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# Effectiveness of medical management in Adenomyosis

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***Abstract*---**Introduction: Adenomyosis is defined by the abnormal location of endometrial tissue within the myometrium associated with hypertrophy or hyperplasia of the myometrial stroma. It is a chronic estrogen dependent condition. Although pathogenesis and etiology of adenomyosis remain unknown, two main theories have been proposed: invagination of the endometrial basal layer and metaplasia of embryonic stem cells. Prevalence of adenomyosis varies widely from 5 to 70% with recent studies showing about 20% prevalence among which the majority were premenopausal. Materials and Methods: A Comparative Study was conducted from March 2022-August 2022. Women attending Gynec OPD with Abnormal Uterine bleeding due to Adenomyosis confirmed by sonography at Vinayaka Mission's Kiruparananda Variyar Medical College and Hospital, Salem. Patients coming to Gynecology OPD with complaints of heavy menstrual bleeding, confirmed diagnosis of adenomyosis by ultrasonography, fulfilling the criteria and ready to followup to be enrolled in the study. A detailed history to be obtained with regard to age, parity, age of menarche, time since bleeding starts, duration and frequency of menstrual cycle. Results: In our study, Women attending Gynec OPD with Abnormal Uterine bleeding due to Adenomyosis confirmed by sonography at Vinayaka Mission's Kiruparananda Variyar Medical College and Hospital, Salem. Mean age was 45.7 years. Out of 100 patients, 43 patients were parity 1, 32 patients were parity 2, 24 patients were parity 3. Mean age of menarche was 11.5 years. Mean time since bleeding starts 2 weeks, duration and frequency of menstrual cycle was 15 days. Severity symptoms were observed in 46, 33, 21, mild, moderate, severe respectively. Conclusion: Medical

treatment plays an important role in the management of adenomyosis, especially in diffuse forms and in those women requiring preservation or restoration of fertility. Medical management is a valid choice for treating pain symptoms and bleeding, resulting very frequently in a more acceptable option than surgical treatment. Novel treatment with GnRH antagonist has already yielded better results when compared with other treatment methods. Patients diagnosed with AD have a decreased quality of life which may improve with a GnRH antagonist.

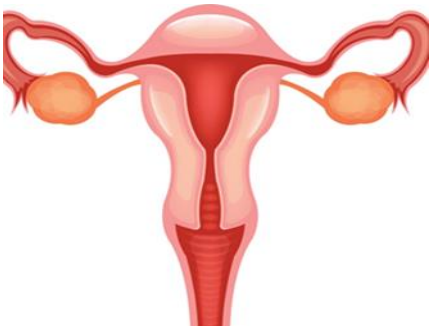
***Keywords***---adenomyosis, hypertrophy, hyperplasia, medical management.

## Introduction

Adenomyosis is defined by the abnormal location of endometrial tissue within the myometrium associated with hypertrophy or hyperplasia of the myometrial stroma.[1] It is a chronic estrogen dependent condition. Although pathogenesis and etiology of adenomyosis remain unknown, two main theories have been proposed: invagination of the endometrial basal layer and metaplasia of embryonic stem cells. Prevalence of adenomyosis varies widely from 5 to 70% with recent studies showing about 20% prevalence among which the majority were premenopausal.[2]

Its most common symptoms include heavy menstrual bleeding, intense pelvic pain, and infertility. The management of patients with adenomyosis is difficult and conservative treatment is required for those who require preservation of fertility and improvement of quality of life.[3] No drug currently available is labelled for the treatment of adenomyosis and no specific guidelines refer on the management of the disease.

## Drugs used for adenomyosis



GnRH analogues
Progestins
Combined oral contraceptives
SERMs
Aromatase inhibitors
SPRMs
NSAIDs

**Medical treatments available for ADENOMYOSIS are**

**GnRH agonist**

Mechanism of action: GnRH-a are drugs used for the treatment of adenomyosis because, binding to the GnRH receptors in thepituitary gland, they cause a downregulation of GnRH activity, and induce a reversible state of medical menopause.Estrogen levels fall, inducing atrophy of the adenomyoticlesions, which in turn results in a reduction in the uterinesize.

Side effects: Hypoestrogenic side effects, including vasomotor syndrome, reduced bone mineral density, genital atrophy, and mood instability. To minimize the GnRH-a-inducingadverse events, an add-back therapy with various kinds ofhormone preparations has been successfully used recently.

**Progestins**

Mechanism of action: Progestins action involves the decidualization and subsequent atrophy of endometrial tissue, modulation of mitotic activity, local growth factors and their receptors, as well as otherparacrine mechanisms and anti-inflammatory mechanisms.

Side effects: progestins are known to causebreakthrough bleeding and other less frequent symptoms,such as changes in menstrual flow, amenorrhea, changes incervical secretions, edema, weight gain or loss, cholestaticjaundice, allergic rash with or without pruritus, melasma orchloasma and mental depression.

**Progestins used for adenomyosis are[4]**

- Norethindrone acetate
- Danazol
- Levonorgestrel- releasing intrauterine system

**Combined oral contraceptives**

Mechanism of action: COCs induce a decreased menstruation, causing decidualization and subsequent atrophy of the endometrium. Aromatase expression in the eutopic endometrium and adenomyotic foci is suppressed by COCs.
Side effects: Irregular bleeding, increased risk of venous thrombosis.

**Selective estrogen receptor modulators (SERMs)**

Mechanism of action: The ideal SERM might have antagonistic activity in the endometrium (adenomyotic lesion) and agonistic activity for bone and lipids. The mechanisms of the tissue-selectivity can be explained by three interactive mechanisms, including differential ER expression in a given target tissue, differential ER conformation on ligand binding, and differential expression and binding to the ER coregulator proteins, which are considered potentially effective therapy for women with adenomyosis.

**Aromatase inhibitors**

Mechanism of action: Aromatase cytochrome P450 (CYP19A1) is a key enzymein the synthesis of estrogen from androgens, involving the conversion of androstenedione and testosterone to estrone and E2. It is an excellent target for inhibition of E2 synthesis.
Side effects: The side effects are headaches, hot flashes, mood changes, muscle aches and breakthrough bleeding.

**Selective progesterone receptor modulators**

Mechanism of action: SPRMs are defined as a new class of progesterone receptor ligands, which exhibit both progesterone agonist and antagonist activities in the endometrium, reducing pain, bleeding, cell proliferation and inhibiting inflammation. Mifepristone given in doses 5,10,15mg.

**Anti inflammatory drugs**

Mechanism of Action: NSAIDs reduce prostaglandin synthesis at the level of the endometrium by inhibiting cyclooxygenase. Endometrial prostaglandin receptors may play a role in developing aberrant vascularization and promoting neoangiogenesis, which can result in AUB. Thus, the inhibition of prostaglandin synthesis aids in reducing menstrual bleeding.[5]

**Aim and objective**

This study is done to compare the effectiveness of management of Adenomyosis by medical methods.

**Objectives**

1. To assess improvement in Quality of life
2. To educate various conservative methods available and their effectiveness

**Materials and Methods**

Study Period: March 2022– August 2022
Study Design: Comparative Study
Study Population: Women attending Gynec OPD with Abnormal Uterine bleeding due to Adenomyosis confirmed by sonography at Vinayaka Mission's KiruparanandaVariyar Medical College and Hospital, Salem.
Sample Size: 100 cases
Statistical Analysis: Once the data collected, they are compelled in microsoft excel and analysed in SPSS (Statistical package for social sciences ) version 26 ,
Student T test, Chi square test.
Inclusion Criteria: All the married women attending Gynecology OPD with complaints of AUB and USG showing features of adenomyosis

**Exclusion criteria**

- Pregnancy and pregnancy related conditions
- Puberty menorrhagia
- Women >50 years
- Women with postmenopausal bleeding
- Malignancy on histopathology
- Uterine fibroids
- Asymptomatic patients with adenomyosis

**Methodology**

Patients coming to Gynecology OPD with complaints of heavy menstrual bleeding, confirmed diagnosis of adenomyosis by ultrasonography, fulfilling the criteria and ready to followup to be enrolled in the study. A detailed history to be obtained with regard to age, parity, age of menarche, time since bleeding starts, duration and frequency of menstrual cycle. Menstrual blood loss to be assessed with Pictorial Blood Assessment Chart score by asking about number of soakage of pads and passage of clots. A thorough clinical examination including general physical examination, built, nutritional status and bimanual pelvic examination to be done. Investigations like hemoglobin, complete blood count, liver function test, kidney function test, thyroid function test, pelvic ultrasound to be done. Endometrial biopsy to be taken to rule out malignancy.

In total 100 participants with consent for medical management, each individual is given medication based on age of the patient, desire of fertility, compliance of the patient, severity of the symptoms. The different medical treatment options like GnRH agonists, Aromatase inhibitors, LNG-IUS, SERMs, SPRMs, progesterone only pills, COC pills, Tranexamic acid. Patients with first episode of menorrhagia, tranexamic acid can be used for treatment, in patients who want to conceive, progestins can be given, patients who require contraception combined oral contraceptive pills or levonorgesterol IUS is used to treat, perimenopausal women can be treated with GnRH agonists or SERMs, patients who are not compliant to hormonal medications, SERMs, SPRMs or GnRH agonists can be given. Obese patients and patients at risk of thrombotic events, estrogen containing drugs should be avoided. Patients who are at risk of breast cancer, hormonal medications to be avoided. Patients have to maintain PBAC score on PBAC graph provided to patient on starting of the treatment. Patients to be followed up monthly for six months of treatment. Improvement in symptoms and better quality of life is assessed in different groups and compared. An USG pelvis is taken at the end of 6 months to asses adenomyotic lesions.

**PBAC (Pictorial Blood Assessment Chart) scoring system**

Based on pad soakage:

- 1point- for each lightly stained pad
- 5 points- for each moderately stained pad
- 20 points – for each completely stained pad

Based on clots passed:

- 1point – for each small clot
- 5 points – for each large clot
- 5 points – for each episode of flooding

A score of >150 points is considered heavy menstrual bleeding

Outcome measured in terms of

- Improvement in PBAC score
- Amenorrhea
- Normal menses
- Scanty menses
- Persistent heavy menstrual flow

**Results**

In our study, Women attending Gynec OPD with Abnormal Uterine bleeding due to Adenomyosis confirmed by sonography at Vinayaka Mission's Kirupara nanda Variyar Medical College and Hospital, Salem. Mean age was 45.7 years. Out of 100 patients, 43 patients were parity 1, 32 patients were parity 2, 24 patients were parity 3. Mean age of menarche was 11.5 years. Mean time since bleeding starts 2 weeks, duration and frequency of menstrual cycle was 15 days. Severity symptoms were observed in 46, 33, 21, mild, moderate, severe respectively.

| S.No | Parameter | Value |
|---|---|---|
| 1 | Mean age | 45.7 |
| 2 | Parity<br>1<br>2<br>3 | <br>43<br>32<br>25 |
| 3 | Mean age of menarche | 11.5 |
| 4 | Mean time since bleeding starts, | 2 weeks |
| 5 | duration and frequency of menstrual cycle | 15 days |
| 6 | Severity of symptoms<br>mild<br>Moderate<br>Severe | <br>46 (46)<br>33 (33)<br>21 (21) |

Table 1: Patients demographics

Out of 100 patients, 23(23%) were less than 20 years, 34(34%) were 21-30 years, 25(25%) were 31-40 years, 18(18%) were 41-50 years.

| S.No | Age group | N (%) |
|---|---|---|
| 1 | <20 years | 23 (23) |
| 2 | 21-30 years | 34 (34) |

| | | |
|---|---|---|
| 3 | 31-40 years | 25 (25) |
| 4 | 41-50 years | 18 (18) |

Table 2: Age distribution

| S.No | parameter | GnRH agonists (26) | Aromatase inhibitors (24) | LNG-IUS (20) | SERMs (15) | SPRMs (10) | Progesterone only pills, COC pills, Tranexamic acid. (5) |
|---|---|---|---|---|---|---|---|
| 1 | Outcome | Recovered | Recovered | recovering | recovering | recovering | recovering |
| 2 | Quality of life | Improved | Improved | Improved | Improved | Improved | Improved |
| 3 | Adverse effects<br>Acne<br>Weight gain<br>Nausea<br>Headache<br>Hirsutism<br>Voice changes<br>Muscle cramps | <br><br>2 (7.69)<br>4 (15.38)<br><br>5 (19.23)<br>2 (7.69)<br>3 (11.53)<br>2 (7.69)<br><br>3 (11.53) | <br><br>3 (12.5)<br>2 (8.33)<br><br>4 (16.66)<br>2 (8.33)<br>1 (4.16)<br>1 (4.16)<br><br>1 (4.16) | <br><br>1 (5)<br>2 (10)<br><br>2 (10)<br>2 (10)<br>0 (0)<br>1 (5)<br><br>2 (10) | <br><br>1 (6.6)<br>2 (13.33)<br><br>2 (13.33)<br>1 (6.6)<br>0 (0)<br>0 (0)<br><br>0 (0) | <br><br>1(1)<br>1 (1)<br><br>1 (1)<br>1 (1)<br>0 (0)<br>0 (0)<br><br>0 (0) | <br><br>1(0.5)<br>0 (0)<br><br>1(0.5)<br>1(0.5)<br>0 (0)<br>0 (0)<br><br>0 (0) |

Tablet 3: Outcome, Quality of life, adverse effects after 6 months follow up

**Discussion**

Medical treatment is the first-line treatment option for adenomyosis aiming to relieve symptoms and maintain fertility with the least possible side effect. This is achieved by disrupting pathways leading to inflammation, neuroangiogenesis, and impaired apoptosis. Currently, several hormonal and non-hormonal options, namely gonadotropin-releasing hormone (GnRH) analogues, progestins, combined oral contraceptives, and non-steroidal anti-inflammatory drugs are being used in an “off label” manner for the symptomatic treatment of adenomyosis.[6] Also, newer drugs, such as aromatase inhibitors, have been investigated by Badawy et al. and Tosti et al., while other therapies such as selective progesterone receptor modulators, GnRH antagonists, valproic acid, and anti-platelet therapies are still under investigation.[7]

The main advantage of medication is symptomatic relief without the need for surgical treatment. Nevertheless, many drawbacks still need to be addressed. This includes the temporary relieve of symptoms, and the common (i.e., menopausal symptoms, irregular bleeding, amenorrhea) and occasionally severe (i.e., thromboembolic) side effects of some drugs. Lack of evidence needed to base choice of drugs also raises the need to perform research into the comparative efficacy of currently used drugs and develop a more standardized approach for patients wanting to conceive while using medication. With a better understanding of pathogenetic mechanisms of adenomyosis, advances in drug development will soon be possible.[8]

The first conservative surgical therapy for adenomyosis in young women, namely adenomyomectomy, dates all the way back to 1952.[9] In the 1970s, cytoreductive

surgery in the form of partial excision of adenomyotic tissue became more popular. Common approaches to conservative partial or complete adenomyosis excision are Partial Reduction Surgery, Complete Adenomyosis Excision, Important Remarks on the Surgical Approach.[10]

**Conclusion**

Medical treatment plays an important role in the management of adenomyosis, especially in diffuse forms and in those women requiring preservation or restoration of fertility. Medical management is a valid choice for treating pain symptoms and bleeding, resulting very frequently in a more acceptable option than surgical treatment. Novel treatment with GnRH antagonist has already yielded better results when compared with other treatment methods. Patients diagnosed with AD have a decreased quality of life which may improve with a GnRH antagonist.

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