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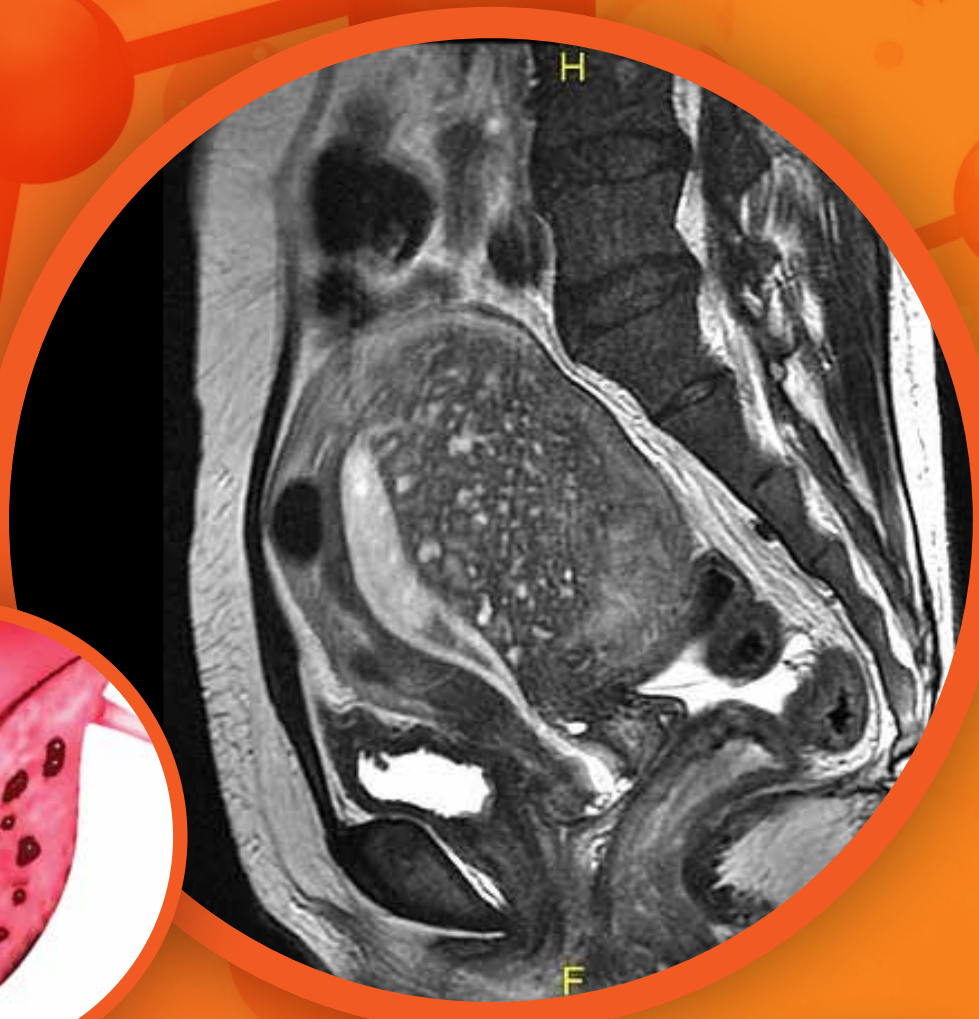
Adenomyosis



Editor :
Prof (Dr) Pankaj Talwar

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ARText

Adenomyosis

DR SOHANI VERMA

PRESIDENT-IFS

It is my great privilege and pleasure to write this message for ArText – 4 of IFS.

I also sincerely thank Cadila Healthcare for participating in this academic activity of IFS.

Knowledge sharing has forever been the motto of Indian Fertility Society. We have always believed in spreading awareness about the common issues in ART and have made constant and endeavours in doing so the past decade. Our latest collaboration with Cadila Healthcare is an initiative in the similar direction. We intend to cover common day to day challenges in the field of clinical ART and thus bring out this E bulletin named ARTexT at regular intervals. The aim would be to simplify the complex issues in clinical ART and present before you in a concise manner.

I am sure that you would appreciate and learn from this academic initiative of publication wing of IFS and will be able to apply the take home messages in your busy daily clinical practice.

In this issue we would be covering a common enigma- adenomyosis in detail and discuss the issues as we face them everyday, while dealing with this disease

DR. K. D. NAYAR

SECRETARY GENERAL IFS

It is always been a matter of great privilege and pride to write this message for the e bulletin of IFS named ARTexT. We believe in spreading awareness about the common issues in ART and try to gather and present the evidence that will undoubtedly help both the clinician and the patient. We intend to cover common day to day challenges in ART practice and probably the most confusing for the clinician is Adenomyosis as no proper guidelines for management given by the standard bodies.

In this bulletin we would learn about the dilemmas of the disease and the common method of dealing with this with the issue.

I am sure you would enjoy reading the bulletin. Indian Fertility society feels proud and congratulates the editors for this bulletin.

I wish the editorial team best of luck for this endeavour.

Prof (Dr) Pankaj Talwar

Joint Secretary-IFS

Editor ARText

At the very onset, the editorial team would like to thank all of you for reading this E-bulletin of ARTexT.

Till date we have published bulletins on hydrosalphinx, endometriosis and poor ovarian reserve.

All have been appreciated by you and that has been our strength.

The bulletins have been named ARTexT - which mean amalgamating different clinical conditions in ART and Reviewing the Text.

Our present edition is focused on simplifying adenomyosis and covers all essential details with nice algorithms.

I am sure it will immensely benefit you all.

We have tried to summarize all the literature available to enhance our understanding of the paradoxes associated with adenomyosis in this bulletin.

Future research and RCTs are needed to enhance our knowledge in managing Adenomyosis.

Feel free to communicate with us at any point of time and contribute critically.

We would also like to place on record our truthful thanks to Cadila health care limited that are helping us in the publication of this bulletin and off course I promise that there is no conflict of interest at any level.

Wish you happy reading and yes don't forget to file this issue.

I would formally like to thank my friend Dr. Rupali from Neelkanth Hospital, Gurgoan who has worked around the clock towards bringing out this issue from conception to end.

Jaihind

Dr Rupali Bassi Goyal

(DNB, Dip in USG, MNAMS)

Subeditor

Adenomyosis is a perplexing disease for the treating gynaecologist, especially when associated with infertility. Adenomyosis and endometriosis are two conditions of similar pathology but varied presentations. Adenomyosis is very pertinent issue which becomes an enigma in routine clinical practice.

Till date there are no separate guidelines for the management of adenomyosis per se. Due to lack of standard treatment guidelines it exasperates the treating physician. In patients with infertility the management of this condition becomes a big hurdle.

This is a comprehensive write up on this highly understated topic. We have tried to discuss all facets, from the basic pathology to the final management in the text. Hope you enjoy reading and get a better understanding in the topic.

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Part -1

PART - 1

Introduction

Adenomyosis, as very aptly described by **Owolabi** etal as "the addendum to textbook chapters on ectopic endometrium; it is the forgotten process and a neglected diagnosis". Since the very inception of this pathological condition it has been the most perplexing disorder for the treating gynaecologist. Lack of substantial evidence in literature and standard treatment guidelines makes it a crucial topic of discussion.

(Owolabi etal1977)

Definition

Adenomyosis is defined as the presence of heterotopic endometrial glands and stroma within the myometrium of the uterus this is usually accompanied by a myometrial hyperplasia and infiltration of inflammatory cells of the surrounding myometrium.

Historical background

The historical background of the current day adenomyosis underwent a lot of interesting turns before the current understanding of this pathological process came into being.

The origin of the condition dates back to the late 17th and the 18th century in Europe. In the beginning for as long as 90 years adenomyosis and endometriosis (except the ovarian endometrioma) were considered as 'adenomyoma'. In the year 1860 that the term **'cystosarcoma adenoids uterinum'** was coined by the German pathologist **Carl Von Rokitansky**, who discovered the presence of endometrial glands in myometrium.

Inspite of a few controversies, the first description of the current day adenomyosis was by **Thomas Stephan Cullen** in the year 1896. He was a gynaecologist so he further classified the adenomyoma in three different types –

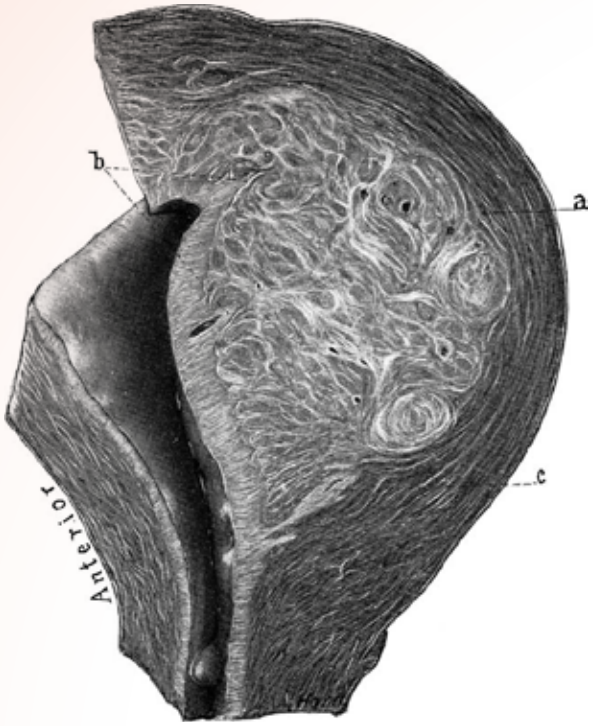
- Adenomyomata in which the uterus preserves a relatively normal contour
- Subperitoneal or intraligamentary adenomyomata
- Submucous adenomyomata.

Cullen also reported that the treatment for this condition would be doing a hysterectomy rather than going for a myoma removal, as this condition is very diffuse.

In the year **1903 Mayer** described in detail a scenario similar to current day secondary endometriosis. His theory of 'epithelial hypertrophy' was suggested as a reason for the 'epithelial invasion of inflammatory cells' leading to adenomyoma

By the year 1920, the endometrial origin of adenomyosis was established. **Frankl** in the year 1925 used the term Adenomyosis uteri, to clearly distinguished adenomyoma an adenomyosis 'In an adenomyoma the glands originate independently within the myoma as an autochthonous growth, while in adenomyosis, even when localized, the direct connection of the endometrium with the islands of mucosa located in the musculature can be established in serial sections. In the majority of cases of genuine adenomyoma, which are extremely rare, the glands are not accompanied by stroma.

It was in the year 1972, that **Bird** stated that: '**Adenomyosis may be defined** as the benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic non-neoplastic, endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium'.



Posterior wall Adenomyoma (Cullen,1908 Philadelphia & London: W.B. Saunders)

(Benagiano G etal 2012; Horng H etal 2014; Benagiano etal 2006; Rokitansky K. 1860; Cullen TS. 1896; Kelly HA & Cullen TS etal 1909; Cullen TS. 1908; Mayer R etal 1903; Frankl Oetal 1925; Bird CC etal 1972)

Prevalence & Incidence

Due to the lack of standard diagnostic criteria, the actual incidence of adenomyosis is not known. In the earlier years, this condition was a diagnosed only post operatively, however with the advent of newer imaging techniques adenomyosis the diagnosis has become more simplified and definitive.

In a prospective study using transvaginal ultrasound, at a gynaecology clinic London, the incidence of adenomyosis in the infertile population was 20.9% (95% CI: 18.5 -23.6%)] women.

(J Naftalin etal 2012)

In one of the largest cross sectional study done at Spain, the prevalence of adenomyosis was 24.4 % amongst the patients undergoing ART. This was comparable to the prevalence in the usual symptomatic population.

(Puente MJ etal 2016)

Amongst the cases of abnormal uterine bleeding in the perimenopausal age group, 44.56% of the patients had adenomyosis on histopathology.

(Exacoustos et al 2011)

Pathogenesis

In adenomyosis endometrial glands and stroma are present within the musculature of the uterus. Various theories hypothesized, as to the possible etiopathogenesis of adenomyosis.

- Direct invasion of the endometrium into the myometrium.

Invagination of the Endometrial basalis

- Invagination due to Myometrial weakness
- Invagination due to Altered Immunological activity
- Embryologic misplaced pleuripotent Mullerian remnants.
- Adenomyotic tissue exhibits higher expression of estradiol receptors and this increased response to estrogen may enhance the invagination and growth of endometriotic tissue into the myometrium.
- Invagination of the basalis endometrium into the myometrium may be due to altered immunological activity at the endometrial-myometrial
- It has been shown that macrophage activated T and B cells produce antibodies and stimulate cytokines that alter the junction zone of the junction zone of the endomyometrium.
- Invagination of the basalis along the intramyometrial lymphatic system

Role of Hormones

Increased Prolactin levels promote myometrial cell degeneration and invasion of endometrial stroma into the myometrium and progression to adenomyosis.

It has been shown in animal models that FSH receptor deficiency was associated with abnormal uterine vascularity and subsequently adenomyosis.

Progesterone plays an important role in regulating the function and receptivity of the endometrial lining throughout the menstrual cycle. In women who have progesterone resistance their endometrium demonstrates an impaired decidualization response, and therefore they are unable to establish and maintain a successful pregnancy.

(J Naftalin etal 2012; Devlieger R etal 2003; F A Taran etal 2013; Ghazala Rizvi etal 2013; Ferenczy A etal1998; Ostrzenski A etal 1998;Ota H 1998, Azziz R etal 1989)

Structural and molecular level changes

It has been observed that the metabolic and molecular abnormalities observed in adenomyosis and endometriosis is similar.

The primary changes are

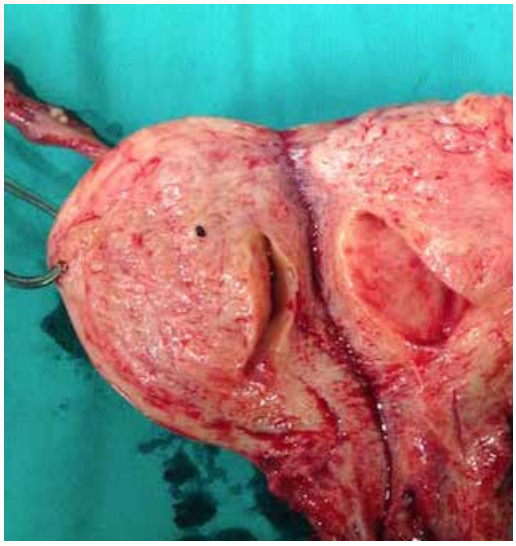
- Increase angiogenesis and proliferation - increased vascular endothelial growth factor (VEGF)
- Decrease apoptosis allow local production of oestrogen
- Progesterone resistance
- Impair cytokine production
- Several possible markers of endometriosis have been identified : **Gagne´ et al.** (2003) found an altered proportion of CD3+, CD16 +, CD32HLADR2, CD32CD45RA2, CD3+CD162, CD3+CD562, CD562CD16+ and CD16b+ leukocytes in the endometrium of women with endometriosis, and utilised this in a predictive model to identify women with a high likelihood of suffering with the condition.
- Oxidative stress and free radical metabolism are responsible for altering endometrial receptivity leading to infertility.
- Steroids and epigenetic factors
- It has been observed that there is an increased local oestrogen production in both endometriosis and adenomyosis. Increased P450 aromatase RNA was reported in Ectopic endometrium and Eutopic endometrium, but not in endometrial samples from women with cervical pathology, which were used as control.

(Campo S 2012; Benagiano G 2014)

Morphological features

This forms the final reference standard or gold standard for the diagnosis of Adenomyosis.

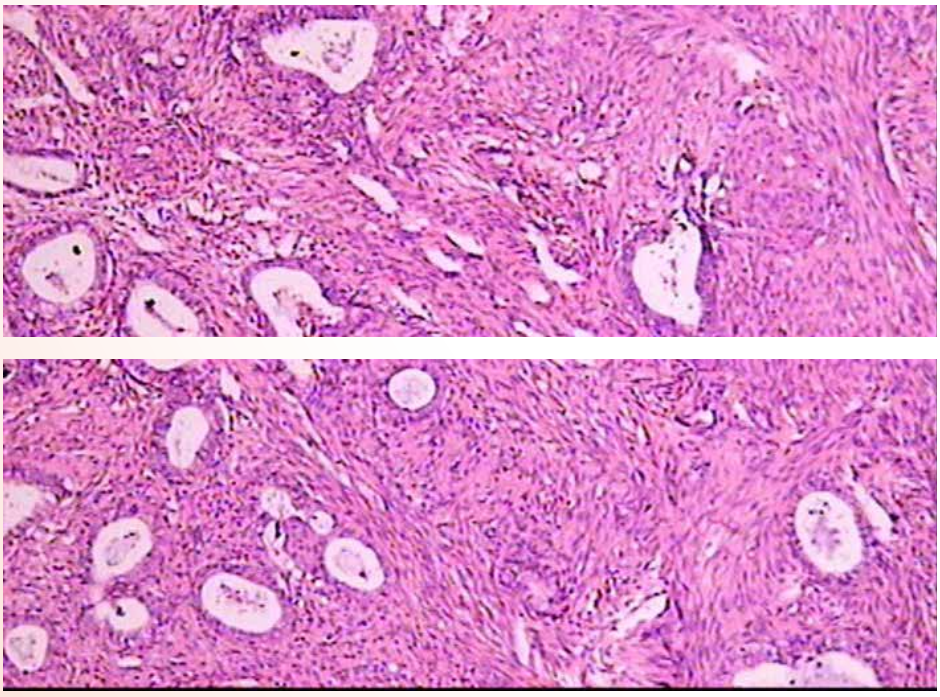
Gross - Pinpoint/small cystic areas of haemorrhage seen within the myometrium with hyperplastic myometrium.



Appearance of the adenomyoma on the anterior myometrium

(Grimbizis FG. 2014)

Microscopic - The main diagnostic features are the presence of ectopic endometrial glands and stroma in the myometrium. The criteria used for confirmation of adenomyosis in some studies was distance between the lower border of endometrium and the affected myometrial area of more than one half of a low power field, whereas others thought that adenomyosis could only be diagnosed when endometrial glands and stroma lay deeper than 2.5 mm below the endometrial surface on a low power field.



Endometrial glands between smooth muscle bundles (H& E stain 50X)

Classification

Various authors have designed different classifications.

Levgur et al devised a grading system to describe the depth of adenomyotic foci such as deep (greater than 80%), intermediate (40-80%), and superficial (less than 40%).

Surgical/histological classification of adenomyosis

Diffuse adenomyosis

- Smooth muscle hyperplasia with ectopic endometrium (junctional zone)
- Micro-dilated ectopic endometrial glands throughout hyperplastic myometrium

Focal adenomyosis

- Adenomyomas
- Cystic adult adenomyosis
- Juvenile cystic adenomyosis

Polypoid adenomyosis

- Typical polypoid adenomyomas
- Atypical polypoid adenomyomas

Special categories

- Adenomyomas of endocervical type
- Retroperitoneal adenomyosis or rectovaginal endometriosis

Ken Tamai from Japan classified Adenomyosis in three categories, based on the Magnetic resonance imaging (MRI) features.

Adenomyoma

One of the most common presentations of this pathological process is a well-circumscribed and localized form, known as adenomyoma. The presentation of this condition is most similar to that of a leyiomyoma. The clinical as well as the imaging pattern is usually similar. The main advantage of this form is that it is amenable to surgical resection.

Adenomyomatous polyp (polypoid adenomyoma)

This form usually presents as a pedunculated or sessile polypoid mass in the lower uterine endometrium or endocervix. It usually occurs in the premenopausal women, with presentation of as abnormal genital bleeding.

Adenomyotic cyst (cystic adenomyosis)

This variant is characterized by the presence of a large haemorrhagic cyst resulting from extensive menstrual bleeding in the ectopic endometrial gland. The lesion can be entirely within the myometrial, submucosal or subserosal tissue. This usually presents as a bulge into the cavity, with or without areas of abnormal vascularisation or fibrosis in the endometrium overlying the cyst.

Histologically, endometrial tissues are observed along the cyst wall composed of myometrial fibres. The differential diagnosis is cystic leiomyoma or myoma with cystic degeneration.

(Levgur M etal 2000; Grimbizis etal 2014; Tamai K etal 2005)

Risk factors

Various studies have shown that the prevalence of adenomyosis was significantly associated with women's age, gravidity and pelvic endometriosis **(P, 0.001).**

- Age
- Increasing parity- multiparous patients. This may be due to the elevated levels of estrogen as described above or secondary to trophoblast invasion into the myometrium at implantation
- Early menarche (≤10 years of age)
- Short menstrual cycles (≤24 days in length)
- Elevated BMI (>24.9)
- Smoking - A history of smoking was associated with a decreased risk (OR 0.7).the postulated mechanism was that cigarette smoking alters hormonal metabolism, leading to a reduced incidence of endometrial abnormalities.
- Previous uterine surgery was suggested for the theory of endometrial trauma as a cause of adenomyosis
- Concomitant Leiyomyoma
- Concomitant Endometriosis
- Previous pregnancy termination (≥1) – consistent with the theory of uterine trauma as a cause of adenomysosis
- Previous caesarean section was more often associated with adenomyosis as compared to a history of previous normal vaginal delivery.
- Tamoxifen therapy - Tamoxifen binds to selective estrogen receptors and can stimulate both normal and ectopic endometrial tissue fostering the development of adenomyosis.

Clinical Manifestations

Symptoms

- Age group- 40 and 50
- Abnormal uterine bleeding (65% of patients)
- Heavy menstrual bleeding (40-60%)

  This is due to secondary to the increased endometrial surface of the enlarged uterus.

  There is an increased vascularisation of the endometrial lining in these patients leading to menorrhagia.

  Improper uterine contractions during menses

  Overproduction of prostaglandins and estrogen.
- Intermenstrual bleeding in cases of an adenomyotic polyp

Dysmenorrhoea and Dyspareunia

It occurs in 15-30% of patients presenting with adenomyosis. The extent of pain is usually associated with both the amount of adenomyotic foci and the depth of invasion. It has been observed that women with adenomyosis and leiomyomas reported more dysmenorrhoea and had an increased risk of dyspareunia and pelvic pain compared to women with leiomyomas alone.

The various mechanisms postulated for dysmenorrhoea are

- Secondary to the increased prostaglandin and eicoisanoid production in adenomyotic tissue.
- **Vasopressin** and **oxytocin** are the most important factors regulating uterine contractions. Vasopressin-1α receptor **(VP1αR)** expression is associated with dysmenorrhoea in adenomyosis, and the in uterine smooth muscle cells is positively correlated with the amplitude of uterine contraction.
- There is an overexpression of oxytocin transmemberane receptor (OTR) in myometrial cells surrounding the stromal cells during adenomyosis.
- The pathophysiology of dysmenorrhoea in adenomyosis occurs via nerve secretory factors, inflammatory factors, PGF2a, and other factors.
- **Nuclear factor (NF)-kB** is a pivotal proinflammatory transcription factor and can be activated by various proinflammatory agents, growth factors, and oxidative stress; nearly all of which are involved in adenomyosis and endometriosis.
- Altered imunoreactivity is also one of the factors leading to dysmenorrhoea. It has been observed that the expression to **secretory glycoprotiens (SLIT) / roundabout (ROBO)** is significantly higher in the ectopic endometrium as compared to eutopic endometrium.

(Taran FA etal 2010; Li B etal 2013; Nie J etal 2011)

Infertility

Vercellini etal did a meta-analysis and found that there was a 28% (95% CI, 5-45%) reduction in the likelihood of clinical pregnancy in infertile women with adenomyosis who underwent IVF/ICSI with autologous oocytes.

There are multiple factors responsible for the decreased pregnancy amongst these patients. Histologically, it has been observed that there is effect, including the chronic inflammatory condition caused by infiltration of endometrial glands in the myometrium and the increased local estrogen production due to aromatase P450.

Few authors have hypothesized a detrimental impact mediated by perturbed uterine peristalsis and reduced endometrial receptivity indicated by the presence of implantation marker defects. However some authors have also reported that there is no statistically significant difference in implantation and pregnancy rates between women with or without adenomyosis diagnosed at TVS.

(VercelliniP etal 2014; Tremellen KP 2012; Martı´nez-Conejero JA etal 2011)

Early pregnancy Losses

Adenomyosis was also associated with a more than doubled risk of miscarriage, thus suggesting a causal relation. The 95% confidence interval for the increase in risk among women with characteristics comparable to the study population is between 20 and 25%.

Pressure symptoms

Enlarging uterus causes a pressure on the surrounding structures. The commonest symptom due to the enlarging uterus is increased frequency of urination. Others symptoms of constipation and pedal edema are also seen in cases of big uteri.

Signs

The main demonstrable clinical feature is uterine enlargement. There is a diffuse uterine enlargement presenting as a globular uterus which is usually globally enlarged. Uterus does not exceed 12 weeks in size. The probable mechanism is proliferation of the ectopic endometrial tissue, which causes smooth muscle cell hyperplasia and hypertrophy. Some women may have a tender uterus on physical examination.

Adenomyosis can also be present in the endometrial cavity as a polypoidal mass or it can form adenomyomas which are focal areas of circumscribed nodular aggregates of smooth muscle.

Diagnostic Modalities

The two primary modalities of diagnosis are the Imaging and Histopathological analysis. In the current era the former is the preferred one as it is non invasive, whereas the latter is more definitive for diagnosing a patient with adenomyosis.

Imaging

Ultrasound

This is the primary modality used for diagnosing adenomyosis in cases of clinical suspicion.

Two-dimensional Transvaginal Ultrasound (2-D TVUS)

USG parameters used define adenomyosis are

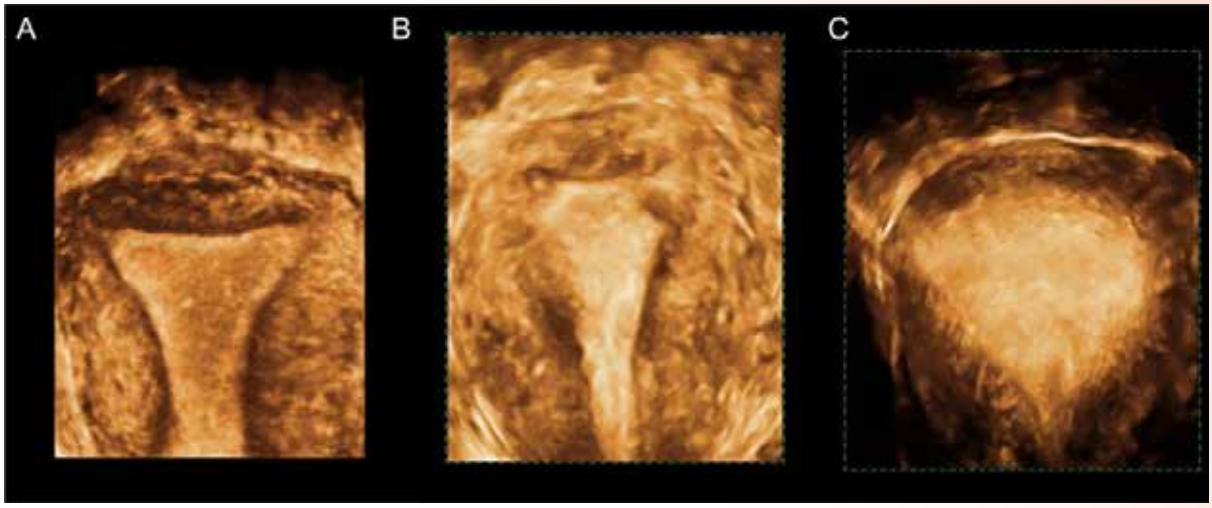
- The most common heterogeneous myometrial echotexture.
- Globular asymmetrically enlarged uterus, usually with a uterine length of not more than 12cms.
- In the Myometrium there is presence of irregular cystic spaces. Myometrial linear striations poor definition of endometrial myometrial junction which also gives the appearance of pseudowidening of the endometrium.
- There is asymmetry of anterior posterior myometrium, which is observed as thickening of anterior and posterior myometrial wall and increased or decreased echogenecity.
- Furthermore, a diffuse spread of small vessels within the myometrium has also been described as a diagnostic feature of adenomyosis
- An adenomyoma is a focal circumscribed nodular collection of ectopic endometrium commonly identified on the posterior uterine wall.
- **Exacoustos et al** found that a 2-D TVUS volume measurement [cm^3], calculated by the ellipsoid formula (uterine longitudinal diameter x transverse diameter x anteroposterior diameter x 0.532), was higher for women without adenomyosis than those with adenomyosis confirmed at histology.
- Myometrial cysts will be observed in 50% of patients. Cysts are dilated glands or hemorrhagic foci in the heterotopic endometrium. These are usually less than 5mm in diameter.
- Cystic adenomyosis, these can be larger (greater than 5mm in diameter).These can appear as echogenic nodules on ultrasound due to the haemorrhagic content.

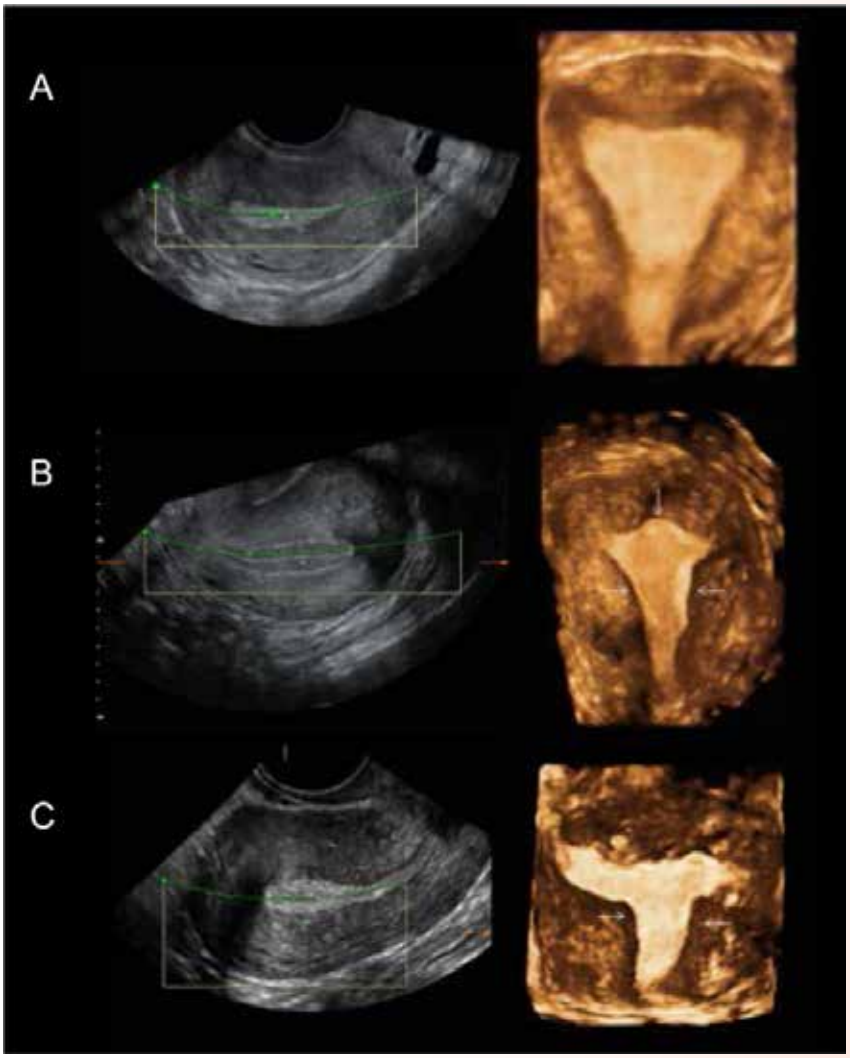
Three-dimensional Transvaginal Ultrasound (3D-TVUS)

3D-TVUS helps us to visualize the junctional zone more clearly compared to 2D-TVUS.

On the coronal view the junctional zone can be identified as a hypoechoic area around the endometrium, an ill-defined junctional zone, and a distortion or infiltration of the hypoechoic inner myometrium.

(Exacoustos C etal 2011)



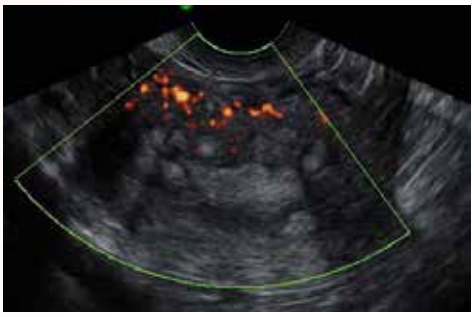


3D USG reconstruction of Junctional zone, thickened, irregular JZ

Colour Doppler studies

Usage of colour Doppler studies helps us to improve the diagnostic accuracy of Ultrasound findings. Presence of intramyometrial cysts, or anechoic areas with myometrial thickness of ≥1 mm and negative for colour

Doppler (power Doppler or high-definition Doppler) were diagnostic of adenomyosis. Overall there is an increased vascularity in the stroma of the myometrium.



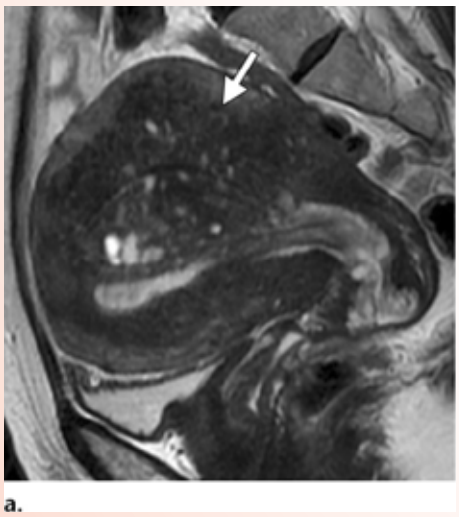
Increased vascularity on Colour flows

Magnetic Resonance Imaging (MRI)

MRI is an excellent diagnostic tool, for management of adenomyosis, although the main drawback with it is the relative cost of the procedure. The main criteria for the definition of adenomyosis on MRI are

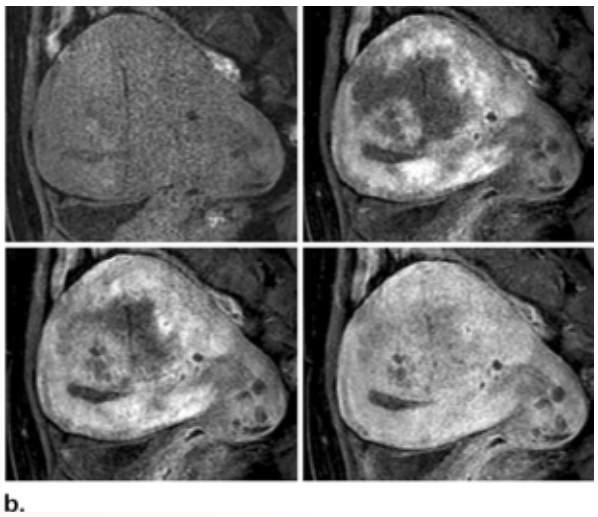
- Enlarged uterus with presence of a distinct or an ill defined myometrial mass with indistinct margins of primarily low intensity.
- Diffuse or local widening of junctional zones on T2 weighted image.
- Increased junctional zone thickness of more than equal to 0.15 mm, this could be localized or diffuse.
- **Champaneria et al** did a systematic review to compare the diagnostic accuracy of MRI and ultrasound. They included 23 articles, involving 2,312 women and found that TVUS had a pooled sensitivity of 72%, specificity of 81%, positive likelihood ratio of 3.7 and negative likelihood ratio of 0.3. MRI had a pooled sensitivity of 77%, specificity of 89%, positive likelihood ratio of 6.5, and negative likelihood ratio of 0.2. They concluded that both TVUS and MRI had high levels of accuracy in diagnosing adenomyosis.

(Champaneria R etal 2010)



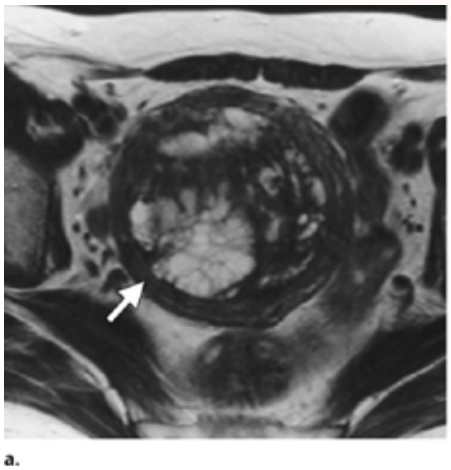
a.

Enlarged uterus with an ill-defined low-signal intensity lesion in the posterior myometrium.



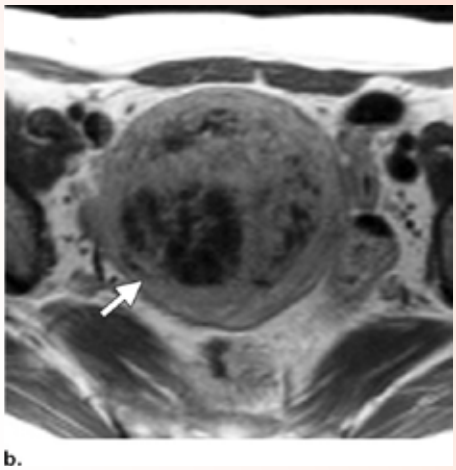
b.

Unenhanced heterogeneous and gradual enhancement of the lesion.



a.

Adenomyomatous polyp



b.

(b) enhancement of the fibrous-muscular components

(Takeuchi M etal 2011.)

Histological features

This forms the final reference standard or gold standard for the diagnosis of Adenomyosis. The features on gross and microscopic examination have been discussed above.

Treatment modalities

The main treatment can be divided into

1. Medical management

- Non Hormonal therapy
  - Analgesics and Anti inflammatory agents
  - Anti angiogenic drugs
- Hormonal therapy
  - Oral contraceptives
  - Danazol - oral and intrauterine system
  - Levonorgesterol Intrauterine System LNG - IUS
  - Gonadotropin Releasing hormone agonists
  - Estrogen Receptor inhibitors
  - Selective estrogen receptor modulators SERMS
  - Selective Progesterone receptor modulators SPRMS
  - Progestins and progestational agents
  - Antiprogestins
  - Aromatase inhibitors

2. Surgical management

- Minimal surgical intervention
- Radical Procedures
  - Hysterectomy

Medical Management

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Women with dysmenorrhoea have elevated levels of prostaglandins, which can result in painful cramps. Women may experience symptom improvement by taking non-steroidal anti-inflammatory drugs, which inhibit cyclooxygenase, the enzyme involved in the production of prostaglandins. Although not devoid of potential adverse effects NSAIDS form the first line of management dysmenorrhoea.

Anti angiogenic agents

Neovascularization forms an integral part in the pathogenesis of adenomyosis. Although an emerging concept various drugs like growth factor inhibitors, endogenous angiogenesis inhibitors, fumagillin analogues, statins, cyclo-oxygenase-2 inhibitors, phytochemical compounds, immunomodulators, dopamine agonists, peroxisome proliferator-activated receptor agonists have been used in adenomyosis and endometriosis patients. These drugs have still been used in experimental settings and are a great potential for further research.

Hormonal Therapy

Oral Contraceptive Pills

Patients may show symptomatic improvement of dysmenorrhoea and heavy menstrual bleeding when taking oral contraception continuously or cyclically. They can be used by Enteral or parenteral routes – Oral / intravaginal / transdermal patches/ implants or intramuscular depot injects.

The main mechanism is prevention of ovulation and thereby the hormonal action. However, these medications help improve symptoms by inducing amenorrhea and for a short period of time may also induce regression of adenomyosis, however randomized control trials are lacking.

Danazol

Danazol can be given by Routes – Oral and Danazol loaded intracervical injections and intrauterine devices. Danazol acts by suppressing pituitary release of FSH and LH,therefore causes atrophy of both normal and ectopic endometrial tissue. Systemic treatment with Danazol has been shown to decrease expression of aromatase cytochrome P450 in disease eutopic endometrium; this may contribute to improvement of symptoms and reduced uterine size.

Oral - However, it is not well tolerated by many patients because of its side effect profile which can include acne, depression, deepening of the voice, hirsutism, hot flashes, decreased high-density lipoprotein levels, increased liver enzyme concentrations, oily skin, muscle cramps, reduced breast size, and weight gain.

Intrauterine injections and device - Novel ways of treating adenomyosis with danazol are being studied such as intracervical injections and with Intrauterine Devices (IUDs). These methods allow local delivery of hormones in an attempt to minimize systemic side effects.

There have been various studies where patients have received cervical Danazol suspension injections and reported that all women had subjective improvement of symptoms by the 24th week. It was observed that the danazol IUD/ and injections did not cause any of the side effects typically observed with oral therapy. There was a significant symptomatic relief and an immediate return of the fertility after withdrawing the administration of Danazol.

(Ishihara H etal 2003; Shawki OA. 2002)

Selective estrogen receptor modulators

Selective estrogen receptor modulators example Tamoxifen, Raloxifene etc may be preferred agents in management of Adenomyosis due to their differential ER expression in a given target tissue. This results in differential expression and binding to the ER coregulator proteins. Ideal Selective estrogen receptor modulators (SERM) should have an antagonist estrogenic activity on endometrium with an agonist activity in the bone and serum.

(Pinkerton JV etal2014: Chen Y J etal 2001)

Selective progesterone receptor modulators

It has been observed that the adenomyotic lesions produce significant quantities of progesterone, although they contain strikingly lower levels of progesterone receptor (PR) with endometrium.

It has been observed that **Selective progesterone receptor modulators (SPRMs)** interact with the PR, allowing the binding of antiprogestins with mixed agonist and antagonist properties, thereby reducing adenomyosis associated pelvic pain.

In 2016 conducted in Italy on patients with adenomyosis and fibroids, who took three months of **Uliprestal acetate** observed a significant improvement in bleeding but worsening of the pain symptoms, following administration for a period of 3 months.

(S. Ferrero etal 2016)

Progestins

The main mechanism by which progestational agents act is causing atrophy and decidualization of the endometrium. The most commonly used progestational agents are Medroxyprogesterone acetate and Norethisterone are more commonly used in cases of adenomyosis. Studies have shown significant symptomatic benefit in term of pain and bleeding, with the use of these agents.

Dienogest

Dienogest is a progestational 19-norsteroid derivative and a synthetic oral progestin with highly selective binding to progesterone receptors. It exerts antiovulatory and mild hypoestrogenic effects, as well as antiproliferative activity on endometrial cells.

Dienogest is used as a treatment for painful symptoms in patients with endometriosis, without causing any severe hypoestrogenic adverse effects. It is also expected to be an effective treatment for painful symptoms associated with adenomyosis.

A randomized, double-blind, multicenter, placebo-controlled phase III study of Dienogest in patients of adenomyosis was conducted at Japan. The efficacy and safety profile of the drug in symptomatic adenomyosis patients was analysed. The results suggest that this drug is effective and well tolerated in the treatment for painful symptoms associated with adenomyosis not complicated by severe uterine enlargement or severe anaemia.

(Osuga Y etal 2017)

Antiprogestins (Gestrinone)

Anti progestational drugs, like Gestrinone (ethylnorgestrienone) have been used for treatment of adenomyosis. The mechanism of action includes a progestational withdrawal effect at the endometrial cellular level and inhibition of ovarian steroidogenesis.

Gonadotropin releasing hormone Agonists

Gonadotropin releasing hormone Agonists (GnRH agonists) cause a suppression of pituitary gonadotropins and thus induce ovarian quiescence, resulting in a medical menopausal, hypoestrogenic state thereby reducing the manifestations of adenomyosis.

Mode of action : Subcutaneous injections or Intranasal spray.

Effect : Studies have shown that patient's symptoms of heavy menstrual bleeding and dysmenorrhoea completely resolved and her uterine volume decreased.

Side Effects : such as hot flushes, vaginal atrophy and accelerated bone demineralization. Additionally, after discontinuation of therapy, symptoms may return and uterine volumes may increase to pre treatment size. Further research is required to determine the duration of GnRH analogue treatment that will result in symptomatic improvement while minimizing risk of long-term side effects and delay in patients wanting to conceive.

(Huang FJ etal 1999)

Aromatase Inhibitors

Aromatase cytochrome P-450 converts androgens to estrogens and its expression has been observed in both eutopic and ectopic endometrium in patients with endometriosis. Studies have shown an improvement in mean pain scores, lesion size and quality of life scores in patients with adenomyosis treated with aromatase inhibitors.

Various studies demonstrated that Aromatase Inhibitors combined with either progestins or Oral contraceptives reduced the severity of endometriosis-related pain and improved quality of life.

(Nawathe A etal 2008)

C. Levonorgestrel Intrauterine Device (LNG-IUD)

The levonorgestrel intrauterine device intrauterine device is an effective treatment modality for adenomyosis.

Mode of action : The main mechanism of action is by releasing 20 mcg of levonorgestrel per day for up to 5 years. It causes primarily decidualization of the endometrium resulting in decreased menstrual flow. It also acts on adenomyotic foci by causing a down regulation of the estrogen receptors.

This causes the ectopic foci of endometrium to reduce in size, allowing the uterus to contract more efficiently, reducing menstrual blood loss, and resulting in decreased prostaglandin production, improving dysmenorrhoea and the pain scores.

There is a documented improvement in symptoms of heavy menstrual bleeding and dysmenorrhoea, alongwith a discernible change in the radiologic changes following the insertion of the LNG-IUD. Radiologically, there was a reduced uterine volume, significant reduction in junctional zone thickness. This further resulted in significant increase in haemoglobin, hematocrit, and serum ferritin one year after of usage.

Side effects : few patients with adenomyosis and intrauterine LNG can have heavy menstrual bleeding, persistent irregular bleeding and expulsion of the IUD after 2 months.

It was observed that there was an overall patient satisfaction rate was 72.5%. They concluded that the LNG-IUD is effective at reducing uterine volume with improvement of vascularity and patient's symptoms; however the beneficial effects would appear after a minimum of 2 years post insertion.

Studies demonstrating the Quality of life (QOL) evaluation, they used the World Health Organization Quality of Life-Short Form, Turkish Version (WHOQOL-BREF TR). In this questionnaire women who had the LNG-IUD showed improvement in all 5 domains (environmental, environmental-TR, physical, physiological, and social).

They concluded that LNG-IUD may be a promising therapy for adenomyosis with results similar to hysterectomy in terms of managing heavy menstrual bleeding and haemoglobin levels and superior to hysterectomy with respect to physiologic, social well-being, and quality of life at one-year follow-up.

(Fong YF etal 1999; Fedele L etal 1997; Sheng J etal 2009; Ozdegirmenci O etal 2011)

ER inhibitor

Fulvestrant, a potent pure antiestrogen with high affinity binding with ER, was approved by the US Food and Drug Administration in 2002 for the treatment of hormonal receptor positive metastatic breast cancer.

Fulvestrant completely attenuates the ability of the ER to activate or inhibit transcription in a ligand-dependent or independent manner, resulting in a blockade of estrogen action. We still need further trials to prove its efficacy in Adenomyosis.

II Surgical

Hysteroscopic procedures form the main stay of conservative uterine surgeries, in case of adenomyosis. They can be divided in ablative or excisional procedures.

Endometrial Ablation and Hysteroscopic Resection

These procedures can be used as a treatment option in patients who have completed childbearing.

Divided in two categories :

Non-resectoscopic e.g. bipolar radiofrequency, cryotherapy, circulating hot water, microwave and thermal balloon

Resectoscopic e.g. wire loop resection, laser or roller ball ablation and Radiofrequency ablation

Disadvantage

Levgur in the year 2007 reviewed over 2000 patients treated by YAG laser for abnormal bleeding. He concluded that there was a higher risk of failure in patients with adenomyosis if foci penetration exceeded 2.5 mm and hysterectomy was considered to be unavoidable in them.

- Depth of the adenomyotic lesions limits the success of the treatment.
- Deep ectopic endometrium can become trapped behind the ablated edge resulting in pain and bleeding.
- Resection is often limited to superficial lesions as there is risk of causing significant bleeding from arteries present approximately 5 mm below the myometrial surface.
- Predictors of amenorrhea were age greater than 45 years of age, uterine length less than 9 cm, endometrial thickness less than 4 mm and the use of radio-frequency ablation instead of thermal balloon ablation.
- Predictors of treatment failure included age younger than 45 years, parity of 5 or greater, prior tubal ligation, and history of dysmenorrhoea.

In 2009 a retrospective cohort study was done at the Mayo Clinic, Rochester, MN, USA, analyzed the patients with menorrhagia undergoing global endometrial ablation either thermal balloon ablation or radiofrequency ablation.

They analysed that women with a diagnosis of adenomyosis on ultrasound who underwent global endometrial ablation had an increased risk of failure and required subsequent hysterectomy or repeat ablation.

(El Nasher etal 2009; Levgur 2007; Wood C etal1998; El-Nashar SA etal 2009)

Adenomyoma excision

Complete excision of the ectopic endometrium of adenomyotic foci is a moderately good therapeutic modality. However the lesions often are not clearly defined and the adenomyosis is present diffusely throughout the myometrium. This can be performed by various routes as in vaginal, laparoscopic or by hysteroscopic means.

One of the largest study, on adenomyomectomy included 165 women treated with surgery alone or with combined surgical-medical treatment (surgery followed by six months administration of a gonadotropin-releasing hormone agonist).

The adenomyomectomy was performed by mini-laparotomy, ultramini-laparotomy, or laparoscopy. There was a statistically significant symptomatic relief and all symptom scores at the end of the 2-year follow-up period. There was a clinical pregnancy rate of 77.5%, and 49 women (69.0%) had a successful delivery.

Disadvantages : The success following excisional treatment is on an average 50% and the risk of relapse is always there.

Advantage : Good reproductive outcomes following treatment. Clinical pregnancy rate reported was 77.5% and 49 women (69.0%) had a successful delivery.

(Wang PH etal 2009)

Uterine Artery Embolization

Uterine artery embolization is another method for managing symptoms of adenomyosis. Patients report improvement in symptoms following uterine artery embolization with significant improvement in symptoms of heavy menstrual bleeding and dysmenorrhoea significant clinical and symptomatic improvements at both a short-term and long-term follow-up.

Side effects : Pelvic pain, nausea, and fever due to ischemic necrosis. 5% of patients suffer a major complication such as infection, haemorrhage, or unplanned surgical procedure. Few cases of decreased ovarian function following uterine artery embolization have also been documented.

Myometrial Electrocoagulation

Myometrial electrocoagulation by laparoscopy or hysteroscopy can cause a decrease in adenomyosis secondary to necrosis.

Indications : This method has been used in both diffuse and localized disease and may be an option in symptomatic patients with extensive adenomyosis, who have failed medical therapy, where excision is not possible, and they want to preserve their uterus but do not wish to conceive.

Disadvantage : This approach is less accurate than surgical excision because the extent of abnormal tissue being treated cannot be confirmed during the time of surgery.

There is formation of scar tissue, which may decrease the strength of the uterus. Patients may be at risk of uterine rupture and therefore permanent contraception should be offered.

(Wood C 2001)

Myometrial reduction

Myometrial reduction is an approach to treating patients with diffuse adenomyosis by removing the abnormal tissue and then completing metroplasty during laparoscopy or laparotomy.

Three approaches

Classical reduction method where the uterus is dissected longitudinally in the midline and there is resection of the anterior and posterior portions of the myometrium. They found this method was not very successful as women developed adenomyosis and required hysterectomy within 1 year.

Modified method a transverse H incision - Fujishita et al in 2004 described this technique of removal of adenomyoma involved one vertical and two crossing horizontal incisions that allowed easier removal of considerable amounts of adenomyotic tissue.

Although, there was no difference in operation time, blood loss, and volume of specimen removed the subjective improvement of symptoms was more apparent in the transverse H technique. The modified group had a greater improvement in pain, return of the reproductive function and lower risk of perforation.

(Fujishita et al 2004)

Triple flap method - This method was described by **Osada et al**, in this method of adenomyomectomy, the adenomyotic tissues were excised and the uterine wall was reconstructed using a triple-flap repair.

In his study, all of 104 patients had adenomyosis involving more than 80% of the anterior and posterior uterine walls with more than 6cm wall thickness, confirmed by MRI and ultrasound. Intraoperatively the uterus was delivered, and a supracervical tourniquet was applied. Following this the uterus was then bisected in the midline and in the sagittal plane, until the uterine cavity was opened.

Adenomyotic tissues were excised from surrounding myometrium leaving a myometrial thickness, from the serosa above and the endometrium below, of 1 cm. The endometrial lining was then approximated and the myometrium repaired with the triple-flap reconstruction

The results showed a definitive improvement in the degree of dysmenorrhoea, menstrual blood loss, and anaemia. On following up the patients there was a reduced recurrence rate. The main advantage was that utilizing this method was the reduced risk of rupture during pregnancy.

Disadvantage : post procedure there is a reduction in the uterine volume, which may hamper the future pregnancy outcome. Patients may be predisposed to spontaneous abortion or premature labour. Uterine scaring caused due to the procedure can lead to decreased uterine wall strength and increased risk of uterine rupture.

(Nishida M etal 2010; Pepas L etal 2012; Osada H etal 2011)

Laparoscopic transient occlusion of bilateral uterine arteries

A recent article in 2017 described the laparoscopic transient occlusion of bilateral uterine arteries as therapeutic in cases of focal adenomyosis. In a seven month follow up of the 105 patients he operated there was a marked improvement in the clinical symptoms of the patient with reduced intraoperative blood loss.

(Young j K etal 2017)

Robotic Assisted Adenomyoma Excision In the year 2010 the first case report of robot-assisted excision of a cystic adenoma in an adolescent girl supplements options available to excise localized adenomyosis

(Akar ME etal 2010)

MRI-guided focused ultrasound surgery for adenomyosis

This procedure uses MRI guided Ultrasound energy to remove the areas of adenomyosis in patients wishing to preserve their reproductive function.

Mode of action : The treatment causes cell death and necrosis of the targeted adenomyotic tissue, preserving the surrounding myometrium and uterine walls. The ultrasound beams are focused on the target and cause thermal coagulation and consequent necrosis. There is excellent anatomic resolution and high thermal imaging sensitivity.

Side effects : Risk of skin burn, nausea and vomiting, and sciatic nerve palsy. It is also found that post treatment the patients has significantly smaller mean uterine volume and lower scores related to heavy menstrual bleeding and bulk during a period of 3 to 6 months.

(Rabinovici J etal 2006; Fukunishi H etal 2008; Zhou M etal 2011)

Hysterectomy

Hysterectomy historically was the primary diagnostic and therapeutic option for patients. Commonly it is the treatment of choice for patients with significant symptoms who have completed childbearing.

Routes : laparoscopy, vaginally, abdominally, robotically assisted.

Among these options, vaginal hysterectomy is preferable to an abdominal hysterectomy because of faster recovery and lower morbidity. However there are varied reports in literature stating that patients undergoing vaginal hysterectomy had an increased risk of bladder injury.

Studies have shown no significant difference between operative time and estimated blood loss when analyzed by uterine weight between the abdominal Vs vaginal groups. However adenomyosis was associated with an increased risk of bladder injury in patients undergoing vaginal hysterectomy. This may be due to difficulty in identifying the supravaginal septum and the vesicovaginal or vesicocervical planes.

Further to this, laparoscopic and robotically assisted hysterectomy is thought to allow better dissection of decreased postoperative pain following laparoscopic hysterectomy compared to vaginal hysterectomy. It should be noted that there is a possibility that patients may still experience pelvic pain following hysterectomy.

(Furuhashi M etal 1998; Ghezzi F etal 2010; Grimbizis 2016; Pepas Letal 2010)

Part -2

PART - 2

FAQ s on adenomyosis

Ques1- What is there a co relation of adenomysosis and infertility?

Ans1-The incidence of adenomyosis in the infertile population has reported to be around 20.9% to 24.4%.

(J Naftalin etal 2012)

Ques 2- What is the likelihood of clinical pregnancy in patients with adenomyosis, undergoing IVF and ICSI?

Ans 2- Meta-analyses have shown that adenomyosis was associated with a 28% (95% CI, 5-45%) reduction in the likelihood of clinical pregnancy in infertile women who underwent In vitro fertilization/Intracytoplasmic sperm Injection with autologous oocytes.

(Vercellini P etal 2014)

Ques 3- Does Adenomyosis affect the implantation rate in In vitro fertilization cycles?

Ans 3- The effect of adenomyosis on implantation has been debated recently. Whereas **Campo et al. (2012)** hypothesized a detrimental impact mediated by perturbed uterine peristalsis and reduced endometrial receptivity indicated by the presence of implantation marker defects, **Martı´nez- Conejero et al.** (2011) and **Vila-Vives et al.** (2012) reported no statistically significant differences in implantation and pregnancy rates between women with or without adenomyosis diagnosed at Transvaginal ultrasound (TVUS). However, if adenomyosis is considered a uterine factor of infertility, it seems logical to infer that impaired implantation constitutes the pathogenic mechanism leading to reduced clinical pregnancy rate.

(Martı´nez- Conejero et al 2011; Vila-Vives et al 2012)

Ques 4- Is there a difference in the techniques of surgical management of adenomyosis, in terms of pregnancy outcome?

Ans 4- If we compared the classical method of adenomyomectomy with a new modified reduction surgery by means of a transverse H incision technique. The classical technique involved a uterine incision followed by stepwise resection of adenomyotic tissue and closure.

The newer technique modified the incision to the shape of an H and this was followed by raising serosal flaps and excision of the adenomyomatous tissue. It was observed that the new technique showed a 50% pregnancy rate, compared with no pregnancy with the older classical method.

The odd of having a live birth with the old classical method compared with the newer technique was 0.14 (95% CI, 0.00 and 4.47). The time to pregnancy was usually around 4 and 6 months.

(Fujishita et al 2004)

Ques 5- What is a better screening modality Magnetic resonance Imaging Vs Transvaginal Ultrasound (TVUS)?

Ans 5- Although MRI may theoretically provide better information than TVUS, the latter approach should be preferred for screening purposes, given its ubiquitous availability and low cost, whereas MRI could be reserved for diagnosis in selected circumstances. **Maheshwari et al** In a systematic review concluded that both magnetic resonance imaging and ultrasound are non-invasive tests with equivalent accuracy in diagnosing adenomyosis (area under curve 0.91 and 0.88, respectively).

(Maheshwari A etal 2011)

Ques 6- Does conservative surgery help in patients with adenomyosis and infertility?

Ans 6- The conservative surgical techniques described in all studies involve excision of the adenomyotic tissue or adenomyoma and hysteroscopy either laparoscopically or via laparotomy. An overall live birth rate of 36.2% (21 of 58) was achieved following the conservative surgery.

Ques 7- Can uterine artery embolization be done in infertility patients?

Ans 7- The effectiveness of uterine artery embolization in the management of adenomyosis and pregnancy as an outcome has been observed by **Kim et al.** in 2005. A live birth rate of 83.3% five of six patients was observed after a follow-up of 35 months.

(Kim et al. 2005)

Ques 8- What is the correlation of adenomyosis with obstetric outcome?

Ans 8- An increased risk of preterm delivery [odds ratio (OR) and 95% CI 21.84; 1.32 -4.31] and preterm premature rupture of membrane (OR and 95% CI 21.98, 1.39 -3.15) was found in women with adenomyosis when compared with those without adenomyosis.

Apart from this case reports on obstetric and/or surgical complications of adenomyosis such as uterine rupture or perforation, uterine atony leading to haemorrhage and ectopic pregnancies (including an ectopic pregnancy in an adenomyosis area). Literature also reports the cases of adenomyosis leading to red degeneration and post-partum haemorrhage.

(Juang et al 2007)

Key Points

1. Adenomyosis is a common condition, not only found in the multiparous population, but also has an increasing incidence amongst the infertile patients.
2. Adenomyosis is a majorly underdiscussed and researched topic.
3. There are no formal guidelines given by any apical body in this regards
4. Unlike endometriosis, surgical modality is not the preferred modality in patients with infertility.
5. There are no single specific diagnostic criteria for the diagnosis of this condition
6. Although, MRI has a better diagnostic value as compared to other modalities, still on a cost benefit analysis , a good 3 D ultrasound also is equally effective in diagnosing adenomyosis
7. Newer drugs like Dienogest , others like Ullipristal have shown a symptomatic improvement in this condition.

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Notes

ZyFSH r 75/150 IU

Recombinant-Human Follicle Stimulating Hormone

ZyhMG HP 75 150

Menotrophin

Ovucet

Cetrorelix Acetate 0.25mg for injection

Letisha

Letrozole 2.5 mg Tablets

ZyStim

Filgrastim 300 µg/ml single dose pre-filled syringe

Contact :

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