Int. j. adv. multidisc. res. stud. 2022; 2(6):182-187

Received: 16-09-2022
Accepted: 26-10-2022

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Conquering the elusive disease

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Abstract

Endometriosis is a mysterious disease as regards to its etiology, pathogenesis, diagnosis and treatment. As per recent estimates by WHO, about 196 million women suffer from Endometriosis globally. Of these, 50 million women belong to India alone!! Endometriosis causes pain and infertility. Average diagnostic delay may vary from 6 to 8 years. Treatment aims at alleviating the pain, preventing the recurrence and promoting the fertility. Patients need lifelong medical management plan and surgery should be minimized. Diagnosis is based on history, clinical examination, imaging modalities like USG, CECT, MRI, biomarkers and trial of treatment, currently there is no role for laparoscopy to diagnose endometriosis. Prevention of endometriosis could be primordial, primary, secondary or tertiary. This aims at prevention of risk factors for endometriosis and life style modifications play a major role in primordial prevention. Identification of the risk factors and regular screening, non-invasive diagnosis, empirical treatment, regular follow up of the patients and intervention at the right time are the modalities for primary prevention. Secondary prevention includes early diagnosis by symptoms, imaging, biomarkers and, empirical treatment which includes COCs, progestins and GnRH analogues. Tertiary prevention includes prevention and treatment of complications like recurrence and pain. Patients who are high risk for endometriosis should undergo primordial and primary prevention even before the disease manifests. Enhanced awareness, followed by yearly checkup and management may slow or halt the natural progression of the disease. Awareness about endometriosis will improve the sexual and reproductive health, quality of life and overall well-being.

Keywords: Endometriosis, Pain, Infertility, Risk factors, Prevention

Introduction

Endometriosis is a mysterious disease as regards to its etiology, pathogenesis, diagnosis and treatment. It is the presence of normal endometrial tissue abnormally implanted in locations other than uterine cavity. Implants grow and invade tissue in their vicinity, causing inflammatory reaction [1]. 1 in 10 women have endometriosis during their reproductive years [2]. As per recent estimates by WHO, about 196 million women suffer from endometriosis globally. Of these, 50 million women belong to India alone!!

Endometriosis is a common disease-causing pain and infertility. Earlier age of occurrence leads to severe disease. 25-40% of women with infertility, 75% of women with chronic pelvic pain and 40-60% of girls with severe dysmenorrhoea suffer from endometriosis.

As per American Society for Reproductive Medicine [ASRM], "Endometriosis should be viewed as a chronic inflammatory disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures" [3]. Treatment aims at alleviating the pain, preventing the recurrence and promoting the fertility. Average diagnostic delay may vary from 6 to 8 years and the patients would have seen minimum of 7 consultants before the diagnosis is made. The natural course of the disease varies. 29% of the disease might progress or remain static and 42% might regress [4].

Diagnosis of endometriosis

It is based on history, clinical examination, imaging modalities, biomarkers, trial of treatment and currently there is no role for laparoscopy to diagnose endometriosis. It should be only for therapeutic purpose. In 2019, there was NO PLACE for diagnostic laparoscopy when endometriosis was clinically suspected according to Prof. Chapron [5].

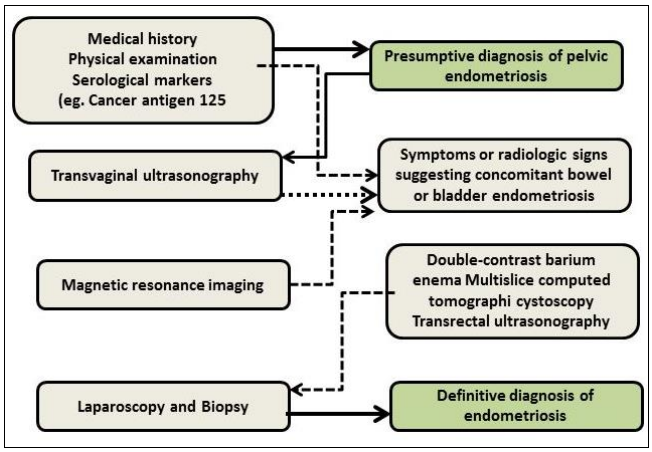

Fig 1: Algorithm for imaging diagnosis of endometriosis

Is prevention possible for endometriosis?

Prevention could be primordial, primary, secondary or tertiary.

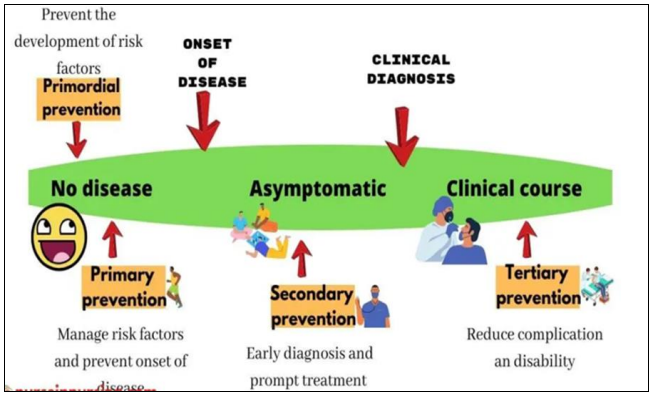

Fig 2: Varying levels of prevention of endometriosis

Primordial prevention

This aims at prevention of risk factors for endometriosis. Life style modification plays a major role in primordial prevention. Moderate exercise, avoiding dairy products, refined sugars, soy products, red meat, trans-fat, caffeine, drugs, alcohol and smoking are beneficial. Omega 3 fatty acids and fruits should be promoted [6].

Primary prevention

Identification of the risk factors and regular screening, non-invasive diagnosis, empirical treatment, regular follow up of the patients and intervention at the right time are the modalities for primary prevention.

Risk factors for endometriosis

Early age of menarche <12 years, frequent and prolonged cycles, girls with low BMI, Family history of endometriosis (6.9 times higher), severe dysmenorrhoea where OCP is used as analgesic and not as contraceptive, pain interfering with daily activities, dyschezia and deep dyspareunia in sexually active girls are the risk factors for endometriosis [7]. School absenteeism due to dysmenorrhoea is an indicator for endometriosis [8].

What other health conditions are linked to endometriosis ?

Allergies, asthma, and chemical sensitivities, autoimmune diseases like multiple sclerosis, lupus, hypothyroidism, exposure to dioxin, pesticides, chronic fatigue syndrome, fibromyalgia and certain cancers like ovarian and breast cancer are linked with endometriosis.

Presence of neonatal uterine bleeding may represent a warning sign for the future development of endometriosis and we need to increase the awareness about the devastating disease in the young woman [9].

Secondary prevention

Includes early diagnosis, empirical treatment and treatment after confirmation. It is always better to treat the symptoms and not the disease. Common symptoms are dysmenorrhoea, dysuria, dyschezia, dyspareunia, abnormal uterine bleeding, diffuse abdominal pain, and difficulty in conception. Women with these symptoms are likely to suffer from endometriosis. Ultimately all these symptoms lead to chronic fatigue and depression. Currently patients can be treated empirically without histological diagnosis. Management includes medical, surgical or combined. Follow up and prevention of complications are essential. Secondary prevention aims at treatment in early stages and prevention of complications.

Early diagnosis

Apart from clinical diagnosis, bio-markers can be used for early diagnosis. Imaging can pick up endometriosis only in advanced stages. Glycoproteins (CA 125, CA 19-9), growth factors, inflammatory cytokines like IL 6 and 8, TN alpha, angiogenic factors (VEGF), oxidative stress markers, Neutrophil / Lymphocyte ratio and miRNA are the common bio-markers used for early diagnosis.

Proteomics

Specific plasma biomarkers obtained during menstruation identifies the protein finger prints which are markers of the disease which can be either up or down regulated. Proteomic technologies along with genetic profiling are newer modalities of non-invasive diagnosis.

Genetic markers

Saliva based diagnosis of genetic marker may replace surgical procedure for diagnosis.

Endometrial nerve fibers in the endometrium of endometriosis patients

Unmyelinated sensory nerve fibers (using the pan-neuronal marker PGP 9.5) in the functional layer of endometrium in women with endometriosis and a significantly increased nerve fiber density in endometrium and myometrium in women with endometriosis compared with women without endometriosis have been reported. Sensory C nerve fibers were only detected in the functional layer of endometrium of women with endometriosis and never in women without endometriosis. There was a higher density of nerve fibers stained with PGP 9.5 in the basal layer of endometrium and in myometrium in women with endometriosis (mean density ± SD, 18 ± 8/mm^2, 3.3 ± 1.2/mm^2, respectively) than in women without endometriosis (mean density ± SD, 0/mm^2, and 0.9 ± 0.8/mm^2).

Endometriosis and vaginal microbiome

Endometriosis appears to be associated with an increased presence of *Proteobacteria*, *Enterobacteriaceae*, *Streptococcus Suppurata and Escherichia Coli* across

various microbiome sites. The association of phylum Firmicutes and the genus Gardnerella remains unclear. Laboratory and clinical studies demonstrate that there are indeed differences in the microbiome composition of hosts with or without endometriosis [10].

Samples from endometrium, DIE lesions and vaginal fluid DNA can be extracted and identify the microbiome by DNA sequencing of the 16S rRNA marker gene which was done using next generation sequencing. Amplicon sequencing showed DIE lesions seems to have different bacterial composition, less predominant of Lactobacillus spp and with more abundant *Alishewanella* spp, *Enterococcus* spp *and Pseudomonas* spp than the control group. There is significant increase in the presence of *Acinetobacter* spp, *Pseudomonas* spp, *Streptococcus* spp, and Enhydrobacter spp. There is significant decrease in *Propionibacterium* spp, *Actinomyces* spp, *and Rothia* spp in the endometriosis group compared to the control group ($p < 0.05$). These findings strongly suggest that microbiome composition is altered in the peritoneal environment in women with endometriosis.

Serum miRNAs

miRNA in endometriosis as a potential bio-marker

These are the numerous miRNA involved in endometriosis

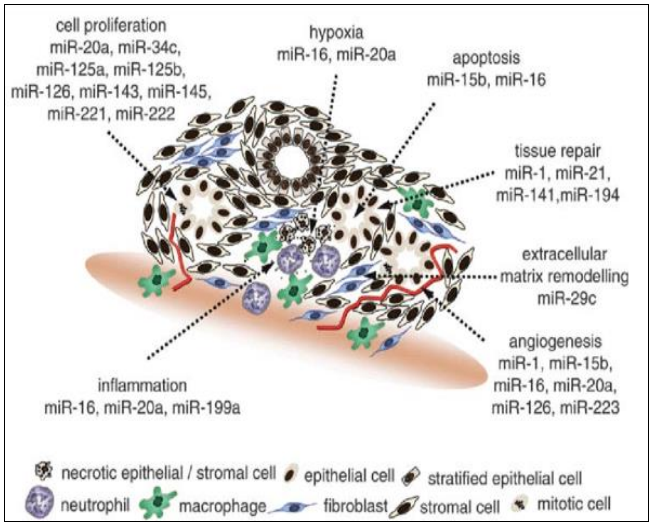

Fig 3: Types of miRNAs

miRNAs are short nucleotide sequence of non-coding RNA involved in regulatory pathways. miRNA expression profiles are gaining appreciation as diagnostic measures in wide variety of diseases [11]. Many studies have shown differences in up-regulation and down-regulation of miRNAs in endometriosis Vs control group. There has been increased validity of panels of candidate miRNAs over a single miRNA. They can be used as a non- invasive bio-marker for diagnosis of endometriosis. Also, they can be used to find out the treatment response to hormones. Moustafa *et al*., 2020 has recently shown that a set of 6 miRNAs are able to distinguish endometriosis from other gynaecological diseases, regardless of hormone treatment or phase of menstrual cycle [12]. miRNA panel used are miRNA 125b, miRNA150, miRNA342, miRNA451a, miRNA3613 and Let-7b. They resulted in 90% sensitivity and specificity. Hence patients presenting with symptoms of endometriosis if subjected to miRNA study, diagnosis can be established and treatment can be started earlier. More over various phenotypes of endometriosis are likely to have various miRNA expression [13].

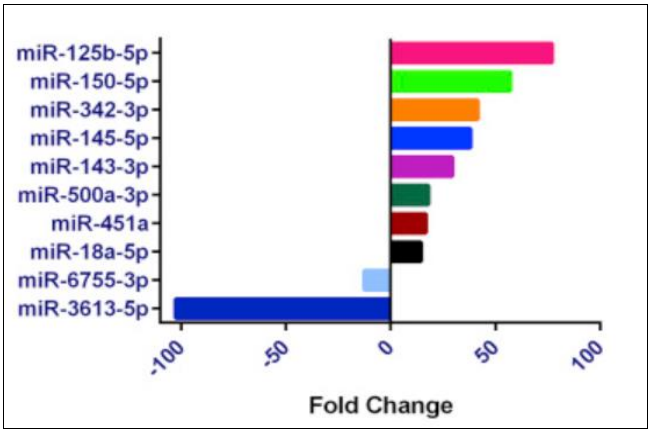

Fig 4: Expression of varying miRNA

Imaging modalities

USG/CD/Elastography, CT, MRI are various imaging modalities which can diagnose endometriosis of multiple phenotypes. Endometriomas are picked up by USG from minimum of 1 cm diameter. But superficial lesions and deep endometriosis can be diagnosed by varying signs. MRI helps in mapping deep endometriosis.

Brosens *et al* 2004 [14] suggested in 1997 that "noninvasive techniques such as color Doppler USG and particularly MRI is more suitable for diagnosis and follow-up of endometriosis".

"The key paradigm shift in the management of women with endometriosis is that we now have specialists who can diagnose endometriosis on ultrasound," Luk Rombauts says [15]. USG is almost like a pre-operative map of chocolate cyst or endometrioma as well as deep endometriosis.

Four basic sonographic steps are described for examining women with clinical suspicion of deep infiltrating endometriosis (DIE) or known endometriosis

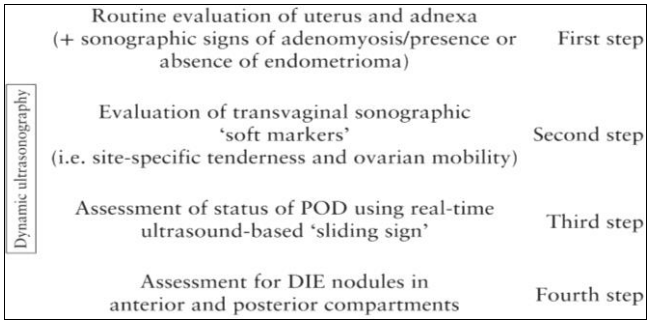

Fig 5: USG diagnosis of DIE

Schematic drawings and corresponding ultrasound images of bowel deep infiltrating endometriosis (DIE) [16].

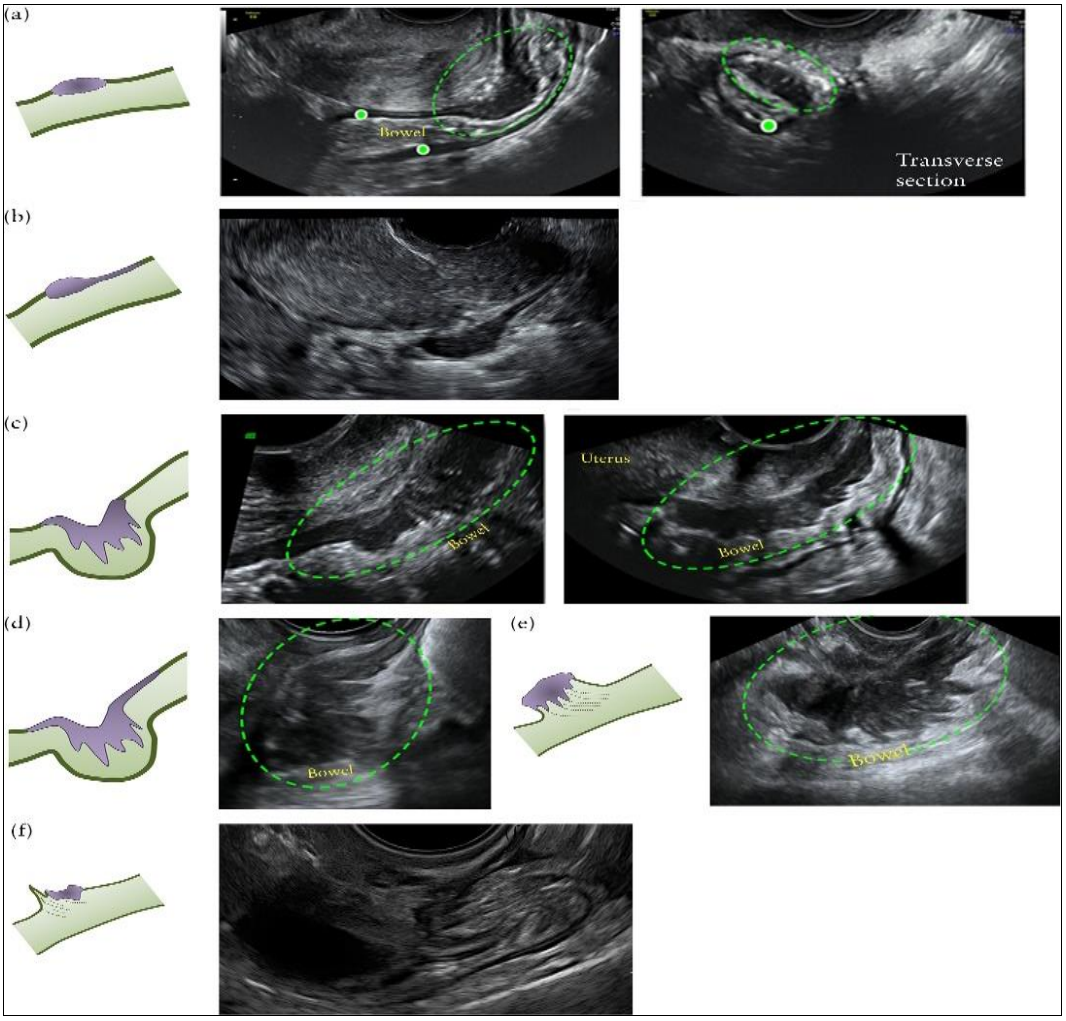

Fig 6: USG showing multiple signs which are indirect signs of DIE

(a)Absence of spikes
(b)Comet sign
(c) Moose antler sign
(d)Indian headdress sign
(e) Pulling sleeve sign

Short ano-genital distance in MRI is a marker for endometriosis

Endometriosis patients had shorter MRI-AGD especially MRI-AGD-AF. (Anterior anal verge to posterior fourchette). As, MRI-AGD was independent of r-ASRM and Enzian classification; it can be used in diagnosing the early stage of disease. Optimal MRI-AGD-AF cut off is 20mm.Since, MRI has sensitivity of only 42% in diagnosing stage I endometriosis – AGD measurement will be helpful for these patients.

Treatment with or without histology

Many esteemed professional bodies like ESHRE, SOGC, ASRM, WES and FOGSI have made recommendations that medical treatment can be prescribed for endometriosis without prior histological confirmation. Mere symptoms are enough for starting empirical treatment.

Empirical treatment

The concept of medical management is to suppress estrogen, reduce the retrograde spill, overcome the progesterone resistance, anti-inflammatory, suppression of aromatase, anti-angiogenic and immunomodulatory effect. Being a chronic disease, one should consider not only the efficacy but also the long-term safety and tolerability. Common drugs used are COCs, progestins and GnRH analogues.

Newer drug therapies

GnRH antagonist, Linzagolix, Relugolix, Elagolix, Progesterone antagonist, Selective Estrogen Receptor Modulators (SERM), Selective Progesterone Receptor Modulators (SPRM), Aromatase inhibitors, Antiangiogenic factors like Rapamycin, Statins and Estrogen receptor Beta ligands are the newer drugs in pipeline.

Mullerian anomaly and endometriosis

Mullerian anomalies are associated with endometriosis. Incidence is more when there is outlet obstruction ($p<0.001$) [17]. In non-obstructive Mullerian anomaly also have endometriosis exist but with lower incidence and severity compared to women without Mullerian anomalies ($p>0.05$) [18]. Girls with early onset dysmenorrhea have to be investigated for Mullerian anomaly and endometriosis. USG /MRI are the mode of diagnosis and treatment is by laparoscopy.

Tertiary prevention

It includes prevention and treatment of complications like recurrence and pain.

Risk factors for recurrence

Table 1: Risk factors for recurrence

Low Risk	High Risk
r AFS score < 70	r AFS score > 70
Unilateral lesions	**Bilateral mass**
OCP/progestins	Family history
Post op medication for a long period	No post op medical management
Older age	Young age
Complete surgery, Endometrial ablation	Suboptimal surgery
Pregnancy	H/O OI drugs for IUI and not IVF
BMI<23	BMI>23

Incidence of recurrence

Reappearance of pain after one year of surgery is 45%. Reappearance of the disease by USG or clinical examination is 9-15%. After conservative surgery and 6 months of medical treatment, 1 year later 26% had pain recurrence and 8% had detectable disease. To prevent recurrence, one should aim at radical clearance of all endometriotic lesions. However smaller atypical lesions are overlooked, leading to persistence of the disease. It is ideal to do the surgery during follicular phase. Drainage of endometriomas (USG or laparoscopy guided) has 80-100% recurrence within 6 months.

Cyst drainage with cyst wall destruction had 3 times more recurrence than cystectomy (18.4 vs 6.4). Resection of recto vaginal nodule gives good pain relief in DIE. Radical surgery is mandatory to prevent recurrence, in patients who have completed family. The reported recurrence rate was high, estimated as 21.5% at 2 years and 40-50% at 5years [19].

During endometriosis surgery, extensive procedure may reduce the ovarian reserve and incomplete surgery may lead to recurrence.

Post-operative medical suppression is needed. Medical treatment increases the apoptotic index, decreases the proliferative activity of the cells and estrogen biosynthesis by the ovary. Biosynthesis of estrogen in the peripheral tissue and endometriotic implants which is controlled by aromatase is not inhibited by routine drugs. But aromatase activity is high in endometrium of endometriotic patients, endometriotic lesions, fat, bone and adrenal tissue. Hence aromatase inhibitors are used.

Post-operative medical management should be instituted to minimize risk of recurrence. Hence it should be continued for a long time which extends beyond pain free period in severe disease after conservative surgery.

Commonly used drugs for post operative suppression of recurrence are GnRH analogues, Dienogest, LNG-IUS and anti-angiogenic drugs.

How long to follow up?

Data from recent large case series have documented cumulative rate of recurrences as high as 30-40% at the end of 2-3 years follow up. 2 years after surgery might be the minimum follow-up period. Many are lost to follow-up if the timing is prolonged beyond 2-3 years. Ideal follow-up is life-long or at least up to menopause [20].

Recurrent Endometrioma and Pain

Recommendation:

Surgery+ Long term suppression

- Only suppression is not effective
- Definitive surgery - based on patient's requirements
- LUNA - Not effective for pain
- PSN - Effective but creates new long-term problems
- If there is unilateral endometrioma, salpingo - oophorectomy followed by LNG-IUS gives excellent relief
- Hysterectomy with/without bilateral salpingo-oophorectomy if family completed or persistence of severe pain. If ovaries are left behind the incidence of recurrence and redo surgeries are high [21].

Awareness about endometriosis

At present, there is no known way to prevent endometriosis. Enhanced awareness, followed by early diagnosis and management may slow or halt the natural progression of the disease. Reduce the long-term burden of its symptoms, including possibly the risk of central nervous system pain sensitization. Endometriosis has significant social, public health and economic implications. It can decrease quality of life due to severe pain, cause fatigue, depression, anxiety, school absenteeism, reduction in work capacity and infertility. Dyspareunia affects sexual health and marital relationship.

Addressing endometriosis will improve the sexual and reproductive health, quality of life and overall well-being. But currently there is no cure; treatment is usually aimed at controlling symptoms. Access to early diagnosis and effective treatment of endometriosis is important, but it is limited in many settings, including in low- and middle-income countries. There is a need for more research and awareness around the world to ensure effective prevention, early diagnosis, and improved management of the disease.

Conclusion

Endometriosis is an elusive disease with variable etiopathogenesis. Its starts from womb and ends in tomb of a women's life. Major components of endometriosis are pain and infertility. As per the advice of ASRM classification endometriosis is a chronic inflammatory disease which needs long term medical management. Surgery should be minimized. The prevention of endometriosis extends from primordial, primary, secondary to tertiary prevention. Patients who are high risk for endometriosis should undergo primordial and primary prevention even before the disease manifest. Young women with symptoms of endometriosis associated pelvic pain should be started on empirical therapy with progestins which comes under secondary prevention. Non-invasive diagnosis of endometriosis should be planned for these women and treatment should be started. Whenever there is presence of visible lesions with pain, medical management should be the first line except in women who want pregnancy. Other patients needing treatment only for pain can be offered medical management, failing which definitive surgical management can be offered. Life style modifications including exercise, diet should be advised. Proper long term post-operative suppression with medical management should be aimed at. Awareness program

regarding endometriosis and periodic follow up for high-risk patients should be advised. Ultimately, we cannot conquer endometriosis but control the symptoms, reduce recurrence and promote fertility.

Compliance with Ethical Standards

Conflict of interest: All the authors declare that they have no conflict of interest and they have not received any grant.

Human animal consent: This article does not contain any studies or animal subjects.

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