The surgical treatment of adenomyosis-related infertility remains a highly controversial issue regarding the impact of surgery on reproductive outcomes. More well designed RCTs are needed to provide strong data on the accuracy, uniformity of diagnostic methods, the pathophysiology and prevalence of adenomyosis, fertility outcomes and the recommended treatment options. This will help formulate good practice guidelines for recommendations in adenomyosis.

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