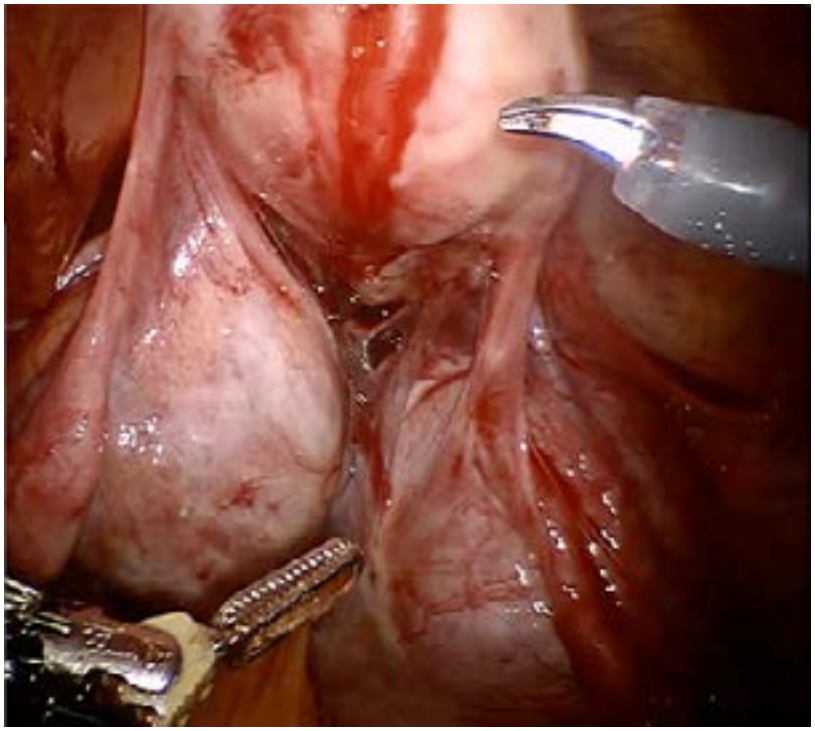
Endometriosis Update

Volume 2- July 2021

Expert Commentary:
Robotic Surgery in Endometriosis- Is there a future?



In this issue:

A publication of Endometriosis Society of India

EDITORS' NOTE

We are delighted to present the second edition of the Endometriosis Society of India's e-journal " Endometriosis Update". This issue covers "A Clinical review on Genetics in endometriosis" by Dr. Suruchi Pandey, St.Georges Hospital, London. Endometriosis has seven times higher incidence among patients with family history, which shows genetic background plays a major role.

Professor Rooma Sinha from Apollo Hospitals, provides expert commentary regarding the role of Robotics in Endometriosis. This article will give an insight regarding the role of robotics in advanced endometriotic surgery. Dr. Sonal Panchal, Radiologist from Ahmedabad, shares images of deep endometriosis which will help discover deep endometriosis in a non-invasive way especially through USG, so that the delay in diagnosis could be overcome and invasive procedures could be avoided for diagnosis.

Dienogest is a wonder molecule which is used in treatment of endometriosis, prevention of recurrence and treatment of recurrence. Dr. Shyam Desai provides an article regarding the clinical use of Dienogest. Dr. Saswathi Sanyal has written a journal scan on recent topics in endometriosis. Recently we've come to know that diets rich in anti-inflammatory agents can help us to control the symptoms of endometriosis whereas, pro-inflammatory diets will propagate the disease. An article contributed by Dr. P. Raghuvendra and Dr. Teena Dasi, from the National Institute of Nutrition, Hyderabad, regarding diet in endometriosis will throw light on the control of the disease. We are providing a video corner in which videos on endometriosis by the Senior laparoscopic surgeon Dr. Nutan Jain have been uploaded.

Dr. Kanthi Bansal and Dr. T. Ramani Devi provide tips for practice on the management of pain, infertility and adolescent endometriosis in the form of algorithmic patterns for easy understanding. Finally, the journal scan is written by Dr. Saswati Sanyal.

I'm sure we can improve our knowledge of endometriosis through this journal. This will enlighten all practitioners, but especially those who have special interest in endometriosis management.

Please take a minute to fill in the membership form at the end of the issue- join our community of members and stay abreast of the developments taking place in the field of endometriosis management.

Dr. T. Ramani Devi, MD, DGO, FICS, FICOG
Consultant at Ramakrishna Medical Centre LLP & Janani Fertility Centre. National Vice President FOGSI 2020. Director, Ramakrishna Medical Centre LLP & Janani Fertility Centre, Trichy
Internal Editorial board member of Bangladesh Journal of Fertility and Sterility. Editorial board member of International Journal of Human Reproduction

Dr. Rooma Sinha, MD, MNAMS, FICOG
Honorary Professor Gynecology, Apollo Hospitals
Associate Professor, Macquarie University, Australia
Director Fellowship program in MARS
Laparoscopic & Robotic Surgeon Apollo hospitals, Hyderabad, India.

Contact us:
- http://endosocind.org
- endosocindia@gmail.com

Editorial Board

Managing Editors

Dr. P. Das Mahapatra MD, FRCOG, FRCS
One of the most experienced Endoscopic Surgeon and Director of Spectrum Clinic and Endoscopy Research Institute, Kolkata. Secretary General of Endometriosis Society of India.

Dr. Pradeep Mitra, MD DGO MNAMS FICS FICOG FACS (USA)
Director: Dr. Pranthosh Mitra Memorial Clinic, Kolkata
Founder Deputy Secretary General: Endometriosis society India
Zonal Coordinator –FOGSI; Founder: PCO Health club, Kolkata

Editorial Board

Dr. Shyam Desai MD DGO DFP MNAMS FCPS
Consultant Port Trust Hospital
Director International Relations SAFOG
Honorary Professor, Wadia Hospital
Chairman Maternal Health AOFOG 2009 to 2013
Vice President SAFOG 2011 to 2016

Dr Rahul Krishnaji Gajbhiye, MBBS, PhD
Scientist & Head Clinical Research Lab (CRL) & Andrology Clinic
DBT Welcome Trust India Alliance Clinical and Public Health
Intermediate Fellow, ICMR National Institute for Research in Reproductive Health
International Ambassador - World Endometriosis Society
Research Advisor - Endometriosis Society India

Dr. Renu Mishra MBBS MS MNAMS
Senior Consultant, Endoscopic surgery & IVF
Sitaram Bhatia Institute of Science & Research
Miracles Fertility & IVF, Gurgaon
Former Additional Professor, All India Institute of Medical Sciences.

Dr Saswati Sanyal Choudhury MD FICMCH-FICOG FIAOG
Professor Dept of O&G. Gauhati Medical College
Vice President ISOPARB
President ISOPARB Assam chapter
Chairperson Medical Education Committee FOGSI.

Dr. Asha Rao MD DGO FICOG
Chairperson Endometriosis Committee, FOGSI 2020-2022.
Director of RAO HOSPITAL & C.A.R.E - Coimbatore
Director Post-Doctoral Fellowship in Reproductive Medicine & Endo gynecology (Affiliated Dr MGR Medical University, Chennai)

Dr. Oby Nagar, MS FMAS FICOG DIPLOMA
Professor and Unit Head SMS Medical College, Jaipur
President - Jaipur Menopause Society 2019-2020
Founder Member – Rajasthan Association of Minimal Access Surgeons.

Dr. SNEHASIKTA SWARNAKAR, Ph.D., Professor AcSIR
Senior Principal Scientist CSIR-Indian Institute of Chemical Biology, Kolkata.
Divisional Head - Infectious Diseases & Immunology CSIR-IICB.
Elected fellow -National Academy of Sciences & WB Academy of Science and Technology. National Bioscience Award for Career Development in 2007.
Full Bright Fellow in 2013-2014.

Dr. Partha Bhattacharya, MBBS, DGO, MS (O&G), MRCOG
Member of Executive Body, Endometriosis Society India
Consultant Obstetrician & Gynaecologist
West Bengal ESI Medical Services
RSV Hospital, Kolkata

Clinical Review

The Genetics of Endometriosis

Dr Shahi Ghani MBBS, BSc, MSc, DHMSA, MSc in Virology, Single Cell Molecular Imaging and Gene Editing.

Dr. Suruchi Pandey. MRCOG DRCOG DFFP PGDipLATHE, Consultant Gynaecologist, St. Georges Hospital, London, UK.

Introduction

Endometriosis affects 10% of the women of the reproductive age group (1). Endometriosis has a significant impact on quality of life of these women who not only have to soldier through heavy menstrual bleeding and pelvic pain but also sub-fertility and distressing bladder and bowel symptoms that come with endometriosis. The gold standard method for diagnosis involves laparoscopy and excision of the endometriotic tissue, however, due to the invasive nature of this, many patients choose not to have surgery (1). Endometriosis can affect pelvic organs like bowel, bladder, fallopian tubes and ovaries and extra-pelvic organs like diaphragm and even lungs. Endometriosis can present as mild peritoneal disease or deep infiltrating disease.

The precise aetiology of this condition is not widely understood due to the heterogeneity of the condition, however, it is now becoming clear that the disease is caused due to a combination of genetic and epigenetic factors. Oestrogen levels, inflammation, metaplasia and epithelial proliferation have all been hypothesised as contributary factors to this condition, in addition to genetics, which contributes approximately 50% of the variation in risk of developing the disease (2).Genes associated with endometriosis are involved with a number of functions which provide insight into the multifactorial pathophysiology of endometriosis involving immune mechanisms, chromatin-remodelling complexes, cell adhesion, angiogenesis as well as effects on biochemical signalling (1).

High-throughput genotyping technology and DNA sequencing have enabled us to identify the genetic factors for endometriosis. A meta-analysis of 17, 045 endometriosis cases identified 14 genomic regions associated with the risk of endometriosis (see Figure 1) with the results being supported from multiple studies (3).

Early work in the determining genetics of endometriosis involved family studies to determine heritability of the condition; as well as whole exome sequencing of endometrial and ectopic tissue which provided insight into the the genes where somatic mutations were identified (1). amilial studies have indicated that if an individual has a diagnosis of endometriosis, between 6-9% will also have a first degree relative with the condition(1). One study which compared the risk of first degree relatives of developing endometriosis in those with surgically confirmed endometriosis compared with control groups, it was found in 10.2% and 0.7% respectively (1).

Familial studies have indicated that if an individual has a diagnosis of endometriosis, between 6-9% will also have a first degree relative with the condition(1). One study which compared the risk of first degree relatives of developing endometriosis in those with surgically confirmed endometriosis compared with control groups, it was found in 10.2% and 0.7% respectively (1). Twin studies have also shown congruence in disease severity between monozygotic twins suggesting the role of genetic mutations in the stage of disease (1).

In the 'genomic era' genome wide association studies (GWAS) have the ability to use computational modelling to analyse entire genomes of affected patient groups compared to healthy patients to identify possible single nucleotide polymorphisms (SNPs) and candidate genes on a much larger scale than previously available due to the ability to analyse the regions in between genes which may further provide insight into the causative factors of this condition and potential biomarkers to aid diagnosis.

This review is intended to aid clinicians through the complex maze of GWAS to try and provide some tips on how to evaluate and draw conclusions from these studies, as well as discuss some of the key findings which have happened over the last few years. It is important to note, however, that the genes and mutations discussed below are simply an evaluation of genes associated with the condition, and as of yet, it is not possible to use genetic testing from GWAS to establish a diagnosis.

Study types and cohorts

A number of genome wide association studies have been conducted across the world using biobanks and information from private genetic testing services such as '23andme' (2, 4-6) which has widened the amount of data that is available regarding these conditions. Clinicians must exercise a degree of scepticism before drawing any conclusion from GWAS, paying particular attention to study design, ethnicity of participants and phenotypic variation of the condition. Many of these studies discuss genes and determine statistically significant mutations associated with endometriosis from their population cohorts, however, when replicating these studies other groups have been unable to achieve significant results. This highlights the variation in genetic mutations which have the potential to cause the condition, therefore meaning that there is no single set of mutations which result in a diagnosis, but rather mutations which are highly suggestive of particular phenotypes within the condition.

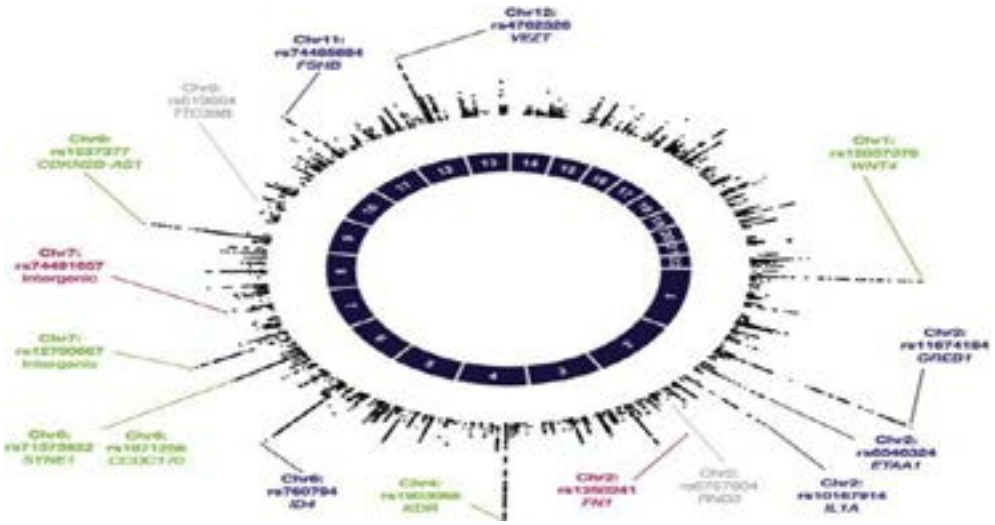


Figure 1 *Circle plot showing chromosome number (dark blue, inner circle) and results of association between individual SNPs and endometriosis plotted as −log10 (P values) (black, outer circle). Each genome-wide significant region identified in multiple published studies. The chromosome, independent index (most significantly associated) SNP(s) in each region, and the nearby biological candidate genes in each region were annotated (Green - significant association in all cases and in moderate–severe (Grade B) endometriosis cases; Blue - significant association in all cases; Red - significant association in Grade B endometriosis cases only). The significant associations identified in independent studies are shown in grey colour (Adapted from Fung et al Best Practice & Research Clinical Obstetrics and Gynaecology 50 (2018) 61-71)(3)*

Study design

Case-control studies are often used where participants are defined as a 'case' based on inclusion criteria. In patients identified from hospital visits, it is likely the patient will require a clinic appointment with a specialist who may undertake a full history of symptoms, blood tests, a physical exam and imaging studies to consider a positive diagnosis of endometriosis (7), if not by laparoscopic diagnosis (2). In contrast, genetic testing services are unlikely to perform any form of investigations and may rely more qualitative analysis using retrospective symptom questionnaires (6). Studies using a case-control design may also differ in their identification of control participants.

In one meta-analysis of seven GWAS related to endometriosis, the control groups varied from women with diseases other than endometriosis, a negative diagnosis following surgery, a negative diagnosis following magnetic resonance imaging (MRI) or women who had no evidence of endometriosis diagnosis however did not report any negative diagnostic criteria (2). When studies that differ so considerably in their methodology are pooled for the purpose of meta-analysis, it can affect the power of the study as well as the likelihood of obtaining a significant result (2).

Ethnicity

Many of the GWAS on endometriosis have been performed on cohorts of European ethnicity (2), therefore potentially missing loci of variants more common in other ethnicities due to different allelic frequency patterns among various groups. Two studies which included only Asian descendants, it was possible to identify 5 SNPs that were strongly associated with endometriosis, however the same SNPs not found in a GWAS of participants from Europe, Oceania and America. participants(2). Rather than contradicting the evidence of the previous study, this may give insight into the heterogeneity of presentation amongst ethnic groups.

Disease variation

Endometriosis can be viewed as a dynamic process advancing from stage I to stage IV (see Table 1) which requires changes in the genetic environment as the disease progresses. This is seen through the variation in genes associated with stage I/II compared with stage III/IV of the condition, whereby most loci are active in stage III/IV of the disease (6). However, the disease is not only a linear progression, it also has phenotypic variation within stages leading to subtypes of the condition with predominantly dysmenorrhoea related symptoms, fertility issues or pelvic pain related symptoms.

Therefore, it is pertinent to consider the stage of the condition as well the predominant symptom a patient may be experiencing when looking at GWAS to find potential mutations. A patient with fertility issues thought to be the result of endometriosis may have a completely different set of mutations within their genome compared with a patient with predominantly pain related symptoms.

Candidate genes

A number of candidate genes have been identified through genetic association studies performed on samples of ectopic tissue and endometrial tissue as well as GWAS which gives insight into underlying processes that are affected in this condition (see Figure 1). These include alterations to genes involved in tumour suppression, detoxification, inflammation, angiogenesis, embryonic development and hormonal signalling (1).

Tumour suppression

Individuals with endometriosis have been found to have significantly higher proportions of chromosome 17 aneuploidy compared with healthy women which is of interest as genomic instability involving this chromosome is known to drive a number of different forms of cancer (1). The gene most implicated on this chromosome is TP53, a tumour suppressor gene which encodes p53, a protein well described for its role in driving cells to apoptosis as well as DNA repair.

There are a number of polymorphisms of this gene which have been implicated in endometriosis , particularly TP53 Arg72Pro which has been linked with endometriosis amongst Asian populations; as well as the C allele of the p53 codon which has also been identified as a potential biomarker for endometriosis (1).

Detoxification

A number of CYP genes which are responsible for the detoxification of exogenous metabolites through phase I and phase II have also been implicated in endometriosis. It is thought that this is achieved through altered metabolism of exogenous substances leading to intermediate compounds that cause false cellular signalling (1). This has particularly been noted in Asian populations where polymorphisms in CYP1A1 were associated with an increased disease risk; interestingly however this association was not seen amongst Caucasians, where the implicated gene was thought to be CYP19, reflecting the variance in genetic profile of the condition in different ethnic groups (1).

Exposure to agents which disrupt endocrine function also have been identified to have an impact on genetic susceptibility to endometriosis due to the effects of these chemicals on gene expression and physiological processes. Organochlorides can disrupt endocrine function through acting similarly to oestrogens, causing steroid hydroxylation, thus affecting fertility as well as susceptibility to cancers (1).

Inflammation and immunity

Various genes encoding interleukins and have been identified via GWAS and genetic association studies to be involved in endometriosis, most notably IL-1 and IL-16 (1, 2). This is thought to occur due to the role of both of these genes in producing pro-inflammatory cytokines causing recruitment of immune cells such as CD4 T lymphocytes, monocytes and eosinophils. Mutations in IL-6 (-634C/G) has been suggested to work synergistically with a mutation in ICAM-1 (469 K/E) to promote the development of endometriosis in Japanese populations, however a study of over 200 women in Brazil found that this mutation had no significant association with development of endometriosis, suggesting that further work is required to understand the role of IL-6 and ICAM-1 in endometriosis (1)

Samples of ectopic tissue from individuals with endometriosis have also been found to express COX2 more avidly than endometrial samples from unaffected individuals, with the number of mRNA replicates for COX2 in ectopic samples reaching up to 5 times that in unaffected individuals (1). This has led to the hypothesis that altered COX-2 activation in the presence of abnormal prostaglandin production may be a key factor in disease severity and progression to more severe forms of the disease (1).

PTPN22 is a gene located on chromosome 1p13.3 encoding Lyp, a downregulator of T-cell activation. A case-control study of Brazilian women identified that polymorphisms in this gene were associated with advanced disease stages of endometriosis, (1).

A systematic review of GWAS into endometriosis identified two SNPs downstream of NFE2L3, a transcription factor involved in inflammation, carcinogenesis and regulation of cell differentiation (2). The exact role of the gene in endometriosis is still unclear however the mutations have been found in three studies and associated with stage III and IV of the condition suggesting it may play a role progression to more severe forms of the condition (1, 2, 5).

Angiogenesis and embryonic development

A few genes involved in angiogenic pathways have been identified to have a role in endometriosis (1, 2). FGF2 is a gene encoding Fibroblast growth factor 2 which is involved in tissue repair, cell grown and morphogenesis. Mutations in this gene have been associated with adenomyosis and endometriosis in Chinese cohorts, however it is still unclear if this presence of mutations in this gene is a marker of increased susceptibility to these conditions (1, 4).
Mutations to the gene encoding VEGF has also been strongly associated with the development of endometriosis as well as a number of gynaecological cancers (1, 2). Confusingly, however, depending on the location of polymorphisms in VEG, as well as the ethnic groups involved in studies, this may either be protective or contributory to development of endometriosis (1) therefore further studies are required to identify any interactions with other regulatory proteins or promoter regions which may be leading to these conflicting data.

Genes involved in embryonic development have also associated with endometriosis, most notably WNT4 which plays an important role in female sexual development, angiogenesis, postnatal uterine development and progesterone signalling (1, 2, 4, 6, 8).

Mutations in WNT4 alter signalling during development and has a role in a number of other gynaecological pain related conditions including uterine leiomyoma and pelvic organ prolapse (2, 4, 8). WNT4 related mutations have further been associated with CDC42 which encodes a GTPase which may act as an enhancer to WTN4 signalling (8).

Mutations to FN1 have been discussed in GWAS related to endometriosis (1, 2). This gene encodes fibronectin, a glycoprotein involved in cell migration, embryogenesis, coagulation and wound healing (2). Samples of ectopic endometrial tissue were found to contain higher levels of fibronectin compared with endometrial tissue within the uterus however there have been conflicting results on its association with endometriosis between studies (2). In one study no association was found between mutations in FN1 and endometriosis, however, two studies have suggested its involvement in stage I/II disease as well as endometriomas (2).

Hormonal signalling

Hormones are thought to be an important factor in the development and progression of endometriosis. This is most often attributed to oestrogen, however, there have been a number of GWAS which have identified mutations in other hormones which have been thought to play a role in endometriosis.

Multiple GWAS have shown that genes altering the function of FSH are seen in individuals with endometriosis, these include mutations to the beta subunit FSHB (2, 4) as well as the receptor FSHR (1). It is likely that mutations to FSHR leads to altered plasma concentrations of FSH; which then can have consequences in oestrogen levels.

It has not been possible to prove that mutations in FSHR increases likelihood of developing endometriosis, however it has been identified as a factor which contributes towards disease progression as well as infertility (1). Mutations in FSHB have been identified via a number of GWAS to have a role in endometriosis, as well as other gynaecological conditions including uterine leiomyoma and pelvic organ prolapse (4-6, 8).

Furthermore, two genes have been identified through GWAS that are thought to affect oestrogen signalling; these are ESR1 and GREB1 (1, 2, 5, 6). Polymorphisms in ESR1 affect the alpha subunit of the oestrogen receptor, thereby casing changes to proliferation of the endometrium in individuals with this mutation, however, there have been conflicting results regarding mutations to this gene (1).

Some studies have suggested up to a 4-fold higher risk of endometriosis, whilst others have shown no association at all; however recent GWAS meta-analysis into endometriosis suggests that these conflicting results may be due to the fact that certain polymorphisms in ESR1 may also act to protect individuals from susceptibility to endometriosis (1). Both GREB1 and ESR1 have also been associated with increased risk of leiomyoma development (2, 4).

Association to other conditions

Recent evidence suggests that there are shared mutations between endometriosis and other gynaecological conditions such as uterine leiomyoma(2, 4) and pelvic organ prolapse (POP) (8). Mutations to GREB1, FN1 and FSHB have been suggested to play a role in leiomyoma, however, Mutations to WNT4 have been found in both leiomyoma and POP (2, 4, 5, 8). Further work is needed to identify whether this is suggestive that these conditions are different phenotypes of the same underlying condition or separate discrete conditions.

One study has used LD score regression to identify association of endometriosis with other conditions identified through GWAS (see Figure 2) (6). These findings suggest there is high correlation between endometriosis and fibroids, leiomyoma of uterus, heavy menstrual bleeding, back pain, osteoarthritis and regional pain syndromes suggesting that there may be a shared underlying process between these conditions (6).

Summary

There have been a number of genes which have been identified via genetic association studies as well as genome wide association studies to have a role in endometriosis. As research in this work continues to grow and larger datasets are being evaluated, clinicians must consider the study design as well as the participants involved in GWAS before considering the relevance of any findings for their own population cohort. There is much heterogeneity in this condition and it is still too early to be able to identify any possible biomarkers or diagnostic tools which may be used in every day practice. However, through analysis of common gene mutations seen amongst different conditions, it is possible to piece together possible cellular and hormonal signalling mechanisms which may play in important role in the pathogenesis and aetiology of these conditions, such that we may produce novel therapeutic targets.

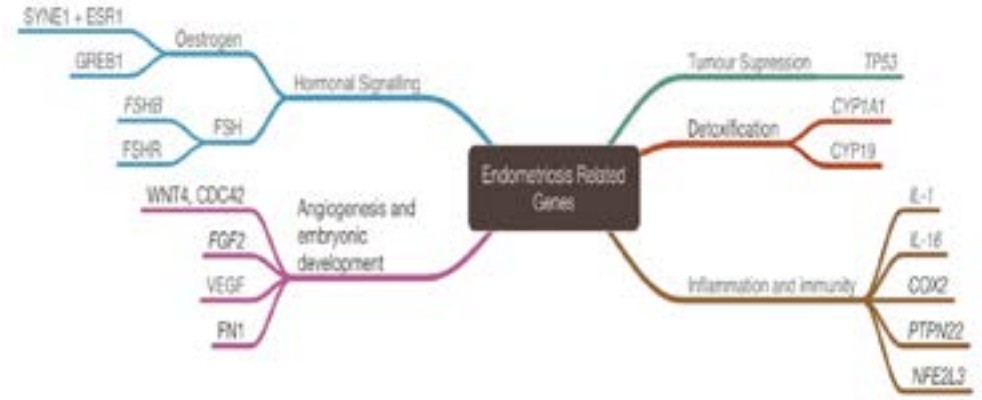


Figure 2 *– Mutations and proposed mechanisms of action of genes associated with endometriosis*

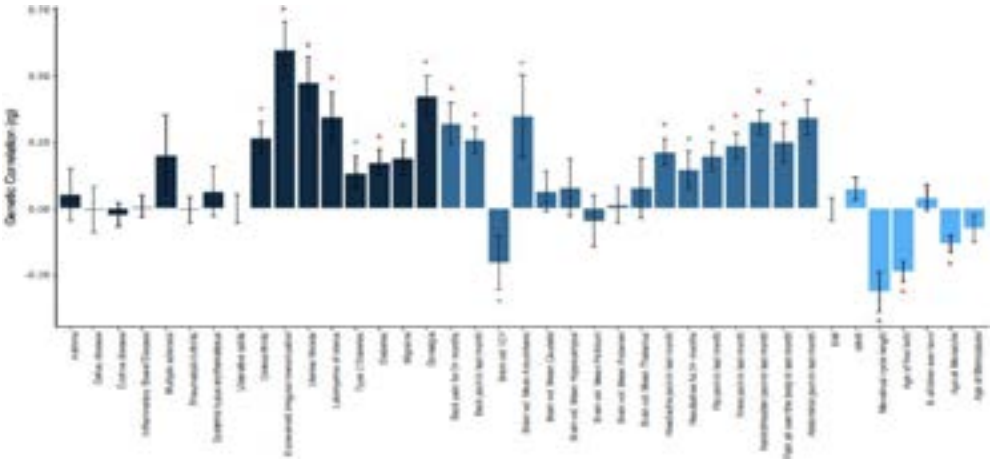


Figure 3 *- LD Score regression results for genetic enrichment between endometriosis and reproductive traits, anthropometric traits, pain-related symptomatology, and reproductive, autoimmune, metabolic and inflammatory conditions. The y-axis shows the genetic correlation (rg) between each condition and endometriosis with standard error bars. The x-axis shows the results per trait/condition. A red star denotes significant genetic enrichment after multiple-testing correction (p<l.28×10− 3) and a green star nominal association (p<0.05). (Adapted from Nilufer et al bioRxiv. 2018:406967) (6).*

References

1. Vassilopoulou L, Matalliotakis M, Zervou MI, Matalliotaki C, Krithinakis K, Matalliotakis I, et al. Defining the genetic profile of endometriosis. Experimental and therapeutic medicine. 2019;17(5):3267-81.
2. Cardoso JV, Perini JA, Machado DE, Pinto R, Medeiros R. Systematic review of genome-wide association studies on susceptibility to endometriosis. Eur J Obstet Gynecol Reprod Biol. 2020;255:74-82.
3. Fung JN, Montgomery GW. Genetics of endometriosis: State of the art on genetic risk factors for endometriosis. Best Pract Res Clin Obstet Gynaecol. 2018;50:61-71.
4. Gallagher CS, Mäkinen N, Harris HR, Rahmioglu N, Uimari O, Cook JP, et al. Genome-wide association and epidemiological analyses reveal common genetic origins between uterine leiomyomata and endometriosis. Nat Commun. 2019;10(1):4857.
5. Galarneau G, Fontanillas P, Clementi C, Hu-Seliger T, Parfitt D-E, Tung JY, et al. Genome-wide association studies on endometriosis and endometriosis-related infertility. BioRxiv. 2018:401448.
6. Nilufer R, Karina B, Paraskevi C, Rebecca D, Genevieve G, Ayush G, et al. Large-scale genome-wide association meta-analysis of endometriosis reveals 13 novel loci and genetically-associated comorbidity with other pain conditions. bioRxiv. 2018:406967.
7. Uno S, Zembutsu H, Hirasawa A, Takahashi A, Kubo M, Akahane T, et al. A genome-wide association study identifies genetic variants in the CDKN2BAS locus associated with endometriosis in Japanese. Nat Genet. 2010;42(8):707-10.
8.Olafsdottir T, Thorleifsson G, Sulem P, Stefansson OA, Medek H, Olafsson K, et al. Genome-wide association identifies seven loci for pelvic organ prolapse in Iceland and the UK Biobank. Commun Biol. 2020;3(1):129.

Expert Commentary

Robotic Surgery in Endometriosis- Is there a future?

Dr. Rooma Sinha
Senior Consultant Gynecologist, Laparoscopic & Robotic Surgeon. Honorary Professor, Apollo Hospital Education and Research Foundation.
Conjoint Associate Professor, Macquarie University Sydney, Australia.
Distinguished Clinician, Apollo Hospitals
Visiting Professor AIIMS Rishikesh
Mentor-Minimal Access & Robotic Fellowship (Apollo), FOGSI Endoscopy (Basic & Advance)
Apollo Health City, Hyderabad, INDIA

Dr. Girija Shankar Mohanty
Fellow, Minimal Access & Robotic Surgery
Department of Gynecology
Apollo Hospitals, Hyderabad

Endometriosis is a benign chronic inflammatory condition which presents as chronic pelvic pain or infertility. It is characterised by the presence and growth of ectopic dysfunction endometrial stroma and/or glands which is associated with reactive fibrosis and smooth muscle metaplasia found outside the uterus and affects approximately 11% of reproductive aged women (1).

Currently both medical and surgical treatment is used to manage endometriosis but persistence of disease and recurrence is a problem which both patients and physicians have to deal with equally. Surgical excision by laparoscopy of all visible endometriotic lesions is considered to be gold standard in treatment of endometriosis (2). However, surgery in advanced endometriosis can be a challenge even for experienced laparoscopic surgeons due to technical difficulties such as the surgeon's dexterity and visualisation of abnormal lesions. The same technical difficulties can be implicated in major complications (bowel injury, bladder or ureteric injury). Endometriosis Surgery is technically challenging mainly because of the occlusive nature of the disease that obliterates the surgical planes. Advanced technology of computer assisted surgery (robotic surgery) is now being increasingly evaluated for its role in surgery to circumvent some of these critical challenges of laparoscopy. Since 2005 when FDA approved the use of DaVinci surgical platform for gynaecological surgery the adoption of this technology in the field of benign gynaecology has been tremendous.

Robotics for endometriosis - A Game changer in three areas

1. Visualisation of disease especially for early and peritoneal lesions
2. The surgical precision in doing endometriosis & endometrioma surgery
3. Resection of deep infiltrating endometriosis

1. Visualization of endometriosis:

Early lesions are picked up with the help of detailed visual inspection of the pelvic cavity. Viewing the cavity through the advanced 3D console with stereoscopic ten times magnified vision of the robotic platform gives an edge in picking up early lesions. Even today visual diagnosis remains the key as imaging modalities like ultrasound or MRI have limited value. Good vision can ensure complete and detailed surgery in cases of endometriosis.(3) Compared to laparoscopic, robotic visualization resulted in detection of more confirmed lesions in all anatomic locations and different types of lesions, including the cul-de-sac (100 vs. 79%), atypical appearance (100 vs. 71.3%) and width <5 mm (100 vs. 62%). (4)

Robotic view of early endometriosis in the pelvis is shown in figures 1a, b, c, d. Such accurate diagnosis is especially important in adolescents. Early detection and intervention in young women will give a better quality of life and also cause lower damage of the ovarian tissue by a minimally invasive ablative surgery. Figure 2 shows vesicular lesions as well as the presence of focal adenomyosis of outer myometrium.

Incomplete resection is the main cause for persistence of pain after surgery. Addition of firefly technology in the robotic platform potentially helps in increasing the removal of invisible endometriosis. Indocyanine green (ICG) is a water-soluble dye that binds to plasma proteins. This is used with the infrared fluorescence imaging system integrated with the robotic platform. When injected the dye measures tissue perfusion and as endometriosis is associated with increased neovascularization, ICG turns these endometriotic lesions dark green, enabling their detection easy. Guan and colleagues found Firefly technology facilitated identification of endometriosis and were able to successfully perform single-site laparoscopic resection of advanced endometriosis nodules overlying the ureter and rectum with complete resolution of pelvic pain symptoms and excellent cosmetic results. (5,6) These lesions are often subtle and are not seen with the naked eye. Robotic surgery can be a game changer in identifying invisible small lesions and helps perform complete excision.

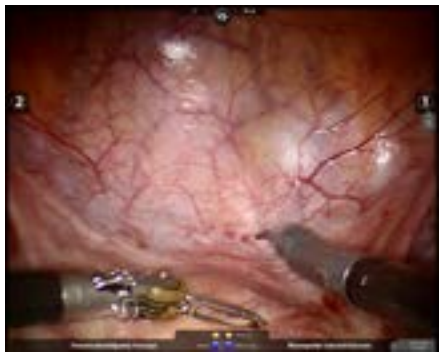


Fig. 1A: Early lesion in uterovesical fold of the peritoneum

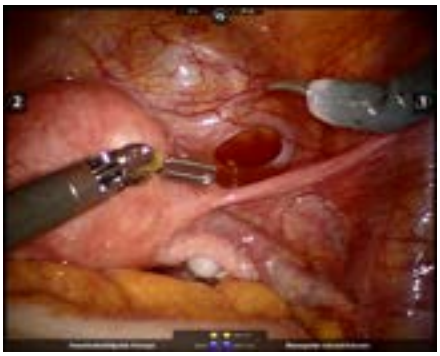


Fig 1B: AllenMasters Defect

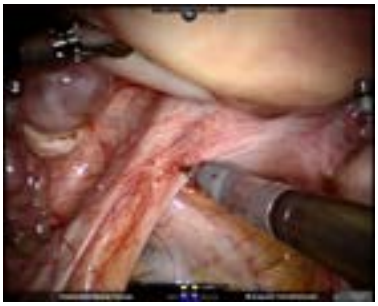


Fig 1C- Early lesion on left on utero-sacral ligament

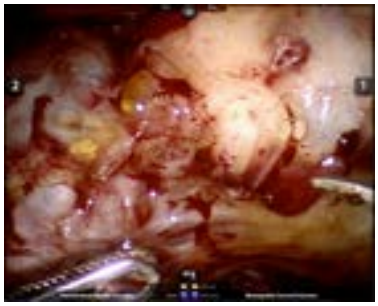


Fig 1D- Vesicular lesions on uterine surface

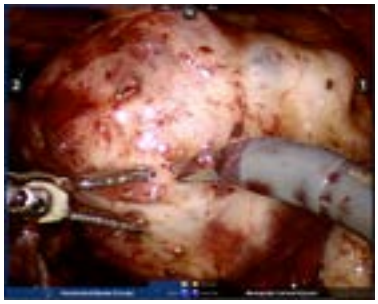


Fig 2- Focal adenomyotic lesions of outer myometrium

The surgical precision in doing endometriosis & endometrioma surgery

Endometriomas should be treated with cystectomy and not drainage and coagulation, as cystectomy reduces endometriosis-associated pain and recurrence (7).

Although cyst excision in endometriosis is a technique recommended by conventional laparoscopy which uses the force of traction and counter traction, the authors find this surgery to be more precise when articulated fine tip robotic instruments are used. Identifying the right planes of dissection is easily achieved.

When compared to laparoscopic traction-countertraction and rolling technique, the cyst wall excision in robotic assisted surgery proceeds step by step. Identification of the fibers between the cyst and ovarian tissue, precise dissection with short bursts of monopolar energy. This technique of cyst wall removal maintains the homeostasis thus avoiding the need for excessive bipolar coagulation for control of bleeding. We believe that such precise dissection has two advantages.

First, microsurgical principles using minute robotic instruments reduce postoperative adhesions Gomel et al advocated the value of robotic platform in performing microsurgery, so important for post-operative fertility outcome. (8)

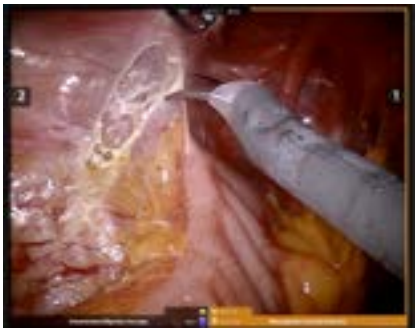


Fig 3: Step 1- Adheosiolysis of sigmoid from the lateral pelvic wall

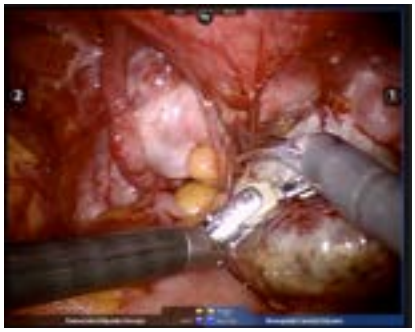


Fig 4: Step 2A- Releasing the endometrioma, the posterior surface of the uterus

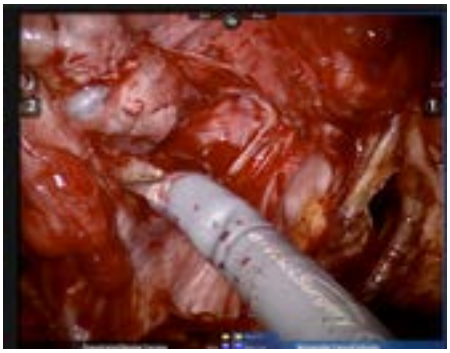


Fig 5: Step 2B- Releasing the left ovary from the ovarian fossa

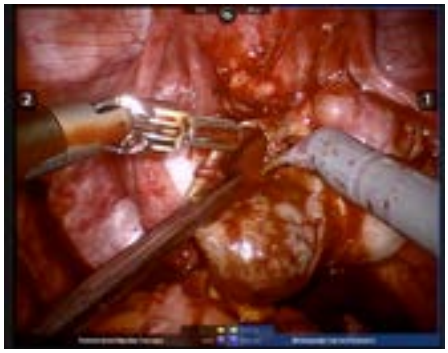


Fig 6: Step 3- Opening of the endometrioma and inspection of cyst wall

Second, there is a possibility that the loss of normal ovarian tissue is as minimal as possible, thus preserving the residual follicular reserve. However, this needs to be further evaluated by trials comparing laparoscopic and robotic techniques and long-term outcomes on future fertility. Figures (3,4,5,6,7) depict the various steps in performing ovarian cystectomy for endometrioma using robotic surgery.

Step 1- release of sigmoid from the lateral pelvic wall.

Step 2 a&b- Releasing the ovarian endometrioma from the posterior surface of the uterus and the ovarian fossa.

Step 3-opening the endometrioma, inspection of cyst lining.

Step 4- Ovarian cystectomy. Figure 8a shows severe pelvic adhesion among endometrioma, the rectum, and the pelvic peritoneum in the posterior cul-de sac and figure 8b depicts successfully performed endometriosis clearance using robotic surgery.

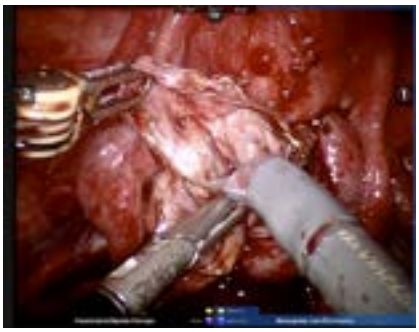


Fig 7: Step 4-Ovarian cystectomy in progress

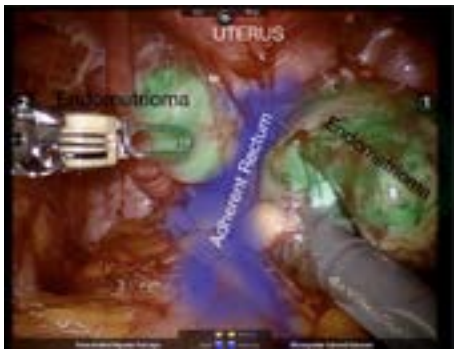


Fig 8A: Intial assessment. Bilateral adherent endometrioma with adhesion of rectum. Obliterated pouch of Douglas.

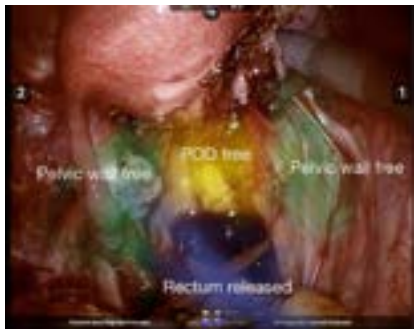


Fig 8B: After completion of surgery. Rectal adhesiolysis done with clear pouch of Douglas. Both ovaries free and both uterosacral ligaments seen.

3. Resection of Deep Infiltrating Endometriosis (DIE)

DIE is diagnosed when endometriosis occurs more than 5 mm deep into the peritoneum. Approximately 30-40% of patients with endometriosis have DIE (9). It commonly involves the recto vaginal space but is also seen in the urinary bladder, ureter and peritoneum. Dense adhesions are present due the infiltrative nature of DIE causing fibrosis and distortion of pelvic structures. As DIE lesions do not respond to medical therapy, complete radical excision and the restoration of normal anatomy are the most important points in managing such patients during surgery. To achieve this goal, advanced skills in dissecting the deep retroperitoneal space, isolating the ureter and the bowel, and suturing technique, are essential. However, those procedures are challenging using conventional laparoscopy and major complications such as bowel perforation and leakage are a reality.

Conversions to open surgery are often resorted to during such difficult dissections. Robotic surgery with all its advantages has the ability to help surgeons perform complex resections in such situations. Nezhat reported the first two cases of successful management for bowel endometriosis (segmental bowel resection and disc excision of the anterior rectal wall) without any complications by robotic surgery (10).
Following this, there are multiple reports of successful surgery for bowel endometriosis. Feasibility and safety of complete debulking of DIE even when segmental rectal resection, rectal shaving, or an ileocecectomy are required is reported with robotic surgery. It gives similar surgical outcomes and fewer complications than laparotomy; without the need for conversion. (11) (12) (13)
DIE of urinary tract can involve the ureter, bladder, and kidney in about 10% of endometriosis cases and can cause symptoms such as dysuria, haematuria, urinary frequency, and ureteral obstruction. Bladder is the most common site. Superficial endometriotic lesions can be treated with excision or fulguration but deep lesions infiltrating into the detrusor muscle or lumen of the ureter require resection and reanastomosis. These procedures need fine dissection and precise suturing. Convention laparoscopy presents many limitations in performing them. In our experience robotics has its advantages in such surgical interventions.

Various case series have reported robotic surgery being used for ureterolysis, ureteroneocystostomy, partial bladder resection compared surgical outcomes. Conventional laparoscopy and robotic surgery for bladder endometriosis showed similar surgical outcomes, including perioperative complications and recurrence rate. Robotic Surgery is safe and feasible for urinary tract endometriosis. (13,15–17)
Morelli et al suggested that Robotics is a better surgical method for the preservation of urinary and sexual function than laparotomy or laparoscopy. (14)

However, one must remember that surgery for deep infiltrating endometriosis, even with robotic assisted laparoscopy, is associated with significant morbidity so a multidisciplinary approach with a colorectal & urological surgeon should be kept in mind.

Discussion

The main advantage with the robotic platform is a shorter learning curve as compared to conventional laparoscopic surgery. The availability of simulations integrated with the console can help younger surgeons to hone their skills before starting surgery on patients. Even amongst the most skilled laparoscopic surgeons, there is a growing consensus that robotic assistance is probably most suited for endometriosis surgery and restoring the pelvic anatomy as a fertility enhancing surgery in advanced stages of endometriosis due to ease of instrument manipulation. The da Vinci Robotic Surgical System allows telestration. This helps the proctoring surgeons to write on a touch screen with a finger or an electronic pen.

This written instruction can be seen by both the console surgeon and the bedside staff. This feature helps the proctor to supervise a surgical step, guiding dissection in difficult planes and instructing when and how a particular step should be performed. The TilePro (Intuitive Surgical, Inc., Sunnyvale, CA) is another feature that allows for image and video input to the console. This can be used during surgery to have input of radiologic data (ultrasonography, computed tomography, or magnetic resonance imaging) during the early phase of the learning curve.

There is no doubt that computer assisted robotic platforms will enable more surgeons to do complex gynecological surgery and convert their open procedures to minimal invasive surgery in the years to come. The ability of the robotic platform to filter and reduce physiologic tremor and to transform surgeon's hand movements into more precise micro-movements can be a game changer in fertility enhancing surgeries especially in endometriosis.

Conclusion

Since the introduction of computer enhanced technology (robotics) to gynecological surgery in 2005, attention has been focused on its advantages and disadvantages. Most surgeons using this technology believe that it enables more surgeons to convert laparotomies to minimally invasive surgeries. Thus, the utility of the robotic platform lies in the management of severe cases of endometriosis. In the coming years this technology will find its place in clinical practice of minimally invasive gynecology, as a complimentary to the present conventional laparoscopy. As more surgeons are trained and utilize this enabling technology, one thing is certain; the number of minimally invasive surgeries for endometriosis will increase, reducing the incidence of open surgery in gynecology. Addressing the cost of equipment and surgeon credentialing will make this more acceptable to surgeons and patients alike.

Citations

1. Clement PB. The pathology of endometriosis: a survey of the many faces of a common disease emphasizing diagnostic pitfalls and unusual and newly appreciated aspects. Adv Anat Pathol. 2007 Jul;14(4):241–60.
2. Kochar kaur K, Allahbadia G, Singh M. Current Role of Surgery in Endometriosis; Indications and Progress. Surg Med Open Access J. 2018 May 11;1.
3. Nezhat C, Nezhat F, Nezhat C. Operative laparoscopy (minimally invasive surgery): state of the art. J Gynecol Surg. 1992;8(3):111–41.
4. Mosbrucker C, Somani A, Dulemba J. Visualization of endometriosis: comparative study of 3-dimensional robotic and 2-dimensional laparoscopic endoscopes. J Robot Surg. 2018 Mar;12(1):59–66.
5. Nezhat FR, Sirota I. Perioperative outcomes of robotic assisted laparoscopic surgery versus conventional laparoscopy surgery for advanced-stage endometriosis. JSLS. 2014 Dec;18(4):e2014.00094.
6. Guan X, Walsh T, Osial P, Xu D, Bridgett K. Robotic Single-Site Endometriosis Resection Using Firefly Technology. J Minim Invasive Gynecol. 2015 Nov 1;22(6):S118.
7. Hart RJ, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD004992.
8. Gomel V. The impact of microsurgery in gynecology. Clin Obstet Gynecol. 1980 Dec;23(4):1301–10.
9. Bellelis P, Dias JA, Podgaec S, Gonzales M, Baracat EC, Abrão MS. Epidemiological and clinical aspects of pelvic endometriosis–a case series. Rev Assoc Medica Bras 1992. 2010 Aug;56(4):467–71.
10. Nezhat C, Hajhosseini B, King LP. Robotic-Assisted Laparoscopic Treatment of Bowel, Bladder, and Ureteral Endometriosis. JSLS. 2011;15(3):387–92.
11. Lim PC, Kang E, Park DH. Robot-assisted total intracorporeal low anterior resection with primary anastomosis and radical dissection for treatment of stage IV endometriosis with bowel involvement: morbidity and its outcome. J Robot Surg. 2011 Dec;5(4):273–8.
12. Ercoli A, D'asta M, Fagotti A, Fanfani F, Romano F, Baldazzi G, et al. Robotic treatment of colorectal endometriosis: technique, feasibility and short-term results. Hum Reprod. 2012 Mar 1;27(3):722–6.
13. Collinet P, Leguevaque P, Neme RM, Cela V, Barton-Smith P, Hébert T, et al. Robot-assisted laparoscopy for deep infiltrating endometriosis: international multicentric retrospective study. Surg Endosc. 2014 Aug;28(8):2474–9.
14. Morelli L, Perutelli A, Palmeri M, Guadagni S, Mariniello MD, Di Franco G, et al. Robot-assisted surgery for the radical treatment of deep infiltrating endometriosis with colorectal involvement: short- and mid-term surgical and functional outcomes. Int J Colorectal Dis. 2016 Mar;31(3):643–52.
15. le Carpentier M, Merlot B, Bot Robin V, Rubod C, Collinet P. [Partial cystectomy for bladder endometriosis: Robotic assisted laparoscopy versus standard laparoscopy]. Gynecol Obstet Fertil. 2016 Jun;44(6):315–21.
16. Frick AC, Barakat EE, Stein RJ, Mora M, Falcone T. Robotic-assisted laparoscopic management of ureteral endometriosis. JSLS. 2011 Sep;15(3):396–9.
17. Giannini A, Pisaneschi S, Malacarne E, Cela V, Melfi F, Perutelli A, et al. Robotic Approach to Ureteral Endometriosis: Surgical Features and Perioperative Outcomes. Front Surg. 2018;5:51.

Update

Dienogest In The Treatment of Endometriosis

Dr. Shyam Desai MD DGO DFP MNAMS
FCPS. Consultant Port Trust Hospital. Director International Relations SAFOG. Honorary Professor, Wadia Hospital. Chairman Maternal Health AOFOG 2009 to 2013

Dr Gaurav S Desai MS FCPS
Assistant Professor, Seth GS Medical College and KEM Hospital. Joint assistant secretary Journal of Obgy of India. Managing Council member MOGS. IAGE Future award & AOFOG young Gynecologist award

Approximately 10% to 15% of women suffer from Endometriosis. Women of various ages may be afflicted but it is usually seen in the reproductive age group. The incidence is much higher in the infertile population amounting to about 30%. Approximately two thirds of women with Endometriosis are asymptomatic especially in the early stages of the disease. Of those who have symptoms Pelvic pain is the most common presenting symptom. The other symptoms seen include dysmenorrhea, dyspareunia, dyschezia, irregular bleeding, low back pain, hematuria and dysuria.The women with endometriosis often complain of fatigue.

The symptoms of endometriosis are due to various reasons. Endometriotic implants have impaired molecular and immunological functions.There is an exaggerated inflammatory response in the endometrial deposits which is associated with fibrous tissue formation and angiogenesis There is seen to be excess production of estrogen, and progesterone resistance. This leads to release of pro-inflammatory cytokines, prostaglandins and metalloproteinases and a failure of immune cells to suppress and clear the inflammatory response.

A constant supply of estrogen is crucial for the growth and persistence of the endometriotic implants, this estrogen comes from multiple sources. First, the endometrial implants have intrinsic aromatase activity, which leads to the conversion of cholesterol to estradiol. The endometrium is rich in PG-E2 receptors and activation of the PG receptor subtype EP-2 leads to activation of cyclic AMP, which increases the expression of key steroidogenic genes, and aromatase activity eventually leading to increased estradiol production. Along with intrinsic aromatase activity estradiol is also produced from the ovary and peripheral fat and this also reaches the sites of endometriosis.
The medical management of endometriosis is targeted towards controlling pain and suppression of the hormonally active endometriotic tissue to improve the quality of life without adverse effects of long term use of therapeutic agents.
A trial of non-steroidal anti-inflammatory drugs (NSAIDs) initially can be helpful in controlling the pain associated with dysmenorrhea.These along with Oral Contraceptives and Progestins are commonly used as first line agents in the treatment of endometriosis. Hormonal and non Hormonal therapies rely on suppression of the endometriotic implants.
The medications used for suppression of endometriosis such as GnRH analogues Danazol, OCs Progesterone derivatives,19 Nor Progesterone derivatives have proved effective in the short term but when administered over a period of time proved to be having drawbacks either with their tolerability or effectiveness and a large discontinuation rate has been observed.

For example even though Gn RH analogues have been proven to be very effective in reducing symptoms of endometriosis their profound estrogen suppression leads to severe menopausal symptoms and loss of BMD leading to the requirement of estrogen add back therapyIn addiction the duration of symptom relief after cessation of treatment is typically short decreasing the cost effectiveness.

Combined OC pills have been widely used for endometriosis treatment however they are not approved for this indication in many countries and their use is legally unsupported by solid clinical evidence. Danazol with its androgenic side effects such as alteration in lipid profile weight gain edema acne hirsutism and oily skin has limited acceptance. Progestins such as MedroxyProgesterone, can affect BMD in the long run and Levonorgestrel, and Norethisterone Acetate though potent can have severe progestogenic effects such as weight gain, acne and hirsutism.There remains therefore the need for a effective safe well tolerated medical therapy. Dienogest is a fourth-generation progestin of 19-nortestosterone derivative. It is almost completely absorbed when administered orally and is excreted completely in 24 hrs in the urine It has a relatively short half life of 10 hrs It has a high oral bioavailability of >90% offering potent progestogenic effects.

It is well tolerated with no androgenic, glucocorticoid or mineralocorticoid activity. binds to the progesterone receptor with high specificity, and produces a potent progestogenic effect related to the high circulating levels of the unbound molecule.

Dienogest is associated with relatively moderate inhibition of gonadotropin secretion, leading to a reduction in the endogenous production of estradiol. Hypoestrogenic, local endocrine environment, causing a decidualization of endometrial tissue followed by atrophy of the endometriotic lesions.As compared to the other Progestins It has high specificity for progesterone receptors and has less androgenic side effects with no affinity for estrogenic glucocorticoid or mineralocorticoid receptors.

Side effects of dienogest include Menstrual irregularities, Headache pain in the back tenderness in the breast hormonal changes induced hot flashes and mood fluctuations, acne, nausea vomiting and abdominal pain as well as weight gain. It has anti-androgenic activity like progesterone and hence has no effect on lipid and carbohydrate levels.
Thus Dienogest combines the advantages of 19 nor progestin derivatives and progesterone derivative classes. It creates a hypoestrogenic hypergestagenic environment locally. Continuous administration of Dienogest leads to decidualization and atrophy of the endometrial lesions. It also has anti-inflammatory, anti-angiogenic and anti-proliferative effects. Most importantly even after cessation of administration the symptom relief continues even as much as a year on. In a dose of 2mg or 4mg per day, dienogest has been shown to have a favorable profile for safety and efficacy, patients reported improvement in the endometriosis related symptoms and an overall improvement in quality of life.
It is in general well tolerate It is almost completely absorbed when administered orally and is excreted completely in 24 hrs in the urine It has a relatively short half life of 10 hrs.

Dienogest at 2 mg once daily is used as the optimal dose in the treatment of endometriosis for a duration of 12-24 weeks. Several trials are going on to assess the role of Dienogest pretreatment for endometriosis in comparison to gonadotropin releasing hormone agonist in patients of endometriosis undergoing IVF, with hypothetical results no significant difference was noted in no. of oocyte retrieved, pregnancy and miscarriage rate. Further studies and trials for validation of these results is still needed.

The optimum dose for safety and efficacy for the management of endometriosis has been based on a number of clinical studies with duration from 12 to 24 weeks. The studies have used doses of dienogest between one and 4 mg once daily. The 1 mg group usually had unsatisfactory results and bleeding patterns. Laparoscopic investigation showed that dienogest 2 mg and 4 mg significantly reduced endometriotic lesions as well as pain. The 2 mg and 4 mg dienogest doses were generally well tolerated and rates of discontinuations due to adverse events were low. Regular bleeding was experienced by nearly half the patients in the 2 mg and 4 mg group.

The separation of oestrogen levels with the 4 mg dose suggest that the 2 mg daily dose may offer lesser adverse effects on the bone mineral density.Hence a dose of 2 mg taken as the optimal dose.

The dose of dienogest in adolescents is particularly important as a higher dose usually leads to loss of bone mineral density and osteoporosis. The help of bones is especially important in growing adolescent girls. Even a dose of 2 mg for 52 week duration has been noted to cause significant bone mineral density decrease.Timely initiation and monitoring of diagnosis treatment is the crux of management of endometriosis in adolescent age group. In adolescents, surgical diagnosis should be avoided as far as possible in favor of clinical diagnosis. Treatment decisions should be made on an individual basis, using a risk–benefit approach that considers efficacy and safety.

Clinical trials of 12 to 24 weeks have shown that dienogest in a dose of 2mg/day provides effective pain relief equivalent to GnRH analogues a reduction of endometriotic lesions with a favorable safety and tolerability profile. A multicentre placebo controlled study carried out in Germany Italy and Ukraine showed extremely favorable findings for the use of Dienogest 2mg. Dienogest administered to patients with endometriosis Stages 1 to 4 showed that 90.5% completed the study There was a significant decrease in pelvic pain noted which lasted for 24 months after cessation of treatment Some patients had irregular bleeding, which improved with time.

To compare efficacy and safety of 1, 2 and 4 mg daily doses of Dienogest for endometriosis an open labelled randomized 24 week comparative trial was carried out by Kohler et al and reported in 2010. Dienogest at 2 and 4 mg was well tolerated with substantial symptom improvement with low rates of treatment discontinuation due to adverse effects The 1mg dose was discontinued because of insufficient bleeding control.
Several trials are going on to assess the role of Dienogest pretreatment for endometriosis in comparison to gonadotropin releasing hormone agonist in patients of endometriosis undergoing IVF, with hypothetical results no significant difference was noted in no. of oocyte retrieved, pregnancy and miscarriage rate. Further studies and trials for validation of these results is still needed

Conclusion
Dienogest provides complete ovulation inhibition at a daily dose of 2 mg. However, women taking dienogest as a treatment for endometriosis are advised to use nonhormonal methods of contraception. For those women who desire to conceive after dienogest therapy it is important to note that ovarian activity resumes rapidly (range 1–43 days) after cessation of dienogest. These observations support studies that describe a prompt return to fertility (eg, mean about 30 days).
Dienogest is contraindicated in patients with undiagnosed vaginal bleeding and during pregnancy and lactation. The woman's menstrual cycle resumes within two months of stopping the drug. Women with a cardiovascular disorder or a coagulation defect disorder or not advised to take dienogest. The group includes women at an older age, hypertension and smoking.Additional contraindication include diabetes, liver disease and hepatic tumours as well as cholestatic jaundice.

Evidence confirms that dienogest reduces endometriosis-associated pain, including pelvic pain, dysmenorrhea, dyspareunia, dysuria, and dyschezia. Before treatment initiation, patients should be counseled on what To expect with dienogest medication. They should be told that bleeding with dienogest 2 mg is not a sign of a lack of efficacy or recurrence of disease. There may be initial bleeding during the first few months, and bleeding/spotting with longer-term use. The Initial bleeding can be consistent and typically lasts for 8–10 days. Spotting me a car during long term treatment.
If the endometrium is found to be thin, a treatment break of 5–7 days to allow for the recovery of the atrophy of the endometrium, or a short-term application of 1 mg oral or transdermal estradiol (5–7 days) might be useful.

Patients with symptomatic DIE can be managed with dienogest 2 mg. Extragenital endometriosis of the urethra, bowel, or kidney, or fistulae in rectovaginal endometriosis Should be treated with surgery. Mood disturbances and depression with dienogest 2 mg requires regular monitoring at follow-up appointments as well as counselling and awareness. Possibly a treatment halt might be needed to reduce chances of more symptoms in patients on long-term treatment. In women with a previous history or a present diagnosis of clinical depression one should involve a psychiatrist and monitor treatment.

REFERENCES

Felice Petralgia et al. Reduced pelvic pain in women with endometriosis efficacy of long term dienogest treatment Arch Gynaecol Obstet 2012

Kohler G Faustmann TA Geringer C Seitz C Muck AO. A dose ranging study to determine the efficacy and safety of 1,2 and 4mg of Dienogest daily for endometriosis Int J Gynaecol Obstet 2011

Sasagawa S Shimizu Y Kami H Takeuchi T Mita S Imada K Kato S Mizuguchi K Dienogest is a selective progesterone receptor agonist in transactivation analysis with potent oral endometrial active its due to its efficient pharmacological profile. Steroids 2008 Feb

Momoeda M, Taketani Y. Randomized double-blind, multicentre, parallel-group dose–response study of dienogest in patients with endometriosis. Jpn Pharmacol Ther. 2007;35:769–783. Japanese.

Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. Am J Obstet Gynecol. 1992;166:740–745. [

Strowitzki T, Faustmann T, Gerlinger C, Seitz C. Dienogest in the treatment of endometriosis-associated pelvic pain: A 12-week, randomized, double-blind, placebo-controlled study. Eur J Obstet Gynecol Reprod Biol. 2010;151(2):193–198.

Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med. 2001;38(6):633–638.

Klipping C, Duijkers I, Faustmann T, Klein SF, Schuett B. Pharmacodynamic study of four oral dosages of dienogest. Fertil Steril. 2010;94 (Suppl 1):S181

Petraglia F, Hornung D, Seitz C, et al. Reduced pelvic pain in women with endometriosis: efficacy of long-term dienogest treatment. Arch Gynecol Obstet. 2011 June 17; [Epub ahead of print.]

Momoeda M, Harada T, Terakawa N, et al. Long-term use of dienogest for the treatment of endometriosis. J Obstet Gynaecol Res. 2009;35(6):1069–1076.

Dienogest 2 mg Daily in the Treatment of Adolescents with Clinically Suspected Endometriosis: The VISanne Study to Assess Safety in Adolescents Journal of Pediatric and Adolescent Gynecology Volume 30, Issue 5, October 2017, Pages 560-567.

IN THREATENED MISCARRIAGE &
RECURRENT PREGNANCY LOSS

TRUST THE EVIDENCE

DOSAGE IN **TM**

40 mg **STAT** followed by 20/30 mg per day until symptoms remit*

IF IT'S **ORALLY** EFFECTIVE, IT'S†

Duphaston®

Dydrogesterone Tablets IP 10 mg

BACKED BY **EVIDENCE**

DOSAGE IN **RPL**

10 mg **twice daily** until 20th week of pregnancy*

GLOBAL GUIDELINES BACK THE **WORLD'S NO. 1** PROGESTOGEN‡ §

1 MISCARRIAGE RANZCOG 2013

2 MISCARRIAGE FOGSI 2015

3 RPL ESHRE 2017

Duphaston® 60 YEARS§ OF DELIVERING INFINITE JOY

Pictures are for representation purpose only and not of actual patients.

TM: Threatened miscarriage. **RPL:** Recurrent pregnancy loss. **RANZCOG:** Royal Australian and New Zealand College of Obstetricians and Gynaecologists. **FOGSI:** Federation of Obstetrics & Gynaecological Societies of India. **ESHRE:** European Society of Human Reproduction and Embryology. † Schindler AE. Progestational effects of dydrogesterone *in vitro, in vivo* and on human endometrium. Maturitas. 2009;65 (1):S3-S11. * Prescribing information of Duphaston®. Version: 8.0, dated 20th November, 2019. ‡ Internal calculations based on Quintiles IMS database, IMS Health Analytics Link MAT03 2017. § Data on file.

References: 1. Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) 2013. http://www.ranzcog.edu.au/doc/progesterone-support-of-the-luteal-phase- and-early-pregnancy.html. Last accessed March 2014. **2.** Information available at http://www.fogsi.org/fogsi- gcpr/Last accessed September, 2016. **3.** Recurrent pregnancy loss.Guideline of the European Society of Human Reproduction and Embryology November 2017. ESHRE Early Pregnancy Guideline Development Group.

Abbreviated Prescribing Information: Dydrogesterone Tablets IP Duphaston® . LABEL CLAIM: Each film coated tablet contains: Dydrogesterone IP 10 mg, Excipients q.s. Colour: Titanium dioxide IP. **INDICATION:** Progesterone deficiencies: Treatment of dysmenorrhoea; Treatment of endometriosis; Treatment of secondary amenorrhoea; Treatment of irregular cycles; Treatment of dysfunctional uterine bleeding; Treatment of pre-menstrual syndrome; Treatment of threatened miscarriage; Treatment of habitual miscarriage; Treatment of infertility due to luteal insufficiency; Luteal support as part of an Assisted Reproductive Technology (ART) treatment and Hormone replacement therapy (To counteract the effects of unopposed oestrogen on the endometrium in hormone replacement therapy for women with disorders due to natural or surgical induced menopause with an intact uterus). **DOSAGE AND ADMINISTRATION:** Dysmenorrhoea: 10 or 20 mg dydrogesterone per day from day 5 to day 25 of the menstrual cycle. Endometriosis: 10 to 30 mg dydrogesterone per day from day 5 to day 25 of the cycle or continuously. Dysfunctional uterine bleeding: When treatment is started to arrest a bleeding episode, 20 or 30 mg dydrogesterone per day is to be given for up to 10 days. Secondary amenorrhoea: 10 or 20 mg dydrogesterone per day, to be given daily for 14 days during the second half of the theoretical menstrual cycle to produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen. Pre-menstrual syndrome: 10 mg dydrogesterone twice daily starting with the second half of the menstrual cycle until the first day of the next cycle. The starting day and the number of treatment days will depend on the individual cycle length. Irregular cycles: 10 or 20 mg dydrogesterone per day starting with the second half of the menstrual cycle until the first day of the next cycle. The starting day and the number of treatment days will depend on the individual cycle length. Threatened miscarriage: An initial dose of up to 40 mg dydrogesterone may be given followed by 20 or 30mg per day until symptoms remit. Habitual miscarriage: 10 mg dydrogesterone twice daily until the twentieth week of pregnancy. Infertility due to luteal insufficiency: 10 or 20 mg dydrogesterone daily starting with the second half of the menstrual cycle until the first day of the next cycle. Treatment should be maintained for at least three consecutive cycles. Luteal support as part of an Assisted Reproductive Technology (ART) treatment: 10 mg dydrogesterone three times a day (30 mg daily) starting at the day of oocyte retrieval and continuing for 10 weeks if pregnancy is confirmed. Hormone replacement therapy: Continuous sequential therapy: An estrogen is dosed continuously and one tablet of 10mg dydrogesterone is added for the last 14 days of every 28-day cycle, in a sequential manner. Cyclic therapy: When an estrogen is dosed cyclically with a treatment-free interval, usually 21 days on and 7 days off. One tablet of 10 mg dydrogesterone is added for the last 12 -14 days of estrogen therapy. **CONTRAINDICATIONS:** Known hypersensitivity to the active substance or to any of the excipients. Known or suspected progestogen dependent neoplasms (e.g. meningioma). Undiagnosed vaginal bleeding. Treatment for luteal support as part of an Assisted Reproductive Technology (ART) treatment should be discontinued upon diagnosis of abortion /miscarriage. Contraindications for the use of estrogens when used in combination with dydrogesterone. **WARNINGS & PRECAUTIONS:** Before initiating dydrogesterone treatment for abnormal bleeding the etiology for the bleeding should be clarified. Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy. If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with dydrogesterone and ceasing the treatment should be considered: Porphyria, Depression and Abnormal liver function values caused by acute or chronic liver disease. **PREGNANCY & LACTATION:** It is estimated that more than 10 million pregnancies have been exposed to dydrogesterone. So far there were no indications of a harmful effect of dydrogesterone use during pregnancy. Dydrogesterone can be used during pregnancy if clearly indicated. Breastfeeding: No data exist on excretion of dydrogesterone in mother's milk. Experience with other progestogens indicate that progestogens and the metabolites pass to mother's milk in small quantities. Whether there is a risk to the child is not known. Therefore, dydrogesterone should not be used during the lactation period. Fertility: There is no evidence that dydrogesterone decreases fertility at therapeutic dose. **ADVERSE REACTIONS:** The most commonly reported adverse drug reactions of patients treated with dydrogesterone in clinical trials of indications without estrogen treatment are migraines/headache, nausea, menstrual disorders and breast pain/tenderness. Undesirable effects in adolescent population: Based on spontaneous reports and limited clinical trial data, the adverse reaction profile in adolescents is expected to be similar to that seen in adults. Undesirable effects that are associated with an estrogen-progestogen treatment (see also 'Warnings and Precautions' and the product information of the estrogen preparation): Breast cancer, endometrial hyperplasia, endometrial carcinoma, ovarian cancer; Venous thromboembolism; Myocardial infarction, coronary artery disease, ischemic stroke Issued date as 20/05/2021 Source: Prepared based on full prescribing information (version 8) dated 20/11/2019.

IND2122433-3 22 Jun 2021

For full prescribing information, please contact:
Abbott India Limited, 16th Floor, Godrej BKC Plot C-68, 'G' Block, BKC, Near MCA Club, Bandra East, Mumbai-400 051. www.abbott.co.in

Abbott

Video Corner

TLH with extensive endometriosis

Dr. Nutan Jain
M.B.B.S. In 1980, from G.S.V.M. Medical College, Kanpur.
M.S. in Obs & Gynae in 1983 from G.S.V.M. Medical College, Kanpur.
Certification & Accreditation by All American Gynae Laparoscopist (AAGL) as Advance Laparoscopic & Hysteroscopic Surgeon. Rare Distinction for an Indian Gynaecologist
Training in Advance Ultrasound, Laparoscopic Microsurgery, Advanced infertility management, Advanced Endoscopic Surgery , Pelvic Floor Repair , Laparoscopy Oncology.
Elected Board member of International Society of Gynecological Endoscopy(ISGE) in 2006.
Nominated for AAGL Board of Directors in 2009 and 2019 to represent Asia Pacific Region

A 40 year old female with previous 2 LSCS presented to our hospital with complaints of severe pelvic pain, dysmenorrhea and dyschezia. Her ultrasonography findings suggested a right sided endometriotic cyst and recto vaginal nodule. We did a multiple port laparoscopy using a 30 degree telescope. The camera port is high up midway between the umbilicus and xiphisternum.

On entering we found the uterus jammed with the rectum and a large endometriotic cyst on the right side. The pelvis is frozen with adhesions obliterating the entire pouch of douglas. We start the case with injecting diluted vasopressin in large amounts around 300 ml in the uterus.

Then we unravel the retroperitoneum from the left pelvic brim with gradual bipolar and cutting scissors. The higher we start dissecting closer to the ureter, the easier it gets exposed upto the ureteric tunnel. The endeavour is to expose the medial pararectal space. Adhesiolyisis done around the endometriotic cyst followed by draining it.

Then we reach the rectovaginal space. Then the same is done from the right side. And after opening the medial pararectal space from both the right and left side, we clear up the rectovaginal space completely. We are using the rectal probe to safeguard the rectum and uterine manipulator to antevert the uterus which delineates the plane of cleavage between the nodule and back surface of the uterus.

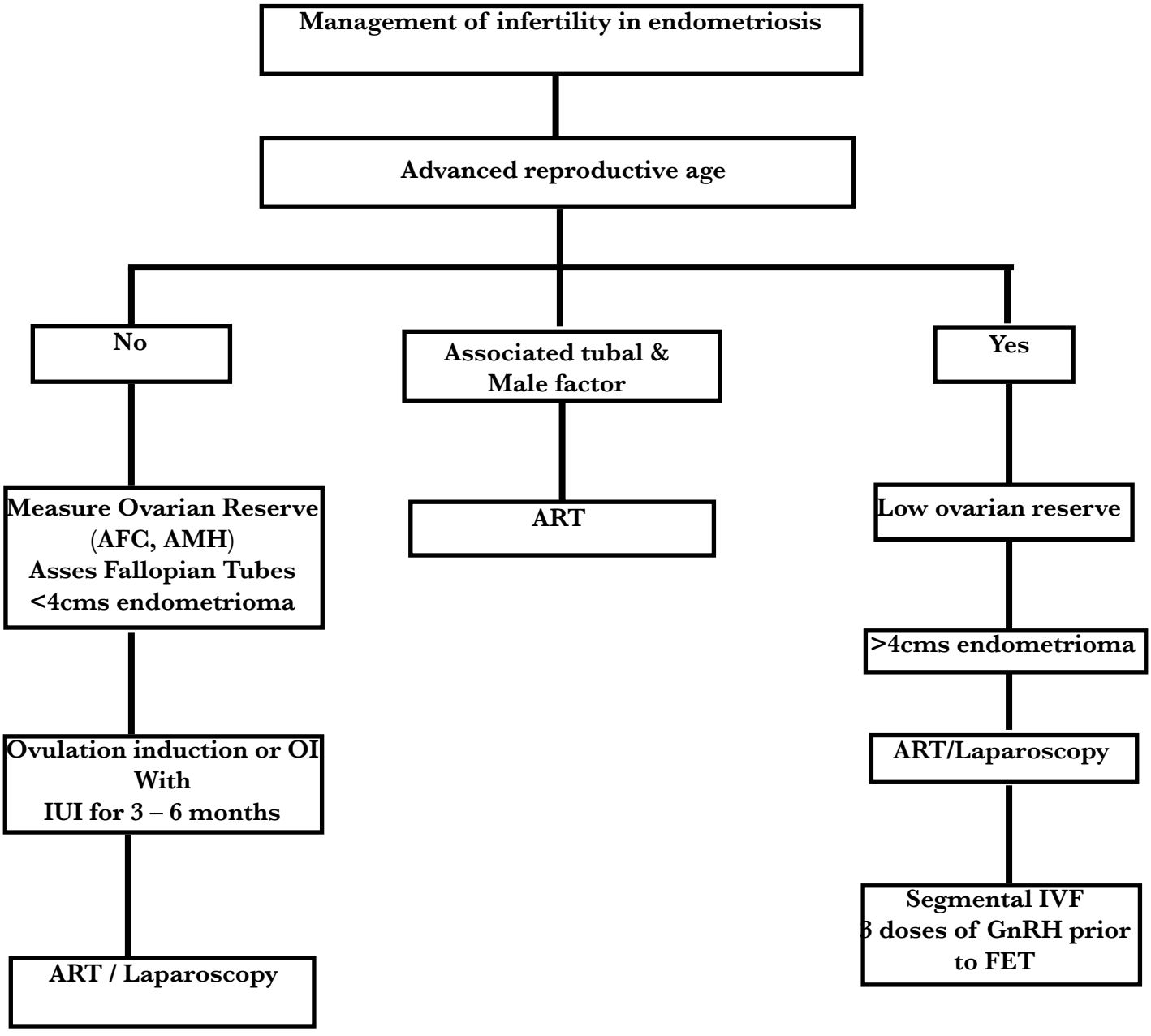
The rectovaginal nodule is shaved out over to the rectosigmoid and then excised out after holding with graspers. Taking care of the ureters, the TLH is commenced with Enseal PTC and Harmonic ACE .Bladder is slowly dissected using Rumi cup aided by harmonic ace followed by circumferential colpotomy through which uterus and rectovaginal nodule is delivered out. Vault sutured in two layers and suspended. Cystoscopy done as a routine which confirmed bilateral ureteric jet and peristalsis.

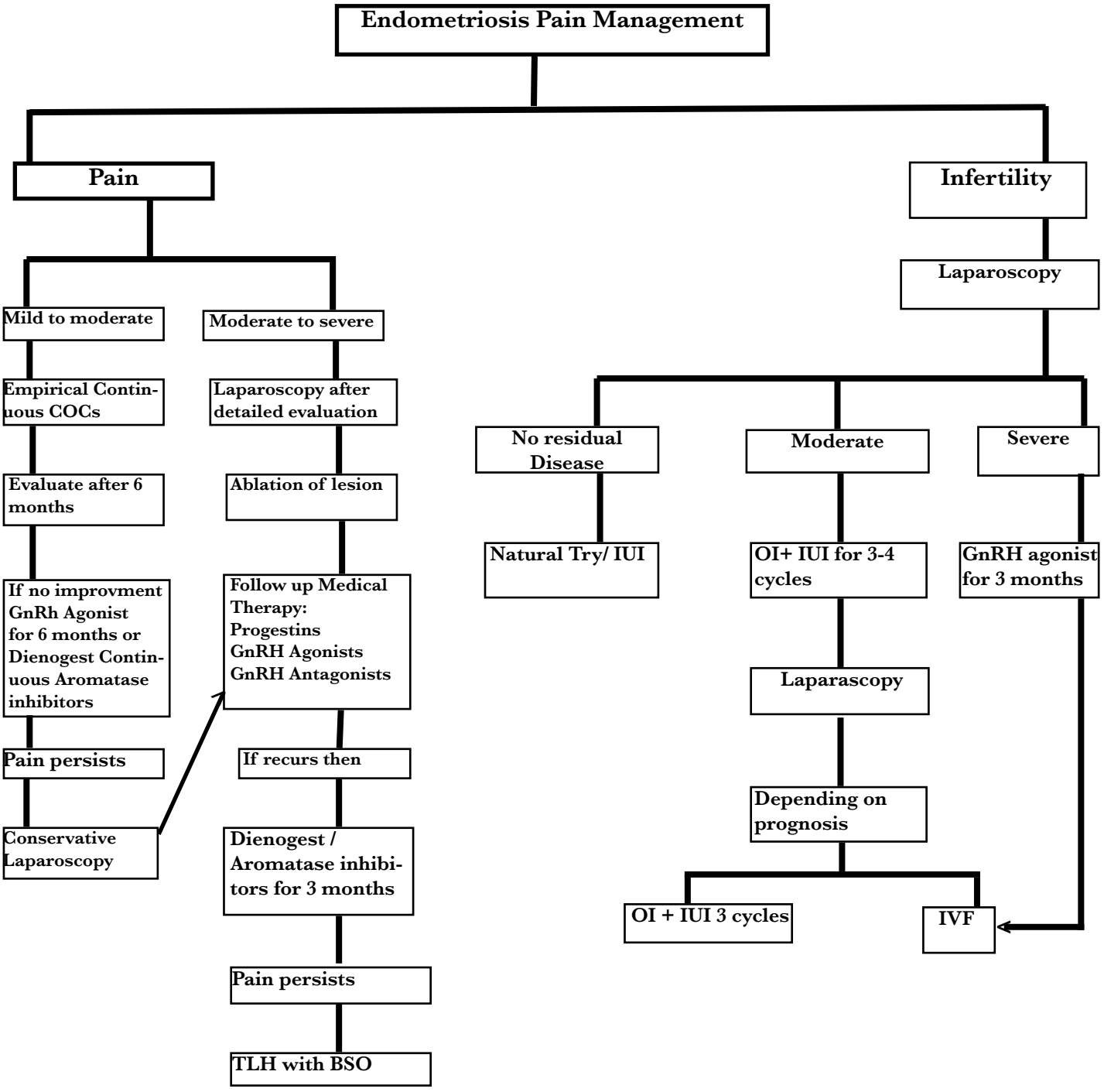
Video link: https://youtu.be/05qT6kbrRIQ

Tips For Your Practice

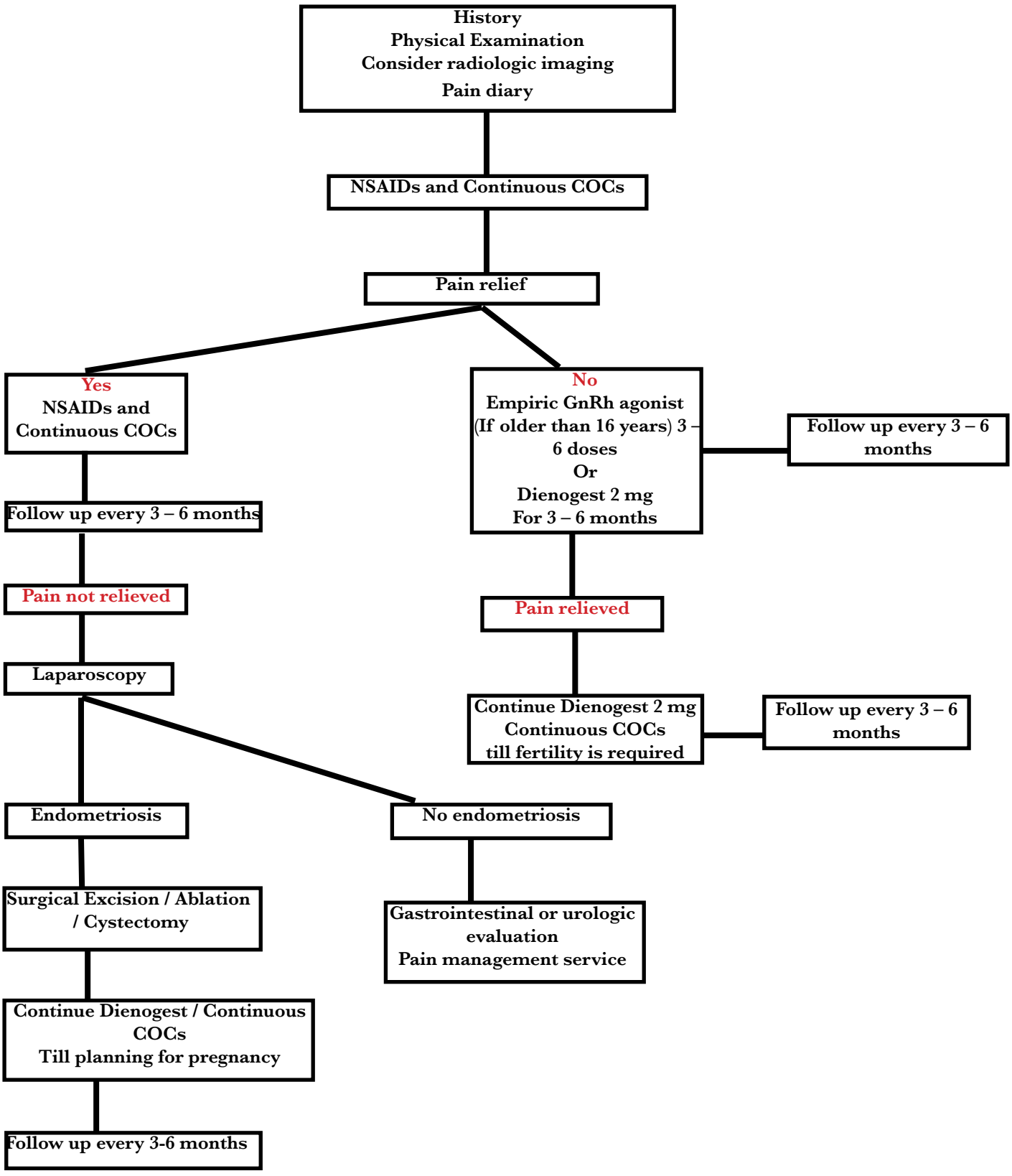
Dr. T. Ramani Devi, MD, DGO, FICS, FICOG.
Consultant at Ramakrishna Medical Centre LLP & Janani Fertility Centre, Trichy

Dr. Kanthi Bansal- Director, Safal Fertility Foundation, Ahmedabad. Founder Chairperson, Endometriosis Committee, FOGSI. Chairperson Endometriosis Committee SAFOG. Editor, European Journal of Endometriosis and Pelvic Pain Disorders.




Endometriosis Pain Management
Pain
Infertility
Mild to moderate
Moderate to severe
Laparoscopy
Empirical Continuous COCs
Laparoscopy after detailed evaluation
No residual Disease
Moderate
Severe
Evaluate after 6 months
Ablation of lesion
Natural Try/ IUI
OI+ IUI for 3-4 cycles
GnRH agonist for 3 months
If no improvment GnRh Agonist for 6 months or Dienogest Continuous Aromatase inhibitors
Follow up Medical Therapy:
Progestins
GnRH Agonists
GnRH Antagonists
Laparascopy
Pain persists
If recurs then
Depending on prognosis
Conservative Laparoscopy
Dienogest / Aromatase inhibitors for 3 months
OI + IUI 3 cycles
IVF
Pain persists
TLH with BSO

Adolescent Endometriosis



Images in Endometriosis

Ultrasound in deep infiltrating endometriosis

Dr. C B Nagori: Director- Dr. Nagori's Institute for Infertility and IVF, Ahmedabad. Faculty for Donald School Master's courses of Human Reproduction. Dr. Nagori's Institute is a centre for training for Donald School fellows for Masters in Human Reproduction and Ultrasound in Obstetrics and Gynecology.

Dr Sonal Panchal Consultant: Dr. Nagori's Institute for Infertility and IVF, Ahmedabad. Professor, Dubrovnik International University, Croatia. National Academic Director, Ian Donald Interuniversity school of medical ultrasound, India.

Introduction:
Deep-infiltrating endometriosis (DIE) is when endometriotic tissue extends >5 mm deep from peritoneal surface. DIE may involve bowel, bladder, uterosacral ligament, vagino-rectal septum, most commonly, and rarely abdominal organs. 4%–13% of women in reproductive age group and in 25%–50% of women with infertility present with DIE. Dysmenorrhea, dyspareunia, chronic pelvic pain are the common presenting symptoms. Dysuria or pain on defecation can be present if it involves bladder or bowel. The pathology of DIE is nodular myeloproliferative lesion with very little glandular and stromal tissue. The intense reactive sterile inflammation that occurs in DIE leads to adhesions and reactive fibrosis.1

Ultrasound techniques for diagnosis:
Transvaginal ultrasound-
performed on partially filled bladder

Systematic assessment is done bases on the consensus of – IDEA (international deep endometriosis analysis)3 which includes the following:

- Complete evaluation of uterus, adnexa and ovaries
- Check for tender points and ovarian mobility
- Confirm positive sliding organ sign during examination especially in POD
- Targeted search for endometriotic nodules in posterior and anterior compartments
- Pull out the probe till introitus and then angulate it posteriorly and slide it slowly over the posterior vaginal wall, critically observing the posterior vaginal wall, anterior anal canal and rectal wall and interface in between.
- Side to side movement along with to assess vault thickness and regularity (normally it is thin and hypoechoic).

Transabdominal assessment-
performed on full bladder

- Exclude hydroureter or hydronephrosis and ureteric involvement
- Look for scar endometriosis
- Identify lesions in small bowel, appendix2, omental endometriosis

Transrectal route-

- When vaginal approach is not possible
- When further evaluation of rectal lesions are required
- For uterosacral ligament thickening
-

Trans labial route-

- For superficial lesions, chiefly involving vaginal wall

3D imaging-

- details about the infiltration of the muscularis of the bowel
- to assess the multiorgan involvement and adhesions

Ultrasound appearance:
Rectosigmoid DIE:

- Solid hypoechoic linear thickening or nodules with or without regular contour in the anterior muscularis of the bowel
- Discontinuity of central line of muscularis (Muscularis is traversed by an echogenic line that separates inner circular and outer longitudinal muscle layer).
- Typical "Red Indian head" appearance with fibrotic retraction in submucosa lesion. (Figures 1a, b)
- On transverse section, signet ring appearance can be identified
- Lesions may be multifocal.
- Negative sliding organ sign between the uterus and the bowel has likelihood ratio of 23.6 for rectal DIE4.
- TRUS has sensitivity of 97% and specificity of 96% and TVS has sensitivity of 99.3% and specificity of 87.2%.5

Vaginal DIE:

- Localized hypoechoic thickening of the vaginal wall with or without anechoic areas. (figure 2a,b)
- More clearly appreciated if probe is placed only superficially in the vaginal canal and the vaginal cavity is filled with gel (Gel Vagino-Sonography) or use 12ml (instead of 4ml routinely used) gel in condom or can fill the rectum with water.

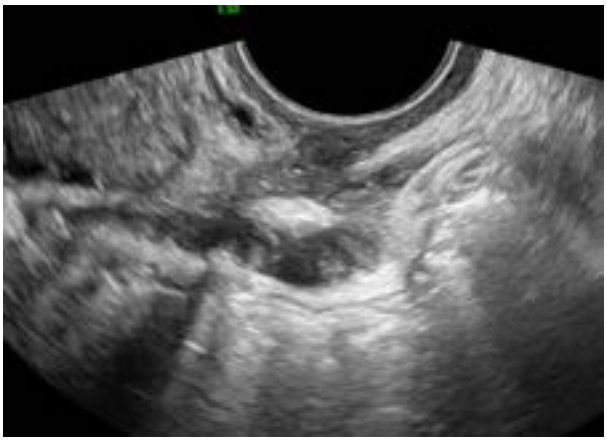


***Figure 1a**: bowel endometriosis- "Red Indian Head" sign as shown by the arrow*

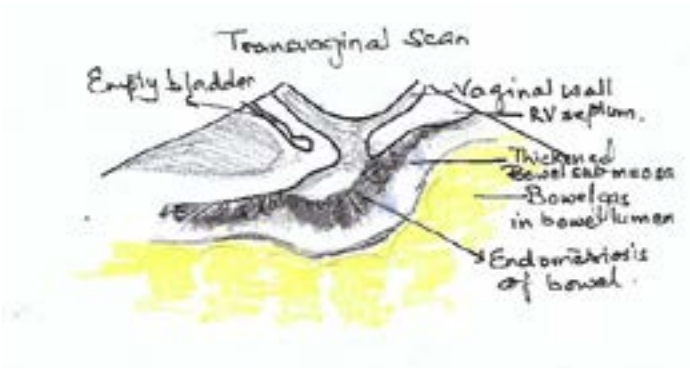


***Figure 1b:** Diagrammatic presentation of the bowel endometriosis- "Red Indian Head" sign*

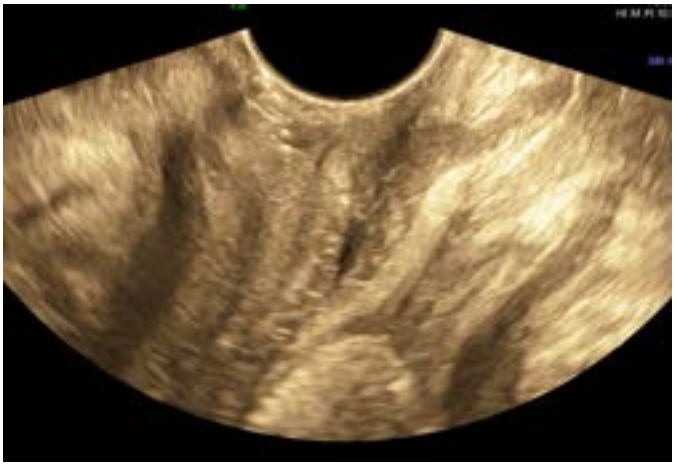


***Figure 2a:** Arrow showing irregular hypoechoic lesion involving the posterior vaginal wall and adjacent rectum- rectovaginal septum endometriosis (arrow)*

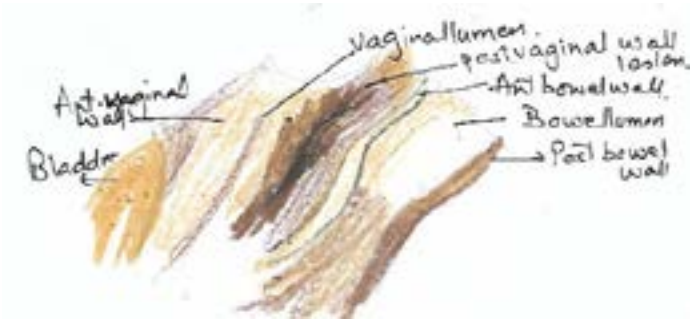


***Figure 2b:** diagrammatic representation of rectovaginal endometriosis*

Cervical DIE:

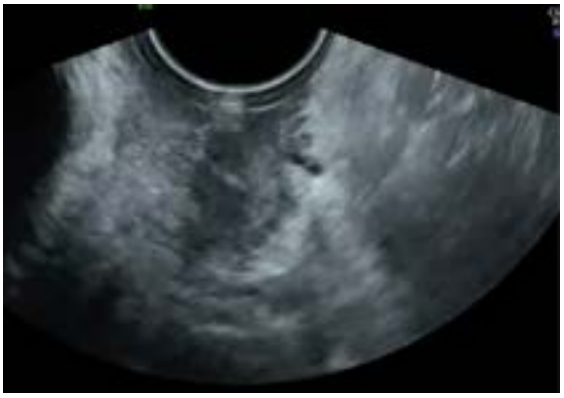
- Thick firm cervical wall appears as hypoechoic area on ultrasound. (Figure 3 a, b)
- ill-defined margins, at times associated with acoustic shadowing on gel Vagino-Sonography.

Uterosacral DIE:

- Thick (> 14mm) uterosacral ligament with hypoechoic, irregular soft tissue mass instead of a string-like structure on both sides of cervix.6
- TVS has sensitivity of 70.6% and specificity of 95.9% for uterosacral endometriosis5
- 3D rendering- endometriotic nodule of typical irregular contour
- Tomographic ultrasound imaging (TUI) to evaluate extension of nodule in rectovaginal septum
- Transrectal scan may be better route

Bladder DIE:

- Localized thickening of bladder wall with hypoechoic and hypovascular area (figure 4a, b) / solid projection on 2D ultrasound. (Figure 5a, b).
- Trigone is most commonly affected may also involve the ureteric insertion and may lead to obstruction and hydronephrosis
- Inflammation and fibrosis may to distortion of surrounding anatomy.



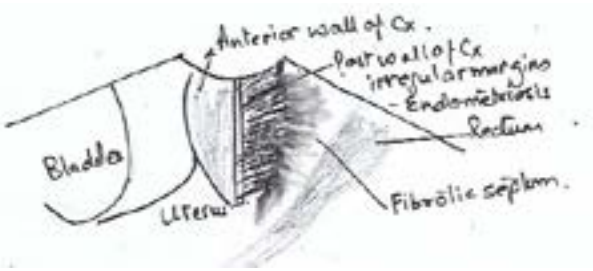
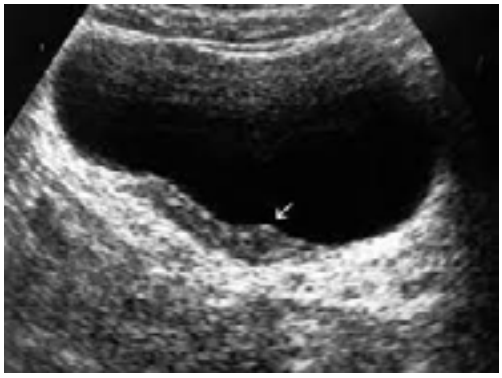


***Figure 3a**: irregular hypoechoic lesion involving posterior cervical lip with irregular margins, outlines by thick hyperechoic margin due to inflammatory hypertrophy surrounding the lesion*

***Figure 3b:** diagrammatic representation of cervical deep infiltrating endometriosis.*



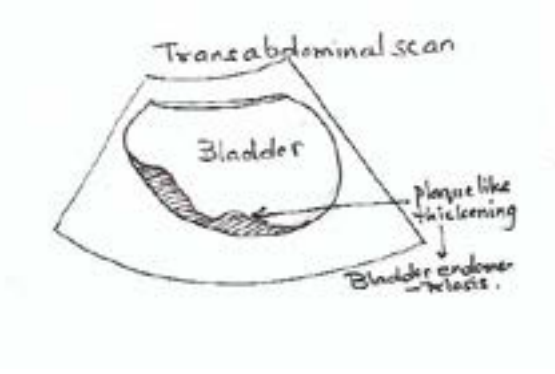
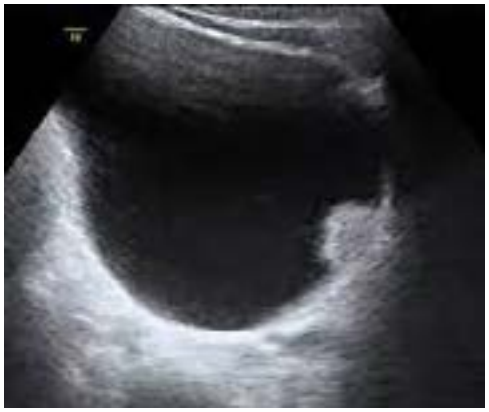


***Figure 4a, b:** Ultrasound image and diagrammatic presentation of plaque like lesion in the bladder- endometriotic patch.*



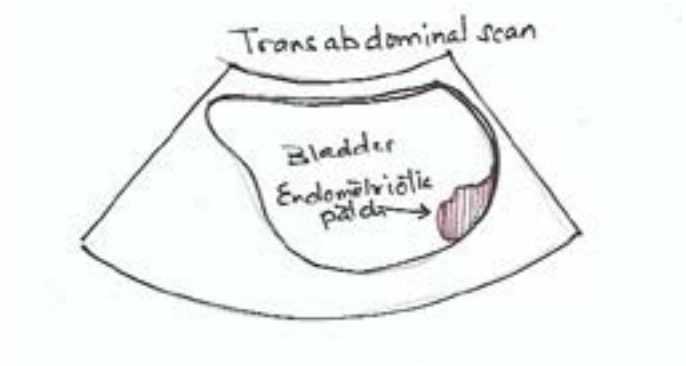


Figure 5a, b: *Ultrasound image and diagrammatic presentation of nodule like lesion in the bladder- endometriotic in origin.*

References:

1. O. Burney and L. C. Giudice, "Pathogenesis and pathophysiology of endometriosis," Fertility and Sterility, vol. 98, no. 3, pp. 511–519, 2012.
2. R. L. Gustofson, N. Kim, S. Liu, and P. Stratton, "Endometriosis and the appendix: a case series and comprehensive review of the literature," Fertility and Sterility, vol. 86, pp. 298–303, 2006.
3. Guerriero S, Condous G, van den Bosch T, et al. Systematic approach to sonographic evaluation of the pelvis in women with suspected endometriosis, including terms, definitions and measurements: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group. Ultrasound Obstet Gynecol. 2016;48:318-32.
4. Hudelist G, et al. Uterine sliding sign: a simple sonographic predictor for presence of deep infiltrating endometriosis of the rectum. Ultrasound Obstet Gynecol. 2013;41: 692-95.
5. Bazot M. Thomassin I, Hourani R, et al. Diagnostic accuracy of transvaginal sonography for deep pelvic endometriosis. Ultrasound Obstet Gynecol. 2004; 24:180-5.
6. Ohba T, Mizutani H, Maeda T, Matsuura K, Okamura H. Evaluation of endometriosis in uterosacral ligaments by transrectal ultrasonog- raphy. Hum Reprod 1996; 11:2014-17

In Chronic Pelvic Pain

℞ LUPRIDE DEPOT 1M 3M

Leuprolide Acetate Depot Inj. 3.75 mg / 11.25 mg

Suppresses Chronic Pelvic Pain & Improves Fertility

ACOG*and RCOG** support the empiric use of GnRH agonist in the diagnosis and management of CPP, even in the absence of confirmation of histology, after exclusion of other causes of pain[1]

ESHRE 2014 guideline: management of women with endometriosis[2]

Guideline development group (GDG), recommends GnRH agonists (Level A) as one of the options, as it reduces endometriosis-associated pain as against hormonal contraceptives (Level B)[2]

Six months of GnRH agonist therapy immediately following surgery

- Reduces the rate of symptom recurrence[4]
- Increases the length of time before symptoms recur[5]
- It is also more effective in managing endometriosis-related pain after surgery than using oral contraceptives[6]

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

1. Michele Morelli et.al Gynecol Endocrinol, 2013; 29(4): 305–308. 2. G.A.J. Dunselman, ESHRE guideline: management of women with endometriosis, Human Reproduction, Vol.0, No.0 pp. 1–13, 2014.
3. A. E. Schindler, Gynecol Endocrinol 2004;19:51–55. 4. Hemmings R. J Reprod Med 1998;43(3):316-320. 5. Schweppe K-W, Hummelshoj L. Recommendations on the use of GnRH in the management of endometriosis. In: Lunenfeld B (ed). GnRH Analogs in Human Reproduction. United Kingdom: Francis & Taylor, 2005:53-66. 6. Muzii L, Marana R, Caruana P, et al.. Am J Obstet Gynecol 2000;183:588-592

* American College of Obstetrics and Gynaecology. ** Royal College of Obstetrics and Gynaecology

Level A recommendation: Meta-analysis or multiple randomized trials (of high quality) Level B recommendation: Meta-analysis or multiple randomized trials (of moderate quality)

In Endometriosis associated Pelvic Pain

℞ EMERSA

Dienogest 2 mg Tablets

Effective Management of Endometriosis with Safety

Provides significantly greater reduction in endometriosis-associated pelvic pain (EAPP) than placebo in a 24-week[1]

Dienogest 2 mg once daily is

- Effective in the long-term management of EAPP in women with endometriosis[1]
- Progressive decreases in EAPP and bleeding irregularities during continued treatment[1]

Long term efficacy

- Highly effective in preventing recurrence after surgery[2]
- Reducing endometriosis-associated pain[2]
- Decreasing the size of recurrent endometrioma[2]

1. J Womens Health (Larchmt) 2019 Feb;28(2):170-177. doi: 10.1089/jwh.2018.7084. Epub 2018 Nov 21.
2. Clin Exp Reprod Med 2016;43(4):215-220.

Inca Life Sciences
a SUN PHARMA division

Alternate Therapies in Endometriosis

Nutritional approach for endometriosis

Dr. P. Raghavendra, Scientist - B, Division of Public Health Nutrition, ICMR - National Institute of Nutrition, Hyderabad.

Dr. Teena Dasi, Scientist - B, Division of Mother and Child Nutrition, ICMR - National Institute of Nutrition, Hyderabad.

Endometriosis is defined as the presence of functioning endometrium-like tissue outside the uterine cavity resulting in a chronic inflammatory condition driven by the hormones oestrogen and progesterone. Various studies conducted in Indian population have shown the incidence of endometriosis to range from 34% to 48% as diagnosed by laparoscopy.1The aetiology and pathogenesis of endometriosis are not yet fully understood.

However, copious evidence suggests that oxidative stress is involved both in the pathogenesis and the pathophysiology of endometriosis.2 Also immunological, endocrinal, genetic and environmental factors all appear to play a significant role in its pathogenesis. Among the environmental aspects, nutrition has been little studied, despite evidence showing its impact on the origin and progression of the disease3, 4.

Endometriosis can currently be treated pharmacologically and/or surgically. Because of the limited amount of success of treatment and because of the chronic character of endometriosis, it is worth exploring the literature to gather evidence on the nutritional approach for reducing the inflammation and pain associated with endometriosis. The current scientific evidence suggests that the diet and lifestyle may influence the presence of inflammation in the body, estrogen activity, menstrual cycle, and prostaglandin metabolism5

Pathophysiology of endometriosis:

In the typical lesions of the disease, the cells grow, differentiate out of the uterus, and retain their ability to respond to hormonal proliferative stimuli. Furthermore, excess estrogen stimulates the formation of large amounts of prostaglandins (from the even series), promoting inflammation and, consequently, a painful stimulus6, 7. During the progression of the disease, changes occur resulting in abnormal immunological antigen-antibody reactions, contributing to the increase of pro-inflammatory agents6. Women with endometriosis have a higher concentration of lipid peroxidation markers in the blood and peritoneal fluid, which promotes cell adhesion and activation of macrophages. These, in turn, release reactive oxygen and nitrogen species, leading to oxidative stress.8

Potential dietary strategies:

With the available literature, diets can be classified as the ones which will affect the occurrence of endometriosis (Preventive effect) and the diets which will affect the existing endometriosis (Therapeutic effect).

Diets which affect the occurrence of endometriosis:

Vegetables: Two studies have analysed the relation between servings/ week or day of green vegetables and fruit intake and risk of endometriosis3, 9 Green vegetable and fruit consumption were inversely associated with the risk of endometriosis3. Increased number of servings/ day of fruit was associated with increased disease risk (two or more versus one or less servings/day: OR 1.5, 95% CI 1.2–2.3, P trend = 0.04), but no association emerged with vegetables9

Fruit: Fruits contain antioxidants, which reduce oxygen free radicals thus having the potential to reduce inflammation (reduction in oxidative stress). This may, theoretically, also lower the risk of developing endometriosis. Fruits may contain organochlorines10 (due to the residual pesticides) which in turn have been positively associated with the risk of endometriosis11 Vitamins: Antioxidants (such as vitamins A, C, E and B 9 [folic acid]) reduce the amount of oxygen free radicals through effects on lipid peroxidation (LPO) and may thus have an anti-inflammatory effect.6, 9, 12. The antioxidant action exerted by vitamins may reduce the clinical consequences of endometriosis.

Fats: A diet that is high in fat is associated with various health effects, both positive and negative. Foods high in saturated fats like red meat and trans fats which are found in processed and deep fried foods are associated with higher risk of developing endometriosis. Whereas diets rich in monounsaturated fatty acids (olive oil, nuts and milk) and poly unsaturated fatty acids (fish, seaweed and nuts) have shown to be associated with low risk of developing endometriosis.

Saturated fats

Saturated fats may lead to higher plasma concentrations of oestradiol or steroid hormones and are therefore associated with the occurrence of oestrogen-dependent diseases 3. In 2018, within the Nurses' Health Study II, Yamamoto et al.13 were able to show that the consumption of red meat at > 2 portions/day was associated with a 56 per cent higher risk of developing endometriosis in comparison with women who only ate red meat once a week

Transfats

Transfats, which rarely occur naturally but can be found in processed and deep-fried foods, are generally categorised as being harmful to health. Trans fats are linked with higher levels of inflammation mediators such as TNF-alpha, interleukin 6 and C-reactive protein and, consequently, with increased inflammation.

Missmer et al.14 were able to show that women in the highest quintile for the consumption of trans fats were 48 per cent more likely to develop endometriosis as compared with women whose trans-fat consumption was in the lowest quintile

Monounsaturated fatty acids

Monounsaturated fatty acids, which occur in olive oil, nuts and milk, for example, have antioxidant properties and have an anti-inflammatory effect. Six studies3,6,9,12,14,15 considered the effect of the consumption of monounsaturated fatty acids on the risk of developing endometriosis. With regard to the potential effect on the risk of endometriosis, none of the cited studies were able to show any clear correlations.

Polyunsaturated fatty acids

Polyunsaturated fatty acids (such as omega-3 fatty acids and omega-6 fatty acids) primarily come from fish, seaweed and nuts. They have been proven to play a role in the regulation and reduction of inflammatory prostaglandins and cytokines (interleukins 1, 2 and 6, TNF-alpha). They were proven to reduce the proliferation of endometriosis lesions both in vivo and in vitro.16,17

Dairy products, vitamin D and magnesium

Kriegel et al.18 were also able to show that vitamin D deficiency could lead to an increased risk of inflammatory diseases. This could also apply to the occurrence of endometriosis. Vitamin D has been proven to stimulate immunosuppressive regulatory T-cells as well as the secretion of interleukin-10 and inhibits pro-inflammatory interleukin-17 and T-helper cells. Several studies19,20 have shown that magnesium leads to the relaxation of smooth muscle cells and can thus have an antispasmodic effect. This suggests that magnesium could influence the pathogenesis of endometriosis (retrograde menstruation) as well as on pain symptoms. Harris et al.21 were able to demonstrate that the consumption of magnesium was associated with a significantly lower risk of endometriosis.

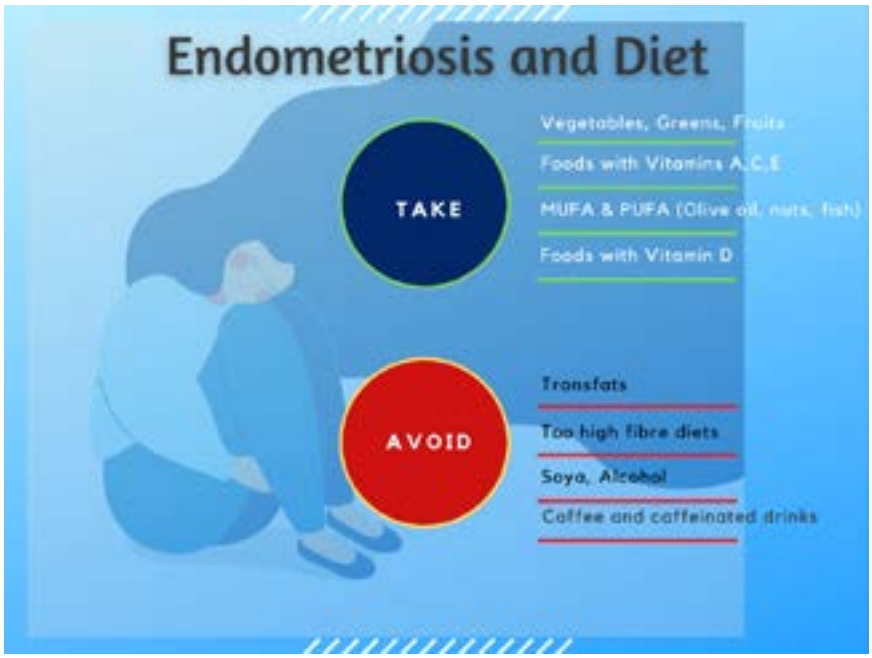
Fibre
A high-fibre diet is generally associated with health benefits. In this case, a high-fibre diet means one that is rich in complex carbohydrates with a low glycaemic index. Increased endometrial proliferation and thus a potentially elevated risk of endometriosis can occur as a result of simple carbohydrates (with a high glycaemic index).

Soya and phytoestrogens (isoflavones)
As a result of their oestrogenic effects, phytoestrogens, which primarily occur in soya, may be linked with the occurrence of endometriosis and other oestrogen-dependent diseases

Coffee and caffeine
According to the literature, the consumption of caffeinated beverages increases the availability of oestrogen and oestrones in the follicular phase as it is positively associated with sex hormone-binding globulin concentrations and inversely with bioavailable testosterone22 In three studies, an increased risk was reported in women reporting any versus no or infrequent coffee consumption.23-25 The association was statistically significant in two of them.

Alcohol
Alcohol is considered a risk factor for developing oestrogen-dependent diseases because it increases the activity of aromatase and thus the availability of oestrogen in the blood. Furthermore, there is a significant correlation between alcohol consumption and the occurrence of some chronic inflammatory diseases. According to a 2013 meta-analysis by Parazzini et al.3, there is a significant correlation between alcohol consumption and the occurrence of endometriosis

Diets which will affect the existing endometriosis:
The comprehensive review by Hansen et al26 showed that increased consumption of omega-3 fatty acids led to lower pain intensity, lower pain duration and lower painkiller use.
Sesti et al.27 investigated the effects of hormone therapy vs. diet-related measures vs. placebo in a randomised study in women having undergone surgery with more severe endometriosis (rASRM grades III and IV)
Women receiving hormone suppressants after surgery or receiving diet-related treatment showed significant pain reductions in all three categories ($p < 0.001$), as well as higher quality of life ($p < 0.001$) as compared with the placebo group.



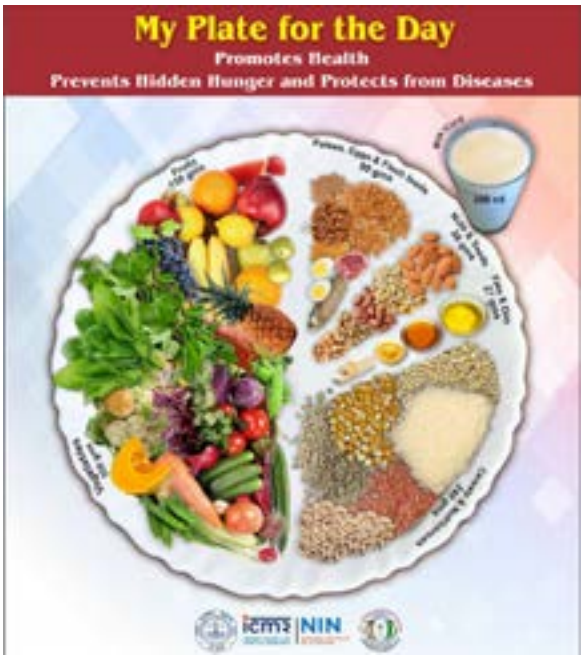
The following table provides insights to the role of diet in occurrence and progression of endometriosis:

Author	Study design	Dietary factor	Effect
Parazzini et al.[28], 2004	Case control study with experimental group (n = 504) consisted of women aged 20-65 years with confirmed endometriosis and the control group (n = 504) consisted of women aged 20–61 years with no gynecological disorders	Vegetables Fruits fats, fish oils, PUFA Red meat Vitamin – D	↓ ↓ ⇔ ⇧ ⇔
Trabert et al.[9], 2010	Case control study with experimental group (n = 284) consisted of women aged 20–65 years diagnosed with endometriosis and the control group (n = 660) consisted of healthy women	Vegetables Fruits fats, fish oils, PUFA Red meat Vitamin D	⇔ ⇧ ↓ ⇔ ↓
Savaris and Amara 6, 2011	Case control study with experimental group (n = 25) consisted of women with stage I–IV endometriosis and the control group (n = 20) consisted of women with no gynecological disorders	Fibre fats, fish oils, PUFA	⇧ ↓
Britton et al.[12], 2000	Case control study with subjects belonging to age:18–74 years, the experimental group (n = 393) – women with benign ovarian tumors, (n = 280) women with endometrial tumors; Control group (n = 351) - women with no diagnosed ovarian tumor or endometrial tumor	fats, fish oils, PUFA	⇧
Missmer et al.[14], 2010	Prospective study with experimental group consisted of n = 1,199 women aged 25–42 years diagnosed with endometriosis and the control group consisted of n = 69,510 healthy women	Omega – 3 FA Trans fatty acids	↓ ⇧
Harris et al.[21], 2013	Prospective cohort study with experimental group (n = 705.56) consisted of women aged 25–42 years including (n = 1.385) women diagnosed with endometriosis and the control group consisted of the healthy women	Vitamin D	↓
Khanaki et al.[29], 2012	Case control study with experimental group (n = 46) women diagnosed with stage I–IV endometriosis, and the control group (n = 74) consisted of women with no gynecological disorders	fats, fish oils, PUFA	⇔
Sesti et al.[27], 2009	RCT with Women diagnosed with endometriosis divided into four groups: placebo group (n = 65), GnRH-a therapy group (n = 65), group treated by continual low doses of the monophasic oral contraceptives, supplements (vitamins, mineral salts, lactic acid, cod liver oil) (n = 65)	fats, fish oils, PUFA	⇔
Heilier et al.[15], 2006	Case control study with experimental group (n = 176) consisted of women with diagnosed endometriosis and endometrial nodules and the control group (n = 88) healthy women	fats, fish oils, PUFA Red meat Vitamin D	⇔ ⇔ ⇔

↓ = decreased risk; ⇧ = increased risk; ⇔ = no influence

Conclusion:

With the available literature, we can conclude that there is evidence that diets influence the pathogenesis and progression of endometriosis. Though hormone therapy is the main mode of the available treatments, often with many side-effects, our focus on diets which lower the risk of developing and progressing endometriosis seems to be a sustainable approach along with regular exercise and weight loss. However, endometriosis being a complex and multifactorial disease, it is difficult to qualify or quantify the diet to be taken for women suffering with this condition. Therefore, the general recommendations for a balanced and varied diet in line with the guidelines of the NIN (My plate for a day) apply good even for endometriosis. In future, we can consider developing individual nutrition plans to ease the progression of endometriosis which requires not only epidemiological studies but also experimental studies to establish the extent to which individual nutrients affect the progression of endometriosis.



References:

1. Rajeshwari M, Ramanidevi T, Kadalmani B. Cohort study of endometriosis in south Indian district. Int J Reprod Contracept Obstet Gynecol. 2016; 5(11):3883–88
2. Augoulea A, Alexandrou A, Creatsa M, Vrachnis N, Lambrinoudaki I. Pathogenesis of endometriosis: the role of genetics, inflammation and oxidative stress. Arch Gynecol Obstet. 2012 Jul;286(1):99-103. doi: 10.1007/s00404-012-2357-8. Epub 2012 May 1. PMID: 22546953.
3. Parazzini F, Viganò P, Candiani M, Felede L. Diet and endometriosis risk: a literature review. Reprod BioMed Online. 2013, 26:323-36.
4. Paris K, Aris A. [Hypothetical link between endometriosis and accumulation of xenobiotics associated with genetically modified foods]. Gynecol Obstet Fertil. 2010; 38:747-53.
5. Jurkiewicz-Przondziono J, Lemm M, Kwiatkowska-Pamuła A, Ziółko E, Wójtowicz MK. Influence of diet on the risk of developing endometriosis. Ginekol Pol. 2017;88(2):96-102. doi: 10.5603/GP.a2017.0017. PMID: 28326519.
6. Savaris, A.L., do Amaral, V.F., 2011. Nutrient intake, anthropometric data and correlations with the systemic antioxidant capacity of women with pelvic endometriosis. Eur. J. Obstet. Gynecol. Reprod. Biol. 158, 314–318.
7. Bulun SE. Endometriosis. N Engl J Med. 2009; 360:368-797
8. Mier-Cabrera J, Aburto-Soto T, Burrola-Méndez S, Jiménez-Zamudio L, Tolentino MC, Casanueva E, et al. Women with endometriosis improved their peripheral antioxidant markers after the application of a high antioxidant diet. Reprod Biol Endocrinol. 2009; 7:54.
9. Trabert, B., De Roos, A.J., Schwartz, S.M., Peters, U., Scholes, D., Barr, D.B., Holt, V.L., 2010. Non-dioxin-like polychlorinated biphenyls and risk of endometriosis. Environ. Health Perspect. 118, 1280–1285.
10. Grassi, P., Fattore, E., Generoso, C., Fanelli, R., Arvati, M., Zuccato, E., 2010. Polychlorobiphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) in fruit and vegetables from an industrial area in northern Italy. Chemosphere 79, 292–298.
11. Buck Louis, G.M., Chen, Z., Peterson, C.M., Hediger, M.L., Croughan, M.S., Sundaram, R., Stanford, J.B., Varner, M.W., Fujimoto, V.Y., Giudice, L.C., Trumble, A., Parsons, P.J., Kannan, K., 2012. Persistent lipophilic environmental chemicals and endometriosis: the ENDO Study. Environ. Health Perspect. 120, 811–816.
12. Britton, J.A., Westhoff, C., Howe, G., Gammon, M.-D., 2000. Diet and benign ovarian tumors (United States). Cancer Causes Control. 11, 389–401.
13. Yamamoto A, Harris H R, Vitonis A F. A prospective cohort study of meat and fish consumption and endometriosis risk. Am J Obstet Gynecol. 2018;219:1780–1.78E12
14. Missmer, S.A., Chavarro, J.E., Malspeis, S., Bertone-Johnson, E.R., Hornstein, M.D., Spiegelman, D., Barbieri, R.L., Willett, W.C., Hankinson, S.E., 2010. A prospective study of dietary fat consumption and endometriosis risk. Hum. Reprod. 25, 1528–1535.
15. Heilier JF, Donnez J, Nackers F, et al. Environmental and host-associated risk factors in endometriosis and deep endometriotic nodules: a matched case-control study. Environ Res. 2007; 103(1): 121–129, doi: 10.1016/j.envres.2006.04.004, indexed in Pubmed: 16781705.
16. Calder P C. N-3 polyunsaturated fatty acids and inflammation: from molecular biology to the clinic. Lipids. 2003;38:343–352. [Europe PMC free article]
17. Gazvani M R, Smith L, Haggarty P. High omega-3:omega-6 fatty acid ratios in culture medium reduce endometrial-cell survival in combined endometrial gland and stromal cell cultures from women with and without endometriosis. Fertil Steril. 2001;76:717–722.
18. Kriegel M A, Manson J E, Costenbader K H. Does vitamin D affect risk of developing autoimmune disease? : a systematic review. Semin Arthritis Rheum. 2011; 40:512–5.31E10.
19. Altura B T, Altura B M. Endothelium-dependent relaxation in coronary arteries requires magnesium ions. Br J Pharmacol. 1987;91:449–451. intracellular Ca2+ without changing intracellular Mg2+ J Clin Invest. 1992;89:1988–1994.

20. D'Angelo E K, Singer H A, Rembold C M. Magnesium relaxes arterial smooth muscle by decreasing intra cellular Ca2+ without changing intracellular Mg2+ J Clin Invest. 1992;89:1988–1994.
21. Harris HR, Chavarro JE, Malspeis S, et al. Dairy-food, calcium, magnesium, and vitamin D intake and endometriosis: a prospective cohort study. Am J Epidemiol. 2013; 177(5): 420–430, doi: 10.1093/aje/kws247, indexed in Pubmed: 23380045.
22. Homan, G.F., Davies, M., Norman, R., 2007. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. Hum. Reprod. Update 13, 209–223.
23. Grodstein, F., Goldman, M.B., Ryan, L., Cramer, D.W., 1993. Relation of female infertility to consumption of caffeinated beverages. Am. J. Epidemiol. 137, 1353–1360.
24. Berube, S., Marcoux, S., Maheux, R., 1998. Characteristics related to the prevalence of minimal or mild en dometriosis in infertile women. Canadian Collaborative Group on Endometriosis. Epidemiology 9, 504–510.
25. Matalliotakis, I.M., Cakmak, H., Fragouli, Y.G., Goumenou, A.G., Mahutte, N.G., Arici, A., 2008. Epide miological characteristics in women with and without endometriosis in the Yale series. Arch. Gynecol. Obstet. 277, 389–393.
26. Hansen, S. O., & Knudsen, U. B. (2013). Endometriosis, dysmenorrhoea and diet. European Journal of Obstetrics & Gynecology and Reproductive Biology, 169(2), 162-171.
27. Sesti F, Capozzolo T, Pietropolli A, et al. Recurrence rate of endometrioma after laparoscopic cystectomy: a comparative randomized trial between post-operative hormonal suppression treatment or dietary therapy vs. placebo. Eur J Obstet Gynecol Reprod Biol. 2009; 147(1): 72–77, doi: 10.1016/j.ejogrb.2009.07.003, indexed in Pubmed: 19665279.
28. Parazzini, F., Chiaffarino, F., Surace, M., Chatenoud, L., Cipriani, S., Chiantera, V., Benzi, G., Fedele, L., 2004. Selected food intake and risk of endometriosis. Hum. Reprod. 19, 1755–1759.
29. Khanaki K, Nouri M, Ardekani AM, et al. Evaluation of the relationship between endometriosis and omega-3 and omega-6 polyunsaturated fatty acids. Iran Biomed J. 2012; 16(1): 38–43, indexed in Pubmed: 22562031.

Journal Scan

Dr. Saswati Sanyal

MD FICMCH FICOG FIAOG
Professor Dept of O&G. Gauhati Medical College
Vice President ISOPARB
President ISOPARB Assam chapter
Chairperson Medical Education Committee FOGSI.

'Does Cabergoline Help in Decreasing Chronic Pelvic Pain Due to Endometriosis Compared to Medroxyprogesterone Acetate?'
A Prospective Randomized Study

Kyal A, Pal A, Mukhopadhyay A, Mukhopadhyay P. J South Asian Feder Obst Gynae 2018;10(3):167-169.

ABSTRACT

Aims & objectives: The study aims to assess the safety and efficacy of cabergoline with respect to medroxyprogesterone acetate in treatment of chronic pelvic pain (CPP) due to endometriosis. Materials and methods: This study was conducted in Medical College, Kolkata from June 2015 to June 2016. Eighty patients of chronic pelvic pain due to endometriosis (diagnosed by USG and laparoscopy) were randomly assigned into two groups of 40 each receiving either medroxyprogesterone acetate (10 mg TDS) or cabergoline (0.5 mg twice weekly) for 12 weeks. Response for pain was measured on a visual analog scale (VAS) of 0–10 scale at the beginning of treatment and at intervals of 1, 3, 4 and 6 months.

Results: The study shows that the decrease in pain scores at various time points was statistically significant in both the groups. However, when the two groups were compared among themselves the reduction in VAS score at various time points were not statistically significant. Patients receiving medroxyprogesterone acetate had more side effects (67.5%) compared to cabergoline (47.5%). The most common side effect in medroxyprogesterone acetate group was amenorrhea (25%) whereas, in the cabergoline group, it was nausea and vomiting (45%).

Conclusion: Cabergoline and medroxyprogesterone acetate are equally effective in decreasing chronic pelvic pain due to endometriosis. However, due to lesser side effects and less frequent dosing, cabergoline has a better acceptance and compliance than medroxyprogesterone acetate. Thus cabergoline can be a better alternative to medroxyprogesterone acetate.

Reviewer's comments:
Dopamine agonists are used mostly in cases of prolactinoma. Cabergoline is a dopamine receptor 2 agonist. Its use is wider than other dopamine agonists like bromocryptine, because of its lesser side effects and dose conveniences. Use of Medroxyprogesterone acetate in endometriosis is mostly symptomatic by making the patient amenorrhoeic and thereby reducing pain. Cabergoline is an anti-angiogenic substance and was found to reduce angiogenesis in endometrial lesion in mouse model. Patient's acceptance is more in drugs which does not cause amenorrhoea but at the same time reduces pain. Cabergoline is better choice for those patients who do not want to be amenorrhoeic as well as do not prefer injectable route of administration.

Does cabergoline help in decreasing endometrioma size compared to LHRH agonist? A prospective randomized study

Amr M Salaheldin Abdel Hamid 1, Wael A Ismail Madkour, Ashraf Moawad, Mohamed Abd Elzaher, Mary P Roberts. Arch Gynecol Obstet. 2014 Oct; 290(4):677-82.

Aim: The aim of this study was to compare the efficiency of dopamine agonist, Cabergoline, in decreasing the size of endometrioma, with that of luteinizing hormone releasing hormone (LHRH) agonist, triptorelin acetate.

Study: This was a prospective, randomized study.

Setting: The setting was in two private medical centers in the UAE, from January 2011 to February 2012.

Patients and methods: One hundred and forty patients complaining of endometrioma, and fulfilling the eligibility criteria, were chosen and divided into two groups as follows: Group I comprised 71 patients; all of them received Cabergoline tablets, 0.5 mg tablets, twice per week for 12 weeks. Group II comprised 69 patients; all of them received LHRH agonist, decapeptyl, 3.75 mg subcutaneous, single injection, once a month for 3 months. All patients underwent vaginal ultrasound before and after the treatment period to compare the change in the size of endometrioma by the same sonography team in each hospital that was blind to the treatment groups.

Outcome: The outcome was measured by the changes in the endometrioma size by vaginal ultrasound after completion of the 3 months' treatment period. The management line was considered to be significantly effective if the endometrioma size was reduced by more than 25 % of its original pretreatment size.

Results:
Group I: 46 out of the 71 patients (64.7 %) had significant decrease in endometrioma size.
Group II: 15 out of 69 patients (21.7 %) had significant decrease in endometrioma size. Paired t test to compare the means of the two groups was highly significant ($p < 0.05$)

Conclusion: Cabergoline (dostinex) yields better results in decreasing the size of endometrioma, compared to LHRH-agonist by exerting antiangiogenic effects through vascular endothelial growth factor receptor-2 (VEGFR-2) inactivation. It has no major side effects, easier to administer, and cheaper than LHRH agonist

Reviewer's Comments: GnRH analogue is an established medication for the conservative treatment of endometrioma. But long-term use results in anti-estrogenic effect with reduction of bone mineral density and needs add-back therapy. Recurrence of endometrioma is observed after the therapy is stopped. GnRH injections are expensive and may not be suitable for a majority of our patients. Neovascularization is seen in endometriosis tissues and cabergoline with its anti-angiogenic property appears to be a suitable option. Endometriosis develops neuronal tissue as shown with immunohistochemistry, Studies have shown that there is significant reduction in neuronal tissue following cabergoline therapy. Long term of implications of cabergoline for endometriosis use needs to be evaluated, however we have used this molecule for long term management of prolactinomas without much adverse events. I have personal experience of using this in a young girl with a small endometrioma for 3 months and the there was considerable decrease in size.

MEMBERSHIP FORM

Member type= LIFE MEMBERSHIP

(Doctors having post graduation (MD or DNB in any field of Medicine or Surgery)
(Membership fees -) 5000/-

Personal Details:

1. Date of Application:
2. Full name:
3. Address (including zip code):
4. Email:
5. Telephone number:
6. Date of birth:
7. Current position:
8. Affiliations with institutions/ organizations/ societies

Qualification Details:

1. University/ College/ Institution:
2. Year of completion of MD/ DNB:
3. Speciality:
4. Medical Registration Number:

Payment Details:

Payment type- Cheque/ DD details

Send DD or cheque addressed to ENDOMETRIOSIS SOCIETY INDIA

6A & 6F, Neelamber, 28B, Shakespeare Sarani, Kolkata – 700017, West Bengal, India
Phone: (91) (033) 22874463, 28650364

Payment type- Bank transfer:

Account Name: ENDOMETRIOSIS SOCIETY INDIA
Account Number: 0673010072605
Account Type: Savings
IFS Code: PUNB0067320

Bank Name : PUNJAB NATIONAL BANK

BRANCH ADDRESS: 28B SHAKESPEARE SARANI,

KOLKATA - 700017

EDITORS' NOTE

We are delighted to present the second edition of the Endometriosis Society of India's e-journal " Endometriosis Update". This issue covers "A Clinical review on Genetics in endometriosis" by Dr. Suruchi Pandey, St.Georges Hospital, London. Endometriosis has seven times higher incidence among patients with family history, which shows genetic background plays a major role.

Professor Rooma Sinha from Apollo Hospitals, provides expert commentary regarding the role of Robotics in Endometriosis. This article will give an insight regarding the role of robotics in advanced endometriotic surgery. Dr. Sonal Panchal, Radiologist from Ahmedabad, shares images of deep endometriosis which will help discover deep endometriosis in a non-invasive way especially through USG, so that the delay in diagnosis could be overcome and invasive procedures could be avoided for diagnosis.

Dienogest is a wonder molecule which is used in treatment of endometriosis, prevention of recurrence and treatment of recurrence. Dr. Shyam Desai provides an article regarding the clinical use of Dienogest. Recently we've come to know that diets rich in anti-inflammatory agents can help us to control the symptoms of endometriosis whereas, pro-inflammatory diets will propagate the disease. An article contributed by Dr. P. Raghuvendra and Dr. Teena Dasi, from the National Institute of Nutrition, Hyderabad, regarding diet in endometriosis will throw light on the control of the disease. We are providing a video corner in which videos on endometriosis by the Senior laparoscopic surgeon Dr. Nutan Jain have been uploaded.

Dr. Kanthi Bansal and Dr. T. Ramani Devi provide tips for practice on the management of pain, infertility and adolescent endometriosis in the form of algorithmic patterns for easy understanding. Finally, the journal scan is written by Dr. Saswati Sanyal Choudary.

I'm sure we can improve our knowledge of endometriosis through this journal. This will enlighten all practitioners, but especially those who have special interest in endometriosis management.

Please take a minute to fill in the membership form at the end of the issue- join our community of members and stay abreast of the developments taking place in the field of endometriosis management.

Dr. T. Ramani Devi, MD, DGO, FICS, FICOG
Consultant at Ramakrishna Medical Centre LLP & Janani Fertility Centre. National Vice President FOGSI 2020. Director, Ramakrishna Medical Centre LLP & Janani Fertility Centre, Trichy
Internal Editorial board member of Bangladesh Journal of Fertility and Sterility. Editorial board member of International Journal of Human Reproduction

Dr. Rooma Sinha, MD, MNAMS, FICOG
Honorary Professor Gynecology, Apollo Hospitals
Associate Professor, Macquarie University, Australia
Director Fellowship program in MARS
Laparoscopic & Robotic Surgeon Apollo hospitals, Hyderabad, India.

Contact us:
• http://endosocind.org
• endosocindia@gmail.com

Editorial Board

Managing Editors

Dr. P. Das Mahapatra MD, FRCOG, FRCS
One of the most experienced Endoscopic Surgeon and Director of Spectrum Clinic and Endoscopy Research Institute, Kolkata. Secretary General of Endometriosis Society of India.

Dr. Pradeep Mitra, MD DGO MNAMS FICS FICOG FACS (USA)
Director: Dr. Pranthosh Mitra Memorial Clinic, Kolkata
Founder Deputy Secretary General: Endometriosis society India
Zonal Coordinator –FOGSI; Founder: PCO Health club, Kolkata

Editorial Board

Dr. Shyam Desai MD DGO DFP MNAMS FCPS
Consultant Port Trust Hospital
Director International Relations SAFOG
Honorary Professor, Wadia Hospital
Chairman Maternal Health AOFOG 2009 to 2013
Vice President SAFOG 2011 to 2016

Dr Rahul Krishnaji Gajbhiye, MBBS, PhD
Scientist & Head Clinical Research Lab (CRL) & Andrology Clinic
DBT Welcome Trust India Alliance Clinical and Public Health
Intermediate Fellow, ICMR National Institute for Research in Reproductive Health
International Ambassador - World Endometriosis Society
Research Advisor - Endometriosis Society India

Dr. Renu Mishra MBBS MS MNAMS
Senior Consultant, Endoscopic surgery & IVF
Sitaram Bhatia Institute of Science & Research
Miracles Fertility & IVF, Gurgaon
Former Additional Professor, All India Institute of Medical Sciences.

Dr Saswati Sanyal Choudhury MD FICMCH-FICOG FIAOG
Professor Dept of O&G. Gauhati Medical College
Vice President ISOPARB
President ISOPARB Assam chapter
Chairperson Medical Education Committee FOGSI.

Dr. Asha Rao MD DGO FICOG
Chairperson Endometriosis Committee, FOGSI 2020-2022.
Director of RAO HOSPITAL & C.A.R.E - Coimbatore
Director Post-Doctoral Fellowship in Reproductive Medicine & Endo gynecology (Affiliated Dr MGR Medical University, Chennai)

Dr. Oby Nagar, MS FMAS FICOG DIPLOMA
Professor and Unit Head SMS Medical College, Jaipur
President - Jaipur Menopause Society 2019-2020
Founder Member – Rajasthan Association of Minimal Access Surgeons.

Dr. SNEHASIKTA SWARNAKAR, Ph.D., Professor AcSIR
Senior Principal Scientist CSIR-Indian Institute of Chemical Biology, Kolkata.
Divisional Head - Infectious Diseases & Immunology CSIR-IICB.
Elected fellow -National Academy of Sciences & WB Academy of Science and Technology. National Bioscience Award for Career Development in 2007.
Full Bright Fellow in 2013-2014.

Dr. Partha Bhattacharya, MBBS, DGO, MS (O&G), MRCOG
Member of Executive Body, Endometriosis Society India
Consultant Obstetrician & Gynaecologist
West Bengal ESI Medical Services
RSV Hospital, Kolkata

Clinical Review

The Genetics of Endometriosis

Dr Shahi Ghani MBBS, BSc, MSc, DHMSA, MSc in Virology, Single Cell Molecular Imaging and Gene Editing.

Dr. Suruchi Pandey. MRCOG DRCOG DFFP PGDipLATHE, Consultant Gynaecologist, St. Georges Hospital, London, UK.

Introduction

Endometriosis affects 10% of the women of the reproductive age group (1). Endometriosis has a significant impact on quality of life of these women who not only have to soldier through heavy menstrual bleeding and pelvic pain but also sub-fertility and distressing bladder and bowel symptoms that come with endometriosis. The gold standard method for diagnosis involves laparoscopy and excision of the endometriotic tissue, however, due to the invasive nature of this, many patients choose not to have surgery (1). Endometriosis can affect pelvic organs like bowel, bladder, fallopian tubes and ovaries and extra-pelvic organs like diaphragm and even lungs. Endometriosis can present as mild peritoneal disease or deep infiltrating disease.

The precise aetiology of this condition is not widely understood due to the heterogeneity of the condition, however, it is now becoming clear that the disease is caused due to a combination of genetic and epigenetic factors. Oestrogen levels, inflammation, metaplasia and epithelial proliferation have all been hypothesised as contributary factors to this condition, in addition to genetics, which contributes approximately 50% of the variation in risk of developing the disease (2).Genes associated with endometriosis are involved with a number of functions which provide insight into the multifactorial pathophysiology of endometriosis involving immune mechanisms, chromatin-remodelling complexes, cell adhesion, angiogenesis as well as effects on biochemical signalling (1).

High-throughput genotyping technology and DNA sequencing have enabled us to identify the genetic factors for endometriosis. A meta-analysis of 17, 045 endometriosis cases identified 14 genomic regions associated with the risk of endometriosis (see Figure 1) with the results being supported from multiple studies (3).

Early work in the determining genetics of endometriosis involved family studies to determine heritability of the condition; as well as whole exome sequencing of endometrial and ectopic tissue which provided insight into the the genes where somatic mutations were identified (1). amilial studies have indicated that if an individual has a diagnosis of endometriosis, between 6-9% will also have a first degree relative with the condition(1). One study which compared the risk of first degree relatives of developing endometriosis in those with surgically confirmed endometriosis compared with control groups, it was found in 10.2% and 0.7% respectively (1).

Familial studies have indicated that if an individual has a diagnosis of endometriosis, between 6-9% will also have a first degree relative with the condition(1). One study which compared the risk of first degree relatives of developing endometriosis in those with surgically confirmed endometriosis compared with control groups, it was found in 10.2% and 0.7% respectively (1). Twin studies have also shown congruence in disease severity between monozygotic twins suggesting the role of genetic mutations in the stage of disease (1).

In the 'genomic era' genome wide association studies (GWAS) have the ability to use computational modelling to analyse entire genomes of affected patient groups compared to healthy patients to identify possible single nucleotide polymorphisms (SNPs) and candidate genes on a much larger scale than previously available due to the ability to analyse the regions in between genes which may further provide insight into the causative factors of this condition and potential biomarkers to aid diagnosis.

This review is intended to aid clinicians through the complex maze of GWAS to try and provide some tips on how to evaluate and draw conclusions from these studies, as well as discuss some of the key findings which have happened over the last few years. It is important to note, however, that the genes and mutations discussed below are simply an evaluation of genes associated with the condition, and as of yet, it is not possible to use genetic testing from GWAS to establish a diagnosis.

Study types and cohorts

A number of genome wide association studies have been conducted across the world using biobanks and information from private genetic testing services such as '23andme' (2, 4-6) which has widened the amount of data that is available regarding these conditions. Clinicians must exercise a degree of scepticism before drawing any conclusion from GWAS, paying particular attention to study design, ethnicity of participants and phenotypic variation of the condition. Many of these studies discuss genes and determine statistically significant mutations associated with endometriosis from their population cohorts, however, when replicating these studies other groups have been unable to achieve significant results. This highlights the variation in genetic mutations which have the potential to cause the condition, therefore meaning that there is no single set of mutations which result in a diagnosis, but rather mutations which are highly suggestive of particular phenotypes within the condition.

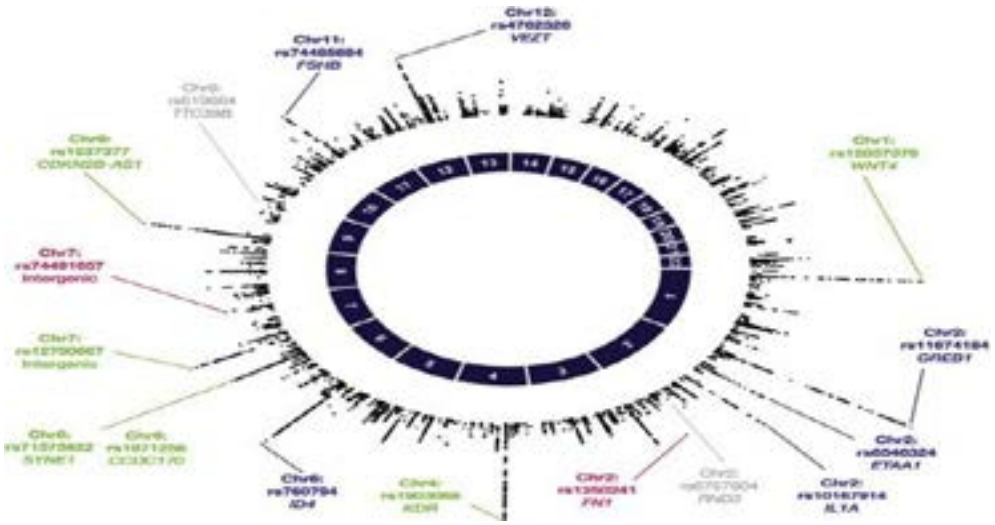


Figure 1 *Circle plot showing chromosome number (dark blue, inner circle) and results of association between individual SNPs and endometriosis plotted as −log10 (P values) (black, outer circle). Each genome-wide significant region identified in multiple published studies. The chromosome, independent index (most significantly associated) SNP(s) in each region, and the nearby biological candidate genes in each region were annotated (Green - significant association in all cases and in moderate–severe (Grade B) endometriosis cases; Blue - significant association in all cases; Red - significant association in Grade B endometriosis cases only). The significant associations identified in independent studies are shown in grey colour (Adapted from Fung et al Best Practice & Research Clinical Obstetrics and Gynaecology 50 (2018) 61-71)(3)*

Study design

Case-control studies are often used where participants are defined as a 'case' based on inclusion criteria. In patients identified from hospital visits, it is likely the patient will require a clinic appointment with a specialist who may undertake a full history of symptoms, blood tests, a physical exam and imaging studies to consider a positive diagnosis of endometriosis (7), if not by laparoscopic diagnosis (2). In contrast, genetic testing services are unlikely to perform any form of investigations and may rely more qualitative analysis using retrospective symptom questionnaires (6). Studies using a case-control design may also differ in their identification of control participants.

In one meta-analysis of seven GWAS related to endometriosis, the control groups varied from women with diseases other than endometriosis, a negative diagnosis following surgery, a negative diagnosis following magnetic resonance imaging (MRI) or women who had no evidence of endometriosis diagnosis however did not report any negative diagnostic criteria (2). When studies that differ so considerably in their methodology are pooled for the purpose of meta-analysis, it can affect the power of the study as well as the likelihood of obtaining a significant result (2).

Ethnicity

Many of the GWAS on endometriosis have been performed on cohorts of European ethnicity (2), therefore potentially missing loci of variants more common in other ethnicities due to different allelic frequency patterns among various groups. Two studies which included only Asian descendants, it was possible to identify 5 SNPs that were strongly associated with endometriosis, however the same SNPs not found in a GWAS of participants from Europe, Oceania and America. participants(2). Rather than contradicting the evidence of the previous study, this may give insight into the heterogeneity of presentation amongst ethnic groups.

Disease variation

Endometriosis can be viewed as a dynamic process advancing from stage I to stage IV (see Table 1) which requires changes in the genetic environment as the disease progresses. This is seen through the variation in genes associated with stage I/II compared with stage III/IV of the condition, whereby most loci are active in stage III/IV of the disease (6). However, the disease is not only a linear progression, it also has phenotypic variation within stages leading to subtypes of the condition with predominantly dysmenorrhoea related symptoms, fertility issues or pelvic pain related symptoms.

Therefore, it is pertinent to consider the stage of the condition as well the predominant symptom a patient may be experiencing when looking at GWAS to find potential mutations. A patient with fertility issues thought to be the result of endometriosis may have a completely different set of mutations within their genome compared with a patient with predominantly pain related symptoms.

Candidate genes

A number of candidate genes have been identified through genetic association studies performed on samples of ectopic tissue and endometrial tissue as well as GWAS which gives insight into underlying processes that are affected in this condition (see Figure 1). These include alterations to genes involved in tumour suppression, detoxification, inflammation, angiogenesis, embryonic development and hormonal signalling (1).

Tumour suppression

Individuals with endometriosis have been found to have significantly higher proportions of chromosome 17 aneuploidy compared with healthy women which is of interest as genomic instability involving this chromosome is known to drive a number of different forms of cancer (1). The gene most implicated on this chromosome is TP53, a tumour suppressor gene which encodes p53, a protein well described for its role in driving cells to apoptosis as well as DNA repair.

There are a number of polymorphisms of this gene which have been implicated in endometriosis , particularly TP53 Arg72Pro which has been linked with endometriosis amongst Asian populations; as well as the C allele of the p53 codon which has also been identified as a potential biomarker for endometriosis (1).

Detoxification

A number of CYP genes which are responsible for the detoxification of exogenous metabolites through phase I and phase II have also been implicated in endometriosis. It is thought that this is achieved through altered metabolism of exogenous substances leading to intermediate compounds that cause false cellular signalling (1). This has particularly been noted in Asian populations where polymorphisms in CYP1A1 were associated with an increased disease risk; interestingly however this association was not seen amongst Caucasians, where the implicated gene was thought to be CYP19, reflecting the variance in genetic profile of the condition in different ethnic groups (1).

Exposure to agents which disrupt endocrine function also have been identified to have an impact on genetic susceptibility to endometriosis due to the effects of these chemicals on gene expression and physiological processes. Organochlorides can disrupt endocrine function through acting similarly to oestrogens, causing steroid hydroxylation, thus affecting fertility as well as susceptibility to cancers (1).

Inflammation and immunity

Various genes encoding interleukins and have been identified via GWAS and genetic association studies to be involved in endometriosis, most notably IL-1 and IL-16 (1, 2). This is thought to occur due to the role of both of these genes in producing pro-inflammatory cytokines causing recruitment of immune cells such as CD4 T lymphocytes, monocytes and eosinophils. Mutations in IL-6 (-634C/G) has been suggested to work synergistically with a mutation in ICAM-1 (469 K/E) to promote the development of endometriosis in Japanese populations, however a study of over 200 women in Brazil found that this mutation had no significant association with development of endometriosis, suggesting that further work is required to understand the role of IL-6 and ICAM-1 in endometriosis (1)

Samples of ectopic tissue from individuals with endometriosis have also been found to express COX2 more avidly than endometrial samples from unaffected individuals, with the number of mRNA replicates for COX2 in ectopic samples reaching up to 5 times that in unaffected individuals (1). This has led to the hypothesis that altered COX-2 activation in the presence of abnormal prostaglandin production may be a key factor in disease severity and progression to more severe forms of the disease (1).

PTPN22 is a gene located on chromosome 1p13.3 encoding Lyp, a downregulator of T-cell activation. A case-control study of Brazilian women identified that polymorphisms in this gene were associated with advanced disease stages of endometriosis, (1).

A systematic review of GWAS into endometriosis identified two SNPs downstream of NFE2L3, a transcription factor involved in inflammation, carcinogenesis and regulation of cell differentiation (2). The exact role of the gene in endometriosis is still unclear however the mutations have been found in three studies and associated with stage III and IV of the condition suggesting it may play a role progression to more severe forms of the condition (1, 2, 5).

Angiogenesis and embryonic development

A few genes involved in angiogenic pathways have been identified to have a role in endometriosis (1, 2). FGF2 is a gene encoding Fibroblast growth factor 2 which is involved in tissue repair, cell grown and morphogenesis. Mutations in this gene have been associated with adenomyosis and endometriosis in Chinese cohorts, however it is still unclear if this presence of mutations in this gene is a marker of increased susceptibility to these conditions (1, 4).
Mutations to the gene encoding VEGF has also been strongly associated with the development of endometriosis as well as a number of gynaecological cancers (1, 2). Confusingly, however, depending on the location of polymorphisms in VEG, as well as the ethnic groups involved in studies, this may either be protective or contributory to development of endometriosis (1) therefore further studies are required to identify any interactions with other regulatory proteins or promoter regions which may be leading to these conflicting data.

Genes involved in embryonic development have also associated with endometriosis, most notably WNT4 which plays an important role in female sexual development, angiogenesis, postnatal uterine development and progesterone signalling (1, 2, 4, 6, 8).

Mutations in WNT4 alter signalling during development and has a role in a number of other gynaecological pain related conditions including uterine leiomyoma and pelvic organ prolapse (2, 4, 8). WNT4 related mutations have further been associated with CDC42 which encodes a GTPase which may act as an enhancer to WTN4 signalling (8).

Mutations to FN1 have been discussed in GWAS related to endometriosis (1, 2). This gene encodes fibronectin, a glycoprotein involved in cell migration, embryogenesis, coagulation and wound healing (2). Samples of ectopic endometrial tissue were found to contain higher levels of fibronectin compared with endometrial tissue within the uterus however there have been conflicting results on its association with endometriosis between studies (2). In one study no association was found between mutations in FN1 and endometriosis, however, two studies have suggested its involvement in stage I/II disease as well as endometriomas (2).

Hormonal signalling

Hormones are thought to be an important factor in the development and progression of endometriosis. This is most often attributed to oestrogen, however, there have been a number of GWAS which have identified mutations in other hormones which have been thought to play a role in endometriosis.

Multiple GWAS have shown that genes altering the function of FSH are seen in individuals with endometriosis, these include mutations to the beta subunit FSHB (2, 4) as well as the receptor FSHR (1). It is likely that mutations to FSHR leads to altered plasma concentrations of FSH; which then can have consequences in oestrogen levels.

It has not been possible to prove that mutations in FSHR increases likelihood of developing endometriosis, however it has been identified as a factor which contributes towards disease progression as well as infertility (1). Mutations in FSHB have been identified via a number of GWAS to have a role in endometriosis, as well as other gynaecological conditions including uterine leiomyoma and pelvic organ prolapse (4-6, 8).

Furthermore, two genes have been identified through GWAS that are thought to affect oestrogen signalling; these are ESR1 and GREB1 (1, 2, 5, 6). Polymorphisms in ESR1 affect the alpha subunit of the oestrogen receptor, thereby casing changes to proliferation of the endometrium in individuals with this mutation, however, there have been conflicting results regarding mutations to this gene (1).

Some studies have suggested up to a 4-fold higher risk of endometriosis, whilst others have shown no association at all; however recent GWAS meta-analysis into endometriosis suggests that these conflicting results may be due to the fact that certain polymorphisms in ESR1 may also act to protect individuals from susceptibility to endometriosis (1). Both GREB1 and ESR1 have also been associated with increased risk of leiomyoma development (2, 4).

Association to other conditions

Recent evidence suggests that there are shared mutations between endometriosis and other gynaecological conditions such as uterine leiomyoma(2, 4) and pelvic organ prolapse (POP) (8). Mutations to GREB1, FN1 and FSHB have been suggested to play a role in leiomyoma, however, Mutations to WNT4 have been found in both leiomyoma and POP (2, 4, 5, 8). Further work is needed to identify whether this is suggestive that these conditions are different phenotypes of the same underlying condition or separate discrete conditions.

One study has used LD score regression to identify association of endometriosis with other conditions identified through GWAS (see Figure 2) (6). These findings suggest there is high correlation between endometriosis and fibroids, leiomyoma of uterus, heavy menstrual bleeding, back pain, osteoarthritis and regional pain syndromes suggesting that there may be a shared underlying process between these conditions (6).

Summary

There have been a number of genes which have been identified via genetic association studies as well as genome wide association studies to have a role in endometriosis. As research in this work continues to grow and larger datasets are being evaluated, clinicians must consider the study design as well as the participants involved in GWAS before considering the relevance of any findings for their own population cohort. There is much heterogeneity in this condition and it is still too early to be able to identify any possible biomarkers or diagnostic tools which may be used in every day practice. However, through analysis of common gene mutations seen amongst different conditions, it is possible to piece together possible cellular and hormonal signalling mechanisms which may play in important role in the pathogenesis and aetiology of these conditions, such that we may produce novel therapeutic targets.

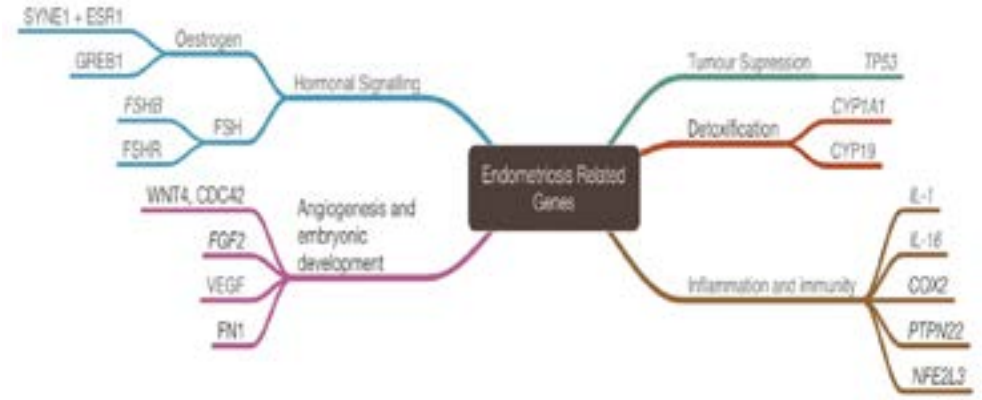


Figure 2 *– Mutations and proposed mechanisms of action of genes associated with endometriosis*

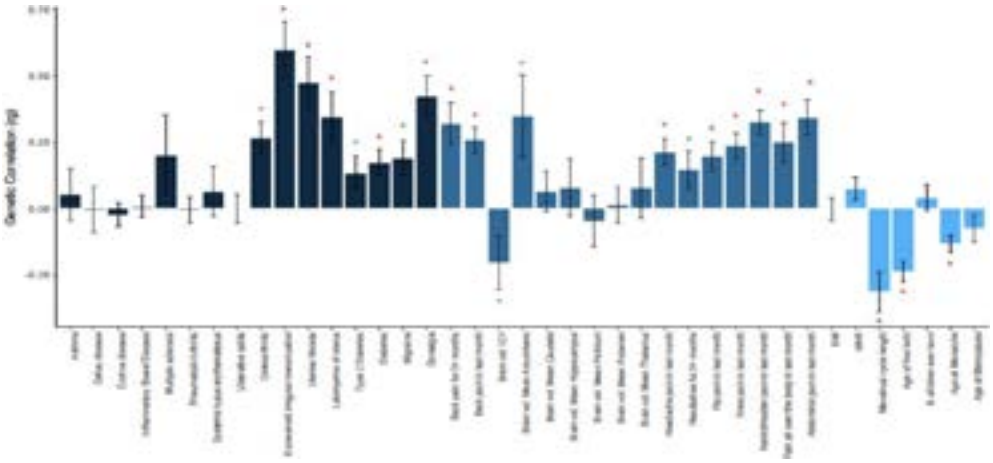


Figure 3 *- LD Score regression results for genetic enrichment between endometriosis and reproductive traits, anthropometric traits, pain-related symptomatology, and reproductive, autoimmune, metabolic and inflammatory conditions. The y-axis shows the genetic correlation (rg) between each condition and endometriosis with standard error bars. The x-axis shows the results per trait/condition. A red star denotes significant genetic enrichment after multiple-testing correction (p<l.28×10− 3) and a green star nominal association (p<0.05). (Adapted from Nilufer et al bioRxiv. 2018:406967) (6).*

References

1. Vassilopoulou L, Matalliotakis M, Zervou MI, Matalliotaki C, Krithinakis K, Matalliotakis I, et al. Defining the genetic profile of endometriosis. Experimental and therapeutic medicine. 2019;17(5):3267-81.
2. Cardoso JV, Perini JA, Machado DE, Pinto R, Medeiros R. Systematic review of genome-wide association studies on susceptibility to endometriosis. Eur J Obstet Gynecol Reprod Biol. 2020;255:74-82.
3. Fung JN, Montgomery GW. Genetics of endometriosis: State of the art on genetic risk factors for endometriosis. Best Pract Res Clin Obstet Gynaecol. 2018;50:61-71.
4. Gallagher CS, Mäkinen N, Harris HR, Rahmioglu N, Uimari O, Cook JP, et al. Genome-wide association and epidemiological analyses reveal common genetic origins between uterine leiomyomata and endometriosis. Nat Commun. 2019;10(1):4857.
5. Galarneau G, Fontanillas P, Clementi C, Hu-Seliger T, Parfitt D-E, Tung JY, et al. Genome-wide association studies on endometriosis and endometriosis-related infertility. BioRxiv. 2018:401448.
6. Nilufer R, Karina B, Paraskevi C, Rebecca D, Genevieve G, Ayush G, et al. Large-scale genome-wide association meta-analysis of endometriosis reveals 13 novel loci and genetically-associated comorbidity with other pain conditions. bioRxiv. 2018:406967.
7. Uno S, Zembutsu H, Hirasawa A, Takahashi A, Kubo M, Akahane T, et al. A genome-wide association study identifies genetic variants in the CDKN2BAS locus associated with endometriosis in Japanese. Nat Genet. 2010;42(8):707-10.
8.Olafsdottir T, Thorleifsson G, Sulem P, Stefansson OA, Medek H, Olafsson K, et al. Genome-wide association identifies seven loci for pelvic organ prolapse in Iceland and the UK Biobank. Commun Biol. 2020;3(1):129.

Expert Commentary

Robotic Surgery in Endometriosis- Is there a future?

Dr. Rooma Sinha
Senior Consultant Gynecologist, Laparoscopic & Robotic Surgeon. Honorary Professor, Apollo Hospital Education and Research Foundation.
Conjoint Associate Professor, Macquarie University Sydney, Australia.
Distinguished Clinician, Apollo Hospitals
Visiting Professor AIIMS Rishikesh
Mentor-Minimal Access & Robotic Fellowship (Apollo), FOGSI Endoscopy (Basic & Advance)
Apollo Health City, Hyderabad, INDIA

Dr. Girija Shankar Mohanty
Fellow, Minimal Access & Robotic Surgery
Department of Gynecology
Apollo Hospitals, Hyderabad

Endometriosis is a benign chronic inflammatory condition which presents as chronic pelvic pain or infertility. It is characterised by the presence and growth of ectopic dysfunction endometrial stroma and/or glands which is associated with reactive fibrosis and smooth muscle metaplasia found outside the uterus and affects approximately 11% of reproductive aged women (1).

Currently both medical and surgical treatment is used to manage endometriosis but persistence of disease and recurrence is a problem which both patients and physicians have to deal with equally. Surgical excision by laparoscopy of all visible endometriotic lesions is considered to be gold standard in treatment of endometriosis (2). However, surgery in advanced endometriosis can be a challenge even for experienced laparoscopic surgeons due to technical difficulties such as the surgeon's dexterity and visualisation of abnormal lesions. The same technical difficulties can be implicated in major complications (bowel injury, bladder or ureteric injury). Endometriosis Surgery is technically challenging mainly because of the occlusive nature of the disease that obliterates the surgical planes. Advanced technology of computer assisted surgery (robotic surgery) is now being increasingly evaluated for its role in surgery to circumvent some of these critical challenges of laparoscopy. Since 2005 when FDA approved the use of DaVinci surgical platform for gynaecological surgery the adoption of this technology in the field of benign gynaecology has been tremendous.

Robotics for endometriosis - A Game changer in three areas

1. Visualisation of disease especially for early and peritoneal lesions
2. The surgical precision in doing endometriosis & endometrioma surgery
3. Resection of deep infiltrating endometriosis

1. Visualization of endometriosis:

Early lesions are picked up with the help of detailed visual inspection of the pelvic cavity. Viewing the cavity through the advanced 3D console with stereoscopic ten times magnified vision of the robotic platform gives an edge in picking up early lesions. Even today visual diagnosis remains the key as imaging modalities like ultrasound or MRI have limited value. Good vision can ensure complete and detailed surgery in cases of endometriosis.(3) Compared to laparoscopic, robotic visualization resulted in detection of more confirmed lesions in all anatomic locations and different types of lesions, including the cul-de-sac (100 vs. 79%), atypical appearance (100 vs. 71.3%) and width <5 mm (100 vs. 62%). (4)

Robotic view of early endometriosis in the pelvis is shown in figures 1a, b, c, d. Such accurate diagnosis is especially important in adolescents. Early detection and intervention in young women will give a better quality of life and also cause lower damage of the ovarian tissue by a minimally invasive ablative surgery. Figure 2 shows vesicular lesions as well as the presence of focal adenomyosis of outer myometrium.

Incomplete resection is the main cause for persistence of pain after surgery. Addition of firefly technology in the robotic platform potentially helps in increasing the removal of invisible endometriosis. Indocyanine green (ICG) is a water-soluble dye that binds to plasma proteins. This is used with the infrared fluorescence imaging system integrated with the robotic platform. When injected the dye measures tissue perfusion and as endometriosis is associated with increased neovascularization, ICG turns these endometriotic lesions dark green, enabling their detection easy. Guan and colleagues found Firefly technology facilitated identification of endometriosis and were able to successfully perform single-site laparoscopic resection of advanced endometriosis nodules overlying the ureter and rectum with complete resolution of pelvic pain symptoms and excellent cosmetic results. (5,6) These lesions are often subtle and are not seen with the naked eye. Robotic surgery can be a game changer in identifying invisible small lesions and helps perform complete excision.

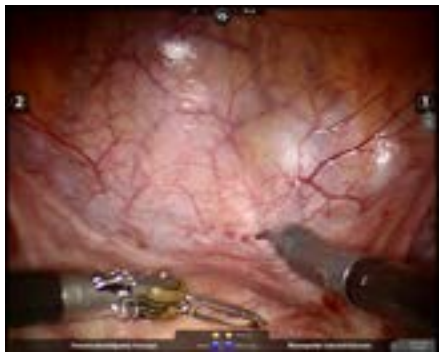


Fig. 1A: Early lesion in uterovesical fold of the peritoneum

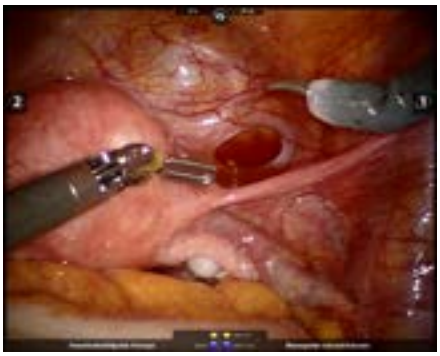


Fig 1B: AllenMasters Defect

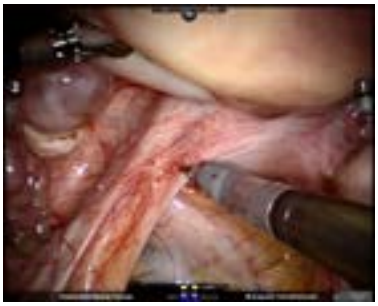


Fig 1C- Early lesion on left on utero-sacral ligament

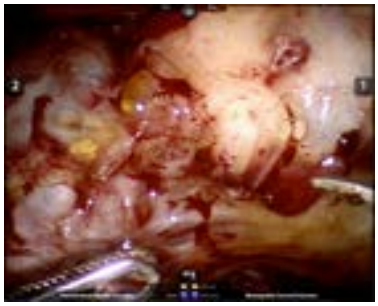


Fig 1D- Vesicular lesions on uterine surface

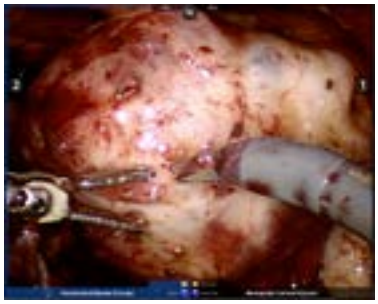


Fig 2- Focal adenomyotic lesions of outer myometrium

The surgical precision in doing endometriosis & endometrioma surgery

Endometriomas should be treated with cystectomy and not drainage and coagulation, as cystectomy reduces endometriosis-associated pain and recurrence (7).

Although cyst excision in endometriosis is a technique recommended by conventional laparoscopy which uses the force of traction and counter traction, the authors find this surgery to be more precise when articulated fine tip robotic instruments are used. Identifying the right planes of dissection is easily achieved.

When compared to laparoscopic traction-countertraction and rolling technique, the cyst wall excision in robotic assisted surgery proceeds step by step. Identification of the fibers between the cyst and ovarian tissue, precise dissection with short bursts of monopolar energy. This technique of cyst wall removal maintains the homeostasis thus avoiding the need for excessive bipolar coagulation for control of bleeding. We believe that such precise dissection has two advantages.

First, microsurgical principles using minute robotic instruments reduce postoperative adhesions Gomel et al advocated the value of robotic platform in performing microsurgery, so important for post-operative fertility outcome. (8)

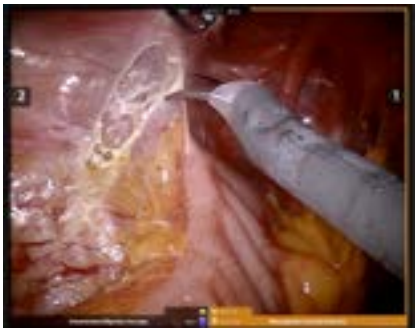


Fig 3: Step 1- Adheosiolysis of sigmoid from the lateral pelvic wall

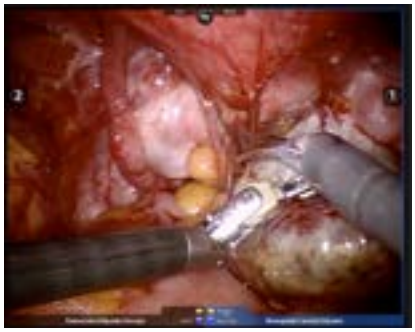


Fig 4: Step 2A- Releasing the endometrioma, the posterior surface of the uterus

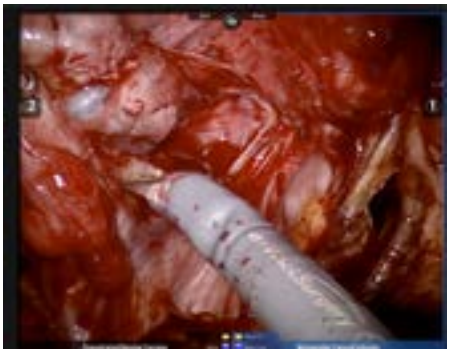


Fig 5: Step 2B- Releasing the left ovary from the ovarian fossa

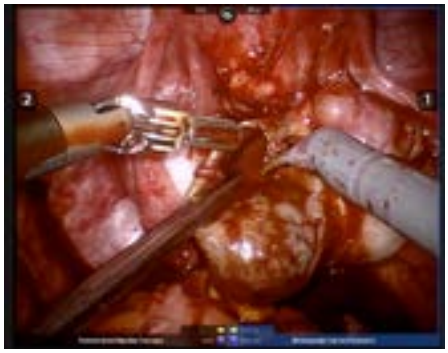


Fig 6: Step 3- Opening of the endometrioma and inspection of cyst wall

Second, there is a possibility that the loss of normal ovarian tissue is as minimal as possible, thus preserving the residual follicular reserve. However, this needs to be further evaluated by trials comparing laparoscopic and robotic techniques and long-term outcomes on future fertility. Figures (3,4,5,6,7) depict the various steps in performing ovarian cystectomy for endometrioma using robotic surgery.

Step 1- release of sigmoid from the lateral pelvic wall.

Step 2 a&b- Releasing the ovarian endometrioma from the posterior surface of the uterus and the ovarian fossa.

Step 3-opening the endometrioma, inspection of cyst lining.

Step 4- Ovarian cystectomy. Figure 8a shows severe pelvic adhesion among endometrioma, the rectum, and the pelvic peritoneum in the posterior cul-de sac and figure 8b depicts successfully performed endometriosis clearance using robotic surgery.

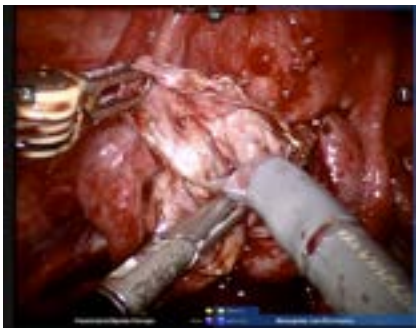


Fig 7: Step 4-Ovarian cystectomy in progress

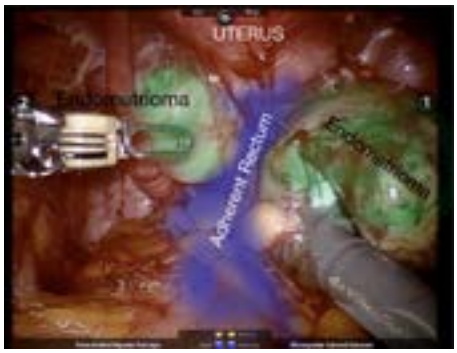


Fig 8A: Intial assessment. Bilateral adherent endometrioma with adhesion of rectum. Obliterated pouch of Douglas.

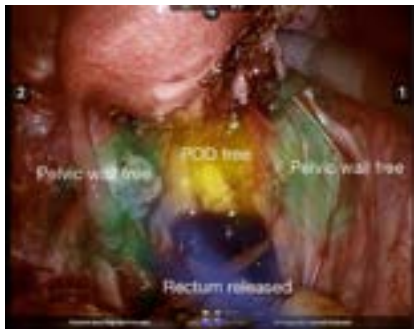


Fig 8B: After completion of surgery. Rectal adhesiolysis done with clear pouch of Douglas. Both ovaries free and both uterosacral ligaments seen.

3. Resection of Deep Infiltrating Endometriosis (DIE)

DIE is diagnosed when endometriosis occurs more than 5 mm deep into the peritoneum. Approximately 30-40% of patients with endometriosis have DIE (9). It commonly involves the recto vaginal space but is also seen in the urinary bladder, ureter and peritoneum. Dense adhesions are present due the infiltrative nature of DIE causing fibrosis and distortion of pelvic structures. As DIE lesions do not respond to medical therapy, complete radical excision and the restoration of normal anatomy are the most important points in managing such patients during surgery. To achieve this goal, advanced skills in dissecting the deep retroperitoneal space, isolating the ureter and the bowel, and suturing technique, are essential. However, those procedures are challenging using conventional laparoscopy and major complications such as bowel perforation and leakage are a reality.

Conversions to open surgery are often resorted to during such difficult dissections. Robotic surgery with all its advantages has the ability to help surgeons perform complex resections in such situations. Nezhat reported the first two cases of successful management for bowel endometriosis (segmental bowel resection and disc excision of the anterior rectal wall) without any complications by robotic surgery (10).
Following this, there are multiple reports of successful surgery for bowel endometriosis. Feasibility and safety of complete debulking of DIE even when segmental rectal resection, rectal shaving, or an ileocecectomy are required is reported with robotic surgery. It gives similar surgical outcomes and fewer complications than laparotomy; without the need for conversion. (11) (12) (13)
DIE of urinary tract can involve the ureter, bladder, and kidney in about 10% of endometriosis cases and can cause symptoms such as dysuria, haematuria, urinary frequency, and ureteral obstruction. Bladder is the most common site. Superficial endometriotic lesions can be treated with excision or fulguration but deep lesions infiltrating into the detrusor muscle or lumen of the ureter require resection and reanastomosis. These procedures need fine dissection and precise suturing. Convention laparoscopy presents many limitations in performing them. In our experience robotics has its advantages in such surgical interventions.

Various case series have reported robotic surgery being used for ureterolysis, ureteroneocystostomy, partial bladder resection compared surgical outcomes. Conventional laparoscopy and robotic surgery for bladder endometriosis showed similar surgical outcomes, including perioperative complications and recurrence rate. Robotic Surgery is safe and feasible for urinary tract endometriosis. (13,15–17)
Morelli et al suggested that Robotics is a better surgical method for the preservation of urinary and sexual function than laparotomy or laparoscopy. (14)

However, one must remember that surgery for deep infiltrating endometriosis, even with robotic assisted laparoscopy, is associated with significant morbidity so a multidisciplinary approach with a colorectal & urological surgeon should be kept in mind.

Discussion

The main advantage with the robotic platform is a shorter learning curve as compared to conventional laparoscopic surgery. The availability of simulations integrated with the console can help younger surgeons to hone their skills before starting surgery on patients. Even amongst the most skilled laparoscopic surgeons, there is a growing consensus that robotic assistance is probably most suited for endometriosis surgery and restoring the pelvic anatomy as a fertility enhancing surgery in advanced stages of endometriosis due to ease of instrument manipulation. The da Vinci Robotic Surgical System allows telestration. This helps the proctoring surgeons to write on a touch screen with a finger or an electronic pen.

This written instruction can be seen by both the console surgeon and the bedside staff. This feature helps the proctor to supervise a surgical step, guiding dissection in difficult planes and instructing when and how a particular step should be performed. The TilePro (Intuitive Surgical, Inc., Sunnyvale, CA) is another feature that allows for image and video input to the console. This can be used during surgery to have input of radiologic data (ultrasonography, computed tomography, or magnetic resonance imaging) during the early phase of the learning curve.

There is no doubt that computer assisted robotic platforms will enable more surgeons to do complex gynecological surgery and convert their open procedures to minimal invasive surgery in the years to come. The ability of the robotic platform to filter and reduce physiologic tremor and to transform surgeon's hand movements into more precise micro-movements can be a game changer in fertility enhancing surgeries especially in endometriosis.

Conclusion

Since the introduction of computer enhanced technology (robotics) to gynecological surgery in 2005, attention has been focused on its advantages and disadvantages. Most surgeons using this technology believe that it enables more surgeons to convert laparotomies to minimally invasive surgeries. Thus, the utility of the robotic platform lies in the management of severe cases of endometriosis. In the coming years this technology will find its place in clinical practice of minimally invasive gynecology, as a complimentary to the present conventional laparoscopy. As more surgeons are trained and utilize this enabling technology, one thing is certain; the number of minimally invasive surgeries for endometriosis will increase, reducing the incidence of open surgery in gynecology. Addressing the cost of equipment and surgeon credentialing will make this more acceptable to surgeons and patients alike.

Citations

1. Clement PB. The pathology of endometriosis: a survey of the many faces of a common disease emphasizing diagnostic pitfalls and unusual and newly appreciated aspects. Adv Anat Pathol. 2007 Jul;14(4):241–60.
2. Kochar kaur K, Allahbadia G, Singh M. Current Role of Surgery in Endometriosis; Indications and Progress. Surg Med Open Access J. 2018 May 11;1.
3. Nezhat C, Nezhat F, Nezhat C. Operative laparoscopy (minimally invasive surgery): state of the art. J Gynecol Surg. 1992;8(3):111–41.
4. Mosbrucker C, Somani A, Dulemba J. Visualization of endometriosis: comparative study of 3-dimensional robotic and 2-dimensional laparoscopic endoscopes. J Robot Surg. 2018 Mar;12(1):59–66.
5. Nezhat FR, Sirota I. Perioperative outcomes of robotic assisted laparoscopic surgery versus conventional laparoscopy surgery for advanced-stage endometriosis. JSLS. 2014 Dec;18(4):e2014.00094.
6. Guan X, Walsh T, Osial P, Xu D, Bridgett K. Robotic Single-Site Endometriosis Resection Using Firefly Technology. J Minim Invasive Gynecol. 2015 Nov 1;22(6):S118.
7. Hart RJ, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD004992.
8. Gomel V. The impact of microsurgery in gynecology. Clin Obstet Gynecol. 1980 Dec;23(4):1301–10.
9. Bellelis P, Dias JA, Podgaec S, Gonzales M, Baracat EC, Abrão MS. Epidemiological and clinical aspects of pelvic endometriosis–a case series. Rev Assoc Medica Bras 1992. 2010 Aug;56(4):467–71.
10. Nezhat C, Hajhosseini B, King LP. Robotic-Assisted Laparoscopic Treatment of Bowel, Bladder, and Ureteral Endometriosis. JSLS. 2011;15(3):387–92.
11. Lim PC, Kang E, Park DH. Robot-assisted total intracorporeal low anterior resection with primary anastomosis and radical dissection for treatment of stage IV endometriosis with bowel involvement: morbidity and its outcome. J Robot Surg. 2011 Dec;5(4):273–8.
12. Ercoli A, D'asta M, Fagotti A, Fanfani F, Romano F, Baldazzi G, et al. Robotic treatment of colorectal endometriosis: technique, feasibility and short-term results. Hum Reprod. 2012 Mar 1;27(3):722–6.
13. Collinet P, Leguevaque P, Neme RM, Cela V, Barton-Smith P, Hébert T, et al. Robot-assisted laparoscopy for deep infiltrating endometriosis: international multicentric retrospective study. Surg Endosc. 2014 Aug;28(8):2474–9.
14. Morelli L, Perutelli A, Palmeri M, Guadagni S, Mariniello MD, Di Franco G, et al. Robot-assisted surgery for the radical treatment of deep infiltrating endometriosis with colorectal involvement: short- and mid-term surgical and functional outcomes. Int J Colorectal Dis. 2016 Mar;31(3):643–52.
15. le Carpentier M, Merlot B, Bot Robin V, Rubod C, Collinet P. [Partial cystectomy for bladder endometriosis: Robotic assisted laparoscopy versus standard laparoscopy]. Gynecol Obstet Fertil. 2016 Jun;44(6):315–21.
16. Frick AC, Barakat EE, Stein RJ, Mora M, Falcone T. Robotic-assisted laparoscopic management of ureteral endometriosis. JSLS. 2011 Sep;15(3):396–9.
17. Giannini A, Pisaneschi S, Malacarne E, Cela V, Melfi F, Perutelli A, et al. Robotic Approach to Ureteral Endometriosis: Surgical Features and Perioperative Outcomes. Front Surg. 2018;5:51.

Update

Dienogest In The Treatment of Endometriosis

Dr. Shyam Desai MD DGO DFP MNAMS
FCPS. Consultant Port Trust Hospital. Director International Relations SAFOG. Honorary Professor, Wadia Hospital. Chairman Maternal Health AOFOG 2009 to 2013

Dr Gaurav S Desai MS FCPS
Assistant Professor, Seth GS Medical College and KEM Hospital. Joint assistant secretary Journal of Obgy of India. Managing Council member MOGS. IAGE Future award & AOFOG young Gynecologist award

Approximately 10% to 15% of women suffer from Endometriosis. Women of various ages may be afflicted but it is usually seen in the reproductive age group. The incidence is much higher in the infertile population amounting to about 30%. Approximately two thirds of women with Endometriosis are asymptomatic especially in the early stages of the disease. Of those who have symptoms Pelvic pain is the most common presenting symptom. The other symptoms seen include dysmenorrhea, dyspareunia, dyschezia, irregular bleeding, low back pain, hematuria and dysuria.The women with endometriosis often complain of fatigue.

The symptoms of endometriosis are due to various reasons. Endometriotic implants have impaired molecular and immunological functions.There is an exaggerated inflammatory response in the endometrial deposits which is associated with fibrous tissue formation and angiogenesis There is seen to be excess production of estrogen, and progesterone resistance. This leads to release of pro-inflammatory cytokines, prostaglandins and metalloproteinases and a failure of immune cells to suppress and clear the inflammatory response.

A constant supply of estrogen is crucial for the growth and persistence of the endometriotic implants, this estrogen comes from multiple sources. First, the endometrial implants have intrinsic aromatase activity, which leads to the conversion of cholesterol to estradiol. The endometrium is rich in PG-E2 receptors and activation of the PG receptor subtype EP-2 leads to activation of cyclic AMP, which increases the expression of key steroidogenic genes, and aromatase activity eventually leading to increased estradiol production. Along with intrinsic aromatase activity estradiol is also produced from the ovary and peripheral fat and this also reaches the sites of endometriosis.
The medical management of endometriosis is targeted towards controlling pain and suppression of the hormonally active endometriotic tissue to improve the quality of life without adverse effects of long term use of therapeutic agents.
A trial of non-steroidal anti-inflammatory drugs (NSAIDs) initially can be helpful in controlling the pain associated with dysmenorrhea.These along with Oral Contraceptives and Progestins are commonly used as first line agents in the treatment of endometriosis. Hormonal and non Hormonal therapies rely on suppression of the endometriotic implants.
The medications used for suppression of endometriosis such as GnRH analogues Danazol, OCs Progesterone derivatives,19 Nor Progesterone derivatives have proved effective in the short term but when administered over a period of time proved to be having drawbacks either with their tolerability or effectiveness and a large discontinuation rate has been observed.

For example even though Gn RH analogues have been proven to be very effective in reducing symptoms of endometriosis their profound estrogen suppression leads to severe menopausal symptoms and loss of BMD leading to the requirement of estrogen add back therapyIn addiction the duration of symptom relief after cessation of treatment is typically short decreasing the cost effectiveness.

Combined OC pills have been widely used for endometriosis treatment however they are not approved for this indication in many countries and their use is legally unsupported by solid clinical evidence. Danazol with its androgenic side effects such as alteration in lipid profile weight gain edema acne hirsutism and oily skin has limited acceptance. Progestins such as MedroxyProgesterone, can affect BMD in the long run and Levonorgestrel, and Norethisterone Acetate though potent can have severe progestogenic effects such as weight gain, acne and hirsutism.There remains therefore the need for a effective safe well tolerated medical therapy. Dienogest is a fourth-generation progestin of 19-nortestosterone derivative. It is almost completely absorbed when administered orally and is excreted completely in 24 hrs in the urine It has a relatively short half life of 10 hrs It has a high oral bioavailability of >90% offering potent progestogenic effects.

It is well tolerated with no androgenic, glucocorticoid or mineralocorticoid activity. binds to the progesterone receptor with high specificity, and produces a potent progestogenic effect related to the high circulating levels of the unbound molecule.

Dienogest is associated with relatively moderate inhibition of gonadotropin secretion, leading to a reduction in the endogenous production of estradiol. Hypoestrogenic, local endocrine environment, causing a decidualization of endometrial tissue followed by atrophy of the endometriotic lesions.As compared to the other Progestins It has high specificity for progesterone receptors and has less androgenic side effects with no affinity for estrogenic glucocorticoid or mineralocorticoid receptors.

Side effects of dienogest include Menstrual irregularities, Headache pain in the back tenderness in the breast hormonal changes induced hot flashes and mood fluctuations, acne, nausea vomiting and abdominal pain as well as weight gain. It has anti-androgenic activity like progesterone and hence has no effect on lipid and carbohydrate levels.
Thus Dienogest combines the advantages of 19 nor progestin derivatives and progesterone derivative classes. It creates a hypoestrogenic hypergestagenic environment locally. Continuous administration of Dienogest leads to decidualization and atrophy of the endometrial lesions. It also has anti-inflammatory, anti-angiogenic and anti-proliferative effects. Most importantly even after cessation of administration the symptom relief continues even as much as a year on. In a dose of 2mg or 4mg per day, dienogest has been shown to have a favorable profile for safety and efficacy, patients reported improvement in the endometriosis related symptoms and an overall improvement in quality of life.
It is in general well tolerate It is almost completely absorbed when administered orally and is excreted completely in 24 hrs in the urine It has a relatively short half life of 10 hrs.

Dienogest at 2 mg once daily is used as the optimal dose in the treatment of endometriosis for a duration of 12-24 weeks. Several trials are going on to assess the role of Dienogest pretreatment for endometriosis in comparison to gonadotropin releasing hormone agonist in patients of endometriosis undergoing IVF, with hypothetical results no significant difference was noted in no. of oocyte retrieved, pregnancy and miscarriage rate. Further studies and trials for validation of these results is still needed.

The optimum dose for safety and efficacy for the management of endometriosis has been based on a number of clinical studies with duration from 12 to 24 weeks. The studies have used doses of dienogest between one and 4 mg once daily. The 1 mg group usually had unsatisfactory results and bleeding patterns. Laparoscopic investigation showed that dienogest 2 mg and 4 mg significantly reduced endometriotic lesions as well as pain. The 2 mg and 4 mg dienogest doses were generally well tolerated and rates of discontinuations due to adverse events were low. Regular bleeding was experienced by nearly half the patients in the 2 mg and 4 mg group.

The separation of oestrogen levels with the 4 mg dose suggest that the 2 mg daily dose may offer lesser adverse effects on the bone mineral density.Hence a dose of 2 mg taken as the optimal dose.

The dose of dienogest in adolescents is particularly important as a higher dose usually leads to loss of bone mineral density and osteoporosis. The help of bones is especially important in growing adolescent girls. Even a dose of 2 mg for 52 week duration has been noted to cause significant bone mineral density decrease.Timely initiation and monitoring of diagnosis treatment is the crux of management of endometriosis in adolescent age group. In adolescents, surgical diagnosis should be avoided as far as possible in favor of clinical diagnosis. Treatment decisions should be made on an individual basis, using a risk–benefit approach that considers efficacy and safety.

Clinical trials of 12 to 24 weeks have shown that dienogest in a dose of 2mg/day provides effective pain relief equivalent to GnRH analogues a reduction of endometriotic lesions with a favorable safety and tolerability profile. A multicentre placebo controlled study carried out in Germany Italy and Ukraine showed extremely favorable findings for the use of Dienogest 2mg. Dienogest administered to patients with endometriosis Stages 1 to 4 showed that 90.5% completed the study There was a significant decrease in pelvic pain noted which lasted for 24 months after cessation of treatment Some patients had irregular bleeding, which improved with time.

To compare efficacy and safety of 1, 2 and 4 mg daily doses of Dienogest for endometriosis an open labelled randomized 24 week comparative trial was carried out by Kohler et al and reported in 2010. Dienogest at 2 and 4 mg was well tolerated with substantial symptom improvement with low rates of treatment discontinuation due to adverse effects The 1mg dose was discontinued because of insufficient bleeding control.
Several trials are going on to assess the role of Dienogest pretreatment for endometriosis in comparison to gonadotropin releasing hormone agonist in patients of endometriosis undergoing IVF, with hypothetical results no significant difference was noted in no. of oocyte retrieved, pregnancy and miscarriage rate. Further studies and trials for validation of these results is still needed

Conclusion
Dienogest provides complete ovulation inhibition at a daily dose of 2 mg. However, women taking dienogest as a treatment for endometriosis are advised to use nonhormonal methods of contraception. For those women who desire to conceive after dienogest therapy it is important to note that ovarian activity resumes rapidly (range 1–43 days) after cessation of dienogest. These observations support studies that describe a prompt return to fertility (eg, mean about 30 days).
Dienogest is contraindicated in patients with undiagnosed vaginal bleeding and during pregnancy and lactation. The woman's menstrual cycle resumes within two months of stopping the drug. Women with a cardiovascular disorder or a coagulation defect disorder or not advised to take dienogest. The group includes women at an older age, hypertension and smoking.Additional contraindication include diabetes, liver disease and hepatic tumours as well as cholestatic jaundice.

Evidence confirms that dienogest reduces endometriosis-associated pain, including pelvic pain, dysmenorrhea, dyspareunia, dysuria, and dyschezia. Before treatment initiation, patients should be counseled on what To expect with dienogest medication. They should be told that bleeding with dienogest 2 mg is not a sign of a lack of efficacy or recurrence of disease. There may be initial bleeding during the first few months, and bleeding/spotting with longer-term use. The Initial bleeding can be consistent and typically lasts for 8–10 days. Spotting me a car during long term treatment.
If the endometrium is found to be thin, a treatment break of 5–7 days to allow for the recovery of the atrophy of the endometrium, or a short-term application of 1 mg oral or transdermal estradiol (5–7 days) might be useful.

Patients with symptomatic DIE can be managed with dienogest 2 mg. Extragenital endometriosis of the urethra, bowel, or kidney, or fistulae in rectovaginal endometriosis Should be treated with surgery. Mood disturbances and depression with dienogest 2 mg requires regular monitoring at follow-up appointments as well as counselling and awareness. Possibly a treatment halt might be needed to reduce chances of more symptoms in patients on long-term treatment. In women with a previous history or a present diagnosis of clinical depression one should involve a psychiatrist and monitor treatment.

REFERENCES

Felice Petralgia et al. Reduced pelvic pain in women with endometriosis efficacy of long term dienogest treatment Arch Gynaecol Obstet 2012

Kohler G Faustmann TA Geringer C Seitz C Muck AO. A dose ranging study to determine the efficacy and safety of 1,2 and 4mg of Dienogest daily for endometriosis Int J Gynaecol Obstet 2011

Sasagawa S Shimizu Y Kami H Takeuchi T Mita S Imada K Kato S Mizuguchi K Dienogest is a selective progesterone receptor agonist in transactivation analysis with potent oral endometrial active its due to its efficient pharmacological profile. Steroids 2008 Feb

Momoeda M, Taketani Y. Randomized double-blind, multicentre, parallel-group dose–response study of dienogest in patients with endometriosis. Jpn Pharmacol Ther. 2007;35:769–783. Japanese.

Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. Am J Obstet Gynecol. 1992;166:740–745. [

Strowitzki T, Faustmann T, Gerlinger C, Seitz C. Dienogest in the treatment of endometriosis-associated pelvic pain: A 12-week, randomized, double-blind, placebo-controlled study. Eur J Obstet Gynecol Reprod Biol. 2010;151(2):193–198.

Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med. 2001;38(6):633–638.

Klipping C, Duijkers I, Faustmann T, Klein SF, Schuett B. Pharmacodynamic study of four oral dosages of dienogest. Fertil Steril. 2010;94 (Suppl 1):S181

Petraglia F, Hornung D, Seitz C, et al. Reduced pelvic pain in women with endometriosis: efficacy of long-term dienogest treatment. Arch Gynecol Obstet. 2011 June 17; [Epub ahead of print.]

Momoeda M, Harada T, Terakawa N, et al. Long-term use of dienogest for the treatment of endometriosis. J Obstet Gynaecol Res. 2009;35(6):1069–1076.

Dienogest 2 mg Daily in the Treatment of Adolescents with Clinically Suspected Endometriosis: The VISanne Study to Assess Safety in Adolescents Journal of Pediatric and Adolescent Gynecology Volume 30, Issue 5, October 2017, Pages 560-567.

IN THREATENED MISCARRIAGE &
RECURRENT PREGNANCY LOSS

TRUST THE EVIDENCE

DOSAGE IN **TM**

40 mg **STAT** followed by 20/30 mg per day until symptoms remit*

IF IT'S **ORALLY** EFFECTIVE, IT'S†

Duphaston®

Dydrogesterone Tablets IP 10 mg

BACKED BY **EVIDENCE**

DOSAGE IN **RPL**

10 mg **twice daily** until 20th week of pregnancy*

GLOBAL GUIDELINES BACK THE **WORLD'S NO. 1** PROGESTOGEN‡ §

1 MISCARRIAGE RANZCOG 2013

2 MISCARRIAGE FOGSI 2015

3 RPL ESHRE 2017

Duphaston® 60 YEARS§ OF DELIVERING INFINITE JOY

Pictures are for representation purpose only and not of actual patients.

TM: Threatened miscarriage. **RPL:** Recurrent pregnancy loss. **RANZCOG:** Royal Australian and New Zealand College of Obstetricians and Gynaecologists. **FOGSI:** Federation of Obstetrics & Gynaecological Societies of India. **ESHRE:** European Society of Human Reproduction and Embryology. † Schindler AE. Progestational effects of dydrogesterone *in vitro, in vivo* and on human endometrium. Maturitas. 2009;65 (1):S3-S11. * Prescribing information of Duphaston®. Version: 8.0, dated 20th November, 2019. ‡ Internal calculations based on Quintiles IMS database, IMS Health Analytics Link MAT03 2017. § Data on file.

References: 1. Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) 2013. http://www.ranzcog.edu.au/doc/progesterone-support-of-the-luteal-phase- and-early-pregnancy.html. Last accessed March 2014. **2.** Information available at http://www.fogsi.org/fogsi- gcpr/Last accessed September, 2016. **3.** Recurrent pregnancy loss.Guideline of the European Society of Human Reproduction and Embryology November 2017. ESHRE Early Pregnancy Guideline Development Group.

Abbreviated Prescribing Information: Dydrogesterone Tablets IP Duphaston® . LABEL CLAIM: Each film coated tablet contains: Dydrogesterone IP 10 mg, Excipients q.s. Colour: Titanium dioxide IP. **INDICATION:** Progesterone deficiencies: Treatment of dysmenorrhoea; Treatment of endometriosis; Treatment of secondary amenorrhoea; Treatment of irregular cycles; Treatment of dysfunctional uterine bleeding; Treatment of pre-menstrual syndrome; Treatment of threatened miscarriage; Treatment of habitual miscarriage; Treatment of infertility due to luteal insufficiency; Luteal support as part of an Assisted Reproductive Technology (ART) treatment and Hormone replacement therapy (To counteract the effects of unopposed oestrogen on the endometrium in hormone replacement therapy for women with disorders due to natural or surgical induced menopause with an intact uterus). **DOSAGE AND ADMINISTRATION:** Dysmenorrhoea: 10 or 20 mg dydrogesterone per day from day 5 to day 25 of the menstrual cycle. Endometriosis: 10 to 30 mg dydrogesterone per day from day 5 to day 25 of the cycle or continuously. Dysfunctional uterine bleeding: When treatment is started to arrest a bleeding episode, 20 or 30 mg dydrogesterone per day is to be given for up to 10 days. Secondary amenorrhoea: 10 or 20 mg dydrogesterone per day, to be given daily for 14 days during the second half of the theoretical menstrual cycle to produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen. Pre-menstrual syndrome: 10 mg dydrogesterone twice daily starting with the second half of the menstrual cycle until the first day of the next cycle. The starting day and the number of treatment days will depend on the individual cycle length. Irregular cycles: 10 or 20 mg dydrogesterone per day starting with the second half of the menstrual cycle until the first day of the next cycle. The starting day and the number of treatment days will depend on the individual cycle length. Threatened miscarriage: An initial dose of up to 40 mg dydrogesterone may be given followed by 20 or 30mg per day until symptoms remit. Habitual miscarriage: 10 mg dydrogesterone twice daily until the twentieth week of pregnancy. Infertility due to luteal insufficiency: 10 or 20 mg dydrogesterone daily starting with the second half of the menstrual cycle until the first day of the next cycle. Treatment should be maintained for at least three consecutive cycles. Luteal support as part of an Assisted Reproductive Technology (ART) treatment: 10 mg dydrogesterone three times a day (30 mg daily) starting at the day of oocyte retrieval and continuing for 10 weeks if pregnancy is confirmed. Hormone replacement therapy: Continuous sequential therapy: An estrogen is dosed continuously and one tablet of 10mg dydrogesterone is added for the last 14 days of every 28-day cycle, in a sequential manner. Cyclic therapy: When an estrogen is dosed cyclically with a treatment-free interval, usually 21 days on and 7 days off. One tablet of 10 mg dydrogesterone is added for the last 12 -14 days of estrogen therapy. **CONTRAINDICATIONS:** Known hypersensitivity to the active substance or to any of the excipients. Known or suspected progestogen dependent neoplasms (e.g. meningioma). Undiagnosed vaginal bleeding. Treatment for luteal support as part of an Assisted Reproductive Technology (ART) treatment should be discontinued upon diagnosis of abortion /miscarriage. Contraindications for the use of estrogens when used in combination with dydrogesterone. **WARNINGS & PRECAUTIONS:** Before initiating dydrogesterone treatment for abnormal bleeding the etiology for the bleeding should be clarified. Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy. If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with dydrogesterone and ceasing the treatment should be considered: Porphyria, Depression and Abnormal liver function values caused by acute or chronic liver disease. **PREGNANCY & LACTATION:** It is estimated that more than 10 million pregnancies have been exposed to dydrogesterone. So far there were no indications of a harmful effect of dydrogesterone use during pregnancy. Dydrogesterone can be used during pregnancy if clearly indicated. Breastfeeding: No data exist on excretion of dydrogesterone in mother's milk. Experience with other progestogens indicate that progestogens and the metabolites pass to mother's milk in small quantities. Whether there is a risk to the child is not known. Therefore, dydrogesterone should not be used during the lactation period. Fertility: There is no evidence that dydrogesterone decreases fertility at therapeutic dose. **ADVERSE REACTIONS:** The most commonly reported adverse drug reactions of patients treated with dydrogesterone in clinical trials of indications without estrogen treatment are migraines/headache, nausea, menstrual disorders and breast pain/tenderness. Undesirable effects in adolescent population: Based on spontaneous reports and limited clinical trial data, the adverse reaction profile in adolescents is expected to be similar to that seen in adults. Undesirable effects that are associated with an estrogen-progestogen treatment (see also 'Warnings and Precautions' and the product information of the estrogen preparation): Breast cancer, endometrial hyperplasia, endometrial carcinoma, ovarian cancer; Venous thromboembolism; Myocardial infarction, coronary artery disease, ischemic stroke Issued date as 20/05/2021 Source: Prepared based on full prescribing information (version 8) dated 20/11/2019.

IND2122433-3 22 Jun 2021

For full prescribing information, please contact:
Abbott India Limited, 16th Floor, Godrej BKC Plot C-68, 'G' Block, BKC, Near MCA Club, Bandra East, Mumbai-400 051. www.abbott.co.in

Abbott

Video Corner

TLH with extensive endometriosis

Dr. Nutan Jain
M.B.B.S. In 1980, from G.S.V.M. Medical College, Kanpur.
M.S. in Obs & Gynae in 1983 from G.S.V.M. Medical College, Kanpur.
Certification & Accreditation by All American Gynae Laparoscopist (AAGL) as Advance Laparoscopic & Hysteroscopic Surgeon. Rare Distinction for an Indian Gynaecologist
Training in Advance Ultrasound, Laparoscopic Microsurgery, Advanced infertility management, Advanced Endoscopic Surgery , Pelvic Floor Repair , Laparoscopy Oncology.
Elected Board member of International Society of Gynecological Endoscopy(ISGE) in 2006.
Nominated for AAGL Board of Directors in 2009 and 2019 to represent Asia Pacific Region

A 40 year old female with previous 2 LSCS presented to our hospital with complaints of severe pelvic pain, dysmenorrhea and dyschezia. Her ultrasonography findings suggested a right sided endometriotic cyst and recto vaginal nodule. We did a multiple port laparoscopy using a 30 degree telescope. The camera port is high up midway between the umbilicus and xiphisternum.

On entering we found the uterus jammed with the rectum and a large endometriotic cyst on the right side. The pelvis is frozen with adhesions obliterating the entire pouch of douglas. We start the case with injecting diluted vasopressin in large amounts around 300 ml in the uterus.

Then we unravel the retroperitoneum from the left pelvic brim with gradual bipolar and cutting scissors. The higher we start dissecting closer to the ureter, the easier it gets exposed upto the ureteric tunnel. The endeavour is to expose the medial pararectal space. Adhesiolyisis done around the endometriotic cyst followed by draining it.

Then we reach the rectovaginal space. Then the same is done from the right side. And after opening the medial pararectal space from both the right and left side, we clear up the rectovaginal space completely. We are using the rectal probe to safeguard the rectum and uterine manipulator to antevert the uterus which delineates the plane of cleavage between the nodule and back surface of the uterus.

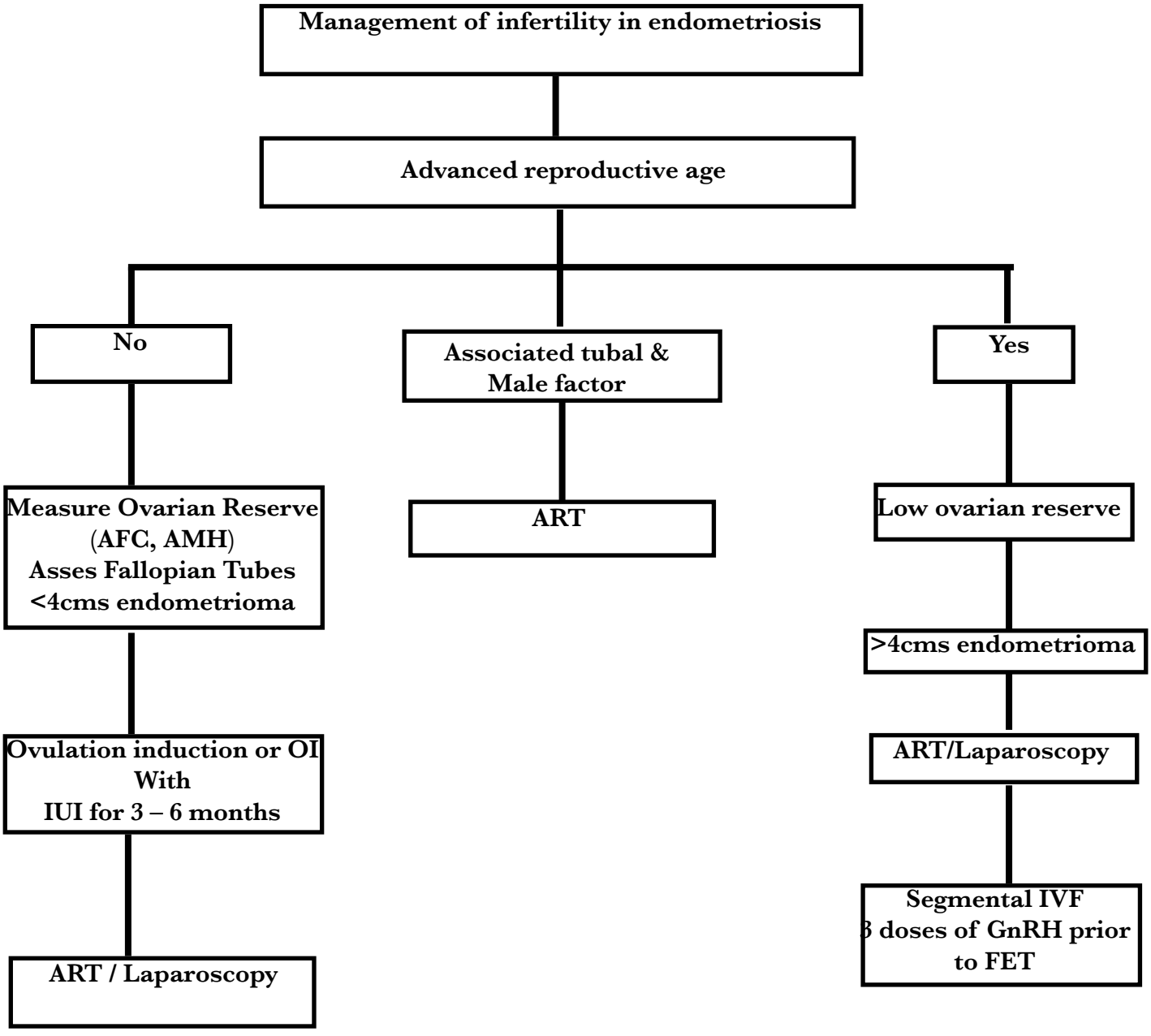
The rectovaginal nodule is shaved out over to the rectosigmoid and then excised out after holding with graspers. Taking care of the ureters, the TLH is commenced with Enseal PTC and Harmonic ACE .Bladder is slowly dissected using Rumi cup aided by harmonic ace followed by circumferential colpotomy through which uterus and rectovaginal nodule is delivered out. Vault sutured in two layers and suspended. Cystoscopy done as a routine which confirmed bilateral ureteric jet and peristalsis.

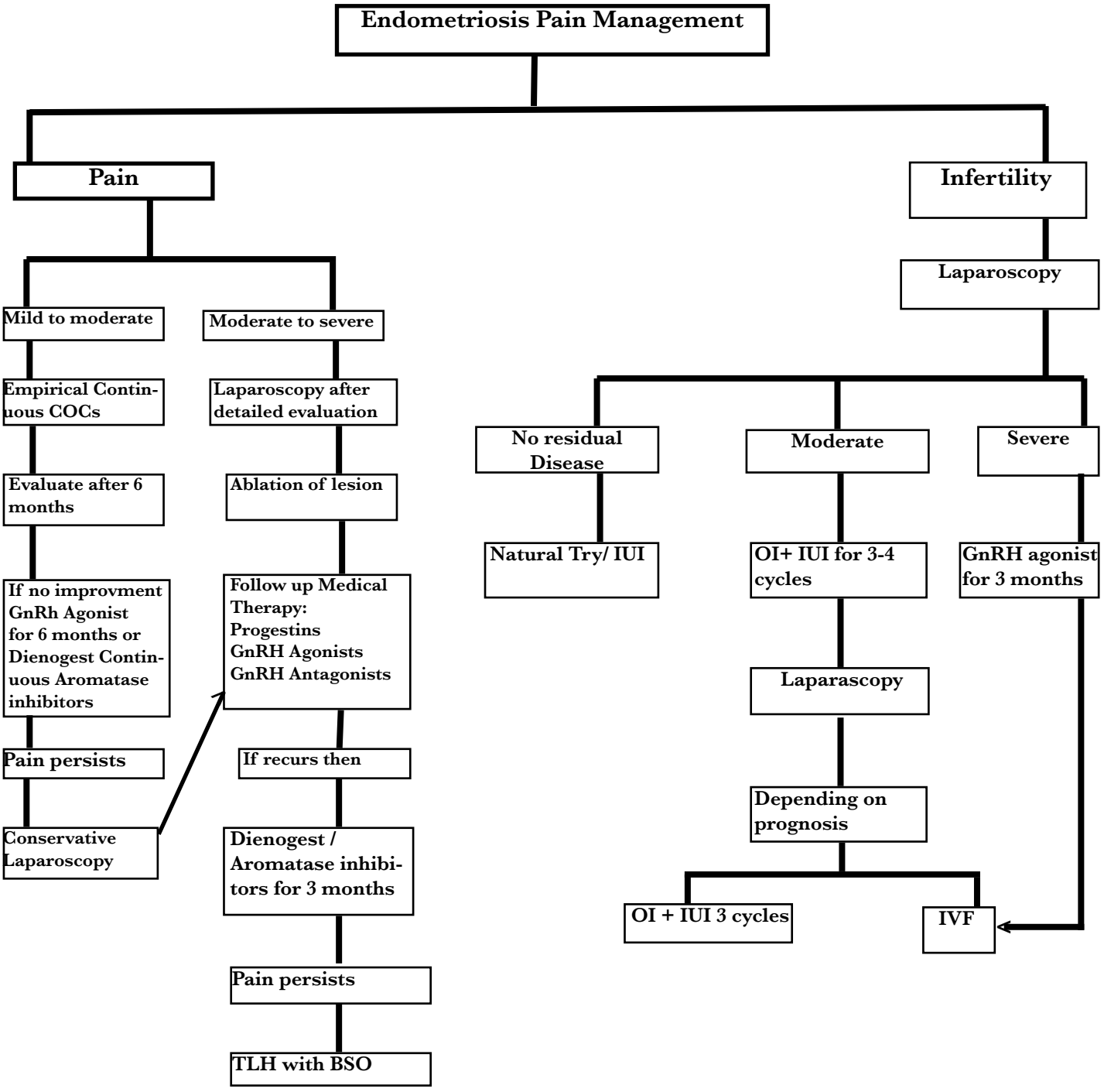
Video link: https://youtu.be/05qT6kbrRIQ

Tips For Your Practice

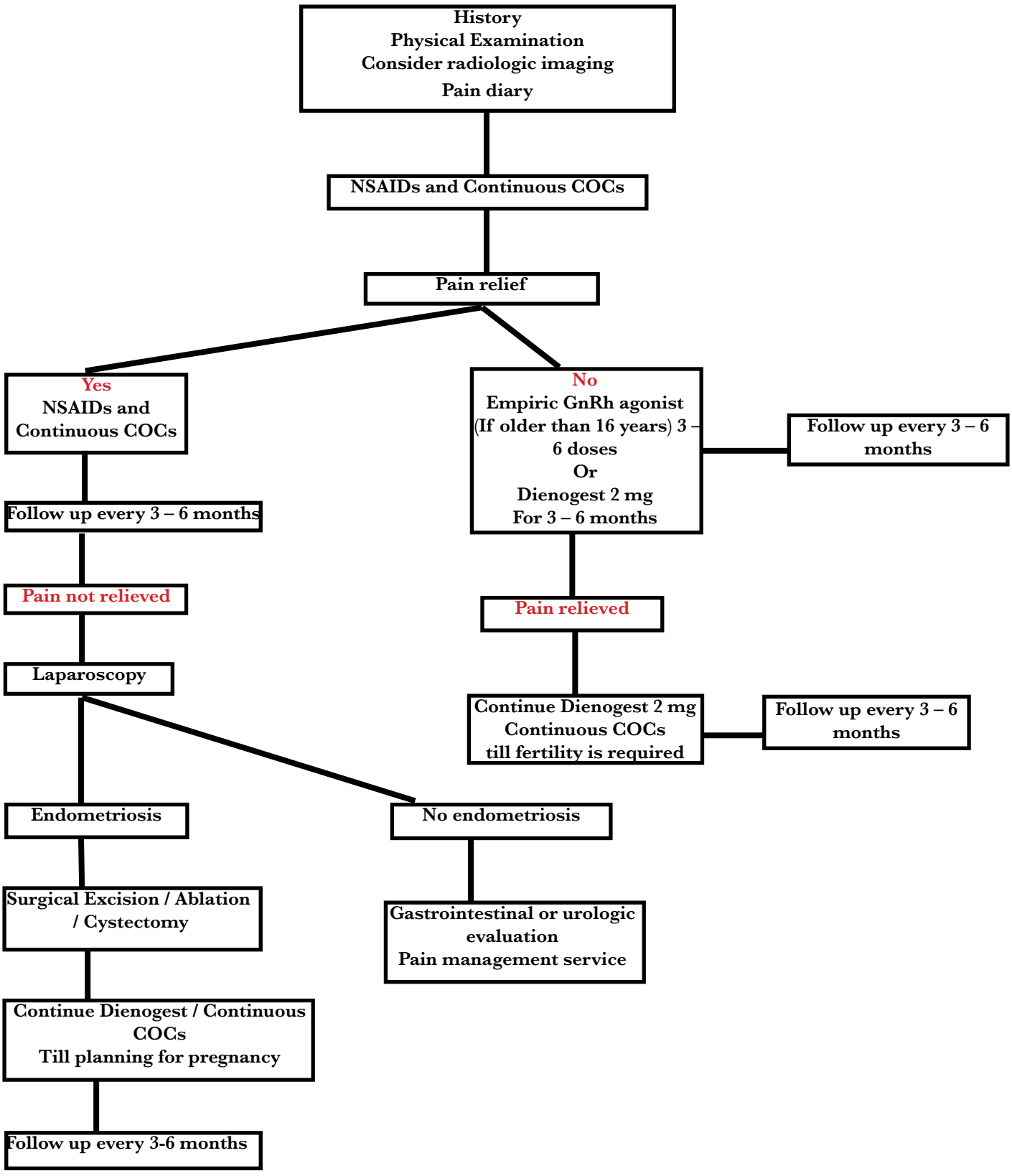
Dr. T. Ramani Devi, MD, DGO, FICS, FICOG.
Consultant at Ramakrishna Medical Centre LLP & Janani Fertility Centre, Trichy

Dr. Kanthi Bansal- Director, Safal Fertility Foundation, Ahmedabad. Founder Chairperson, Endometriosis Committee, FOGSI. Chairperson Endometriosis Committee SAFOG. Editor, European Journal of Endometriosis and Pelvic Pain Disorders.




Endometriosis Pain Management
Pain
Infertility
Mild to moderate
Moderate to severe
Laparoscopy
Empirical Continuous COCs
Laparoscopy after detailed evaluation
No residual Disease
Moderate
Severe
Evaluate after 6 months
Ablation of lesion
Natural Try/ IUI
OI+ IUI for 3-4 cycles
GnRH agonist for 3 months
If no improvment GnRh Agonist for 6 months or Dienogest Continuous Aromatase inhibitors
Follow up Medical Therapy:
Progestins
GnRH Agonists
GnRH Antagonists
Laparascopy
Pain persists
If recurs then
Depending on prognosis
Conservative Laparoscopy
Dienogest / Aromatase inhibitors for 3 months
OI + IUI 3 cycles
IVF
Pain persists
TLH with BSO

Adolescent Endometriosis



Images in Endometriosis

Ultrasound in deep infiltrating endometriosis

Dr. C B Nagori: Director- Dr. Nagori's Institute for Infertility and IVF, Ahmedabad. Faculty for Donald School Master's courses of Human Reproduction. Dr. Nagori's Institute is a centre for training for Donald School fellows for Masters in Human Reproduction and Ultrasound in Obstetrics and Gynecology.

Dr Sonal Panchal Consultant: Dr. Nagori's Institute for Infertility and IVF, Ahmedabad. Professor, Dubrovnik International University, Croatia. National Academic Director, Ian Donald Interuniversity school of medical ultrasound, India.

Introduction:
Deep-infiltrating endometriosis (DIE) is when endometriotic tissue extends >5 mm deep from peritoneal surface. DIE may involve bowel, bladder, uterosacral ligament, vagino-rectal septum, most commonly, and rarely abdominal organs. 4%–13% of women in reproductive age group and in 25%–50% of women with infertility present with DIE. Dysmenorrhea, dyspareunia, chronic pelvic pain are the common presenting symptoms. Dysuria or pain on defecation can be present if it involves bladder or bowel. The pathology of DIE is nodular myeloproliferative lesion with very little glandular and stromal tissue. The intense reactive sterile inflammation that occurs in DIE leads to adhesions and reactive fibrosis.1

Ultrasound techniques for diagnosis:
Transvaginal ultrasound-
performed on partially filled bladder

Systematic assessment is done bases on the consensus of – IDEA (international deep endometriosis analysis)3 which includes the following:

- Complete evaluation of uterus, adnexa and ovaries
- Check for tender points and ovarian mobility
- Confirm positive sliding organ sign during examination especially in POD
- Targeted search for endometriotic nodules in posterior and anterior compartments
- Pull out the probe till introitus and then angulate it posteriorly and slide it slowly over the posterior vaginal wall, critically observing the posterior vaginal wall, anterior anal canal and rectal wall and interface in between.
- Side to side movement along with to assess vault thickness and regularity (normally it is thin and hypoechoic).

Transabdominal assessment-
performed on full bladder

- Exclude hydroureter or hydronephrosis and ureteric involvement
- Look for scar endometriosis
- Identify lesions in small bowel, appendix2, omental endometriosis

Transrectal route-

- When vaginal approach is not possible
- When further evaluation of rectal lesions are required
- For uterosacral ligament thickening
-

Trans labial route-

- For superficial lesions, chiefly involving vaginal wall

3D imaging-

- details about the infiltration of the muscularis of the bowel
- to assess the multiorgan involvement and adhesions

Ultrasound appearance:
Rectosigmoid DIE:

- Solid hypoechoic linear thickening or nodules with or without regular contour in the anterior muscularis of the bowel
- Discontinuity of central line of muscularis (Muscularis is traversed by an echogenic line that separates inner circular and outer longitudinal muscle layer).
- Typical "Red Indian head" appearance with fibrotic retraction in submucosa lesion. (Figures 1a, b)
- On transverse section, signet ring appearance can be identified
- Lesions may be multifocal.
- Negative sliding organ sign between the uterus and the bowel has likelihood ratio of 23.6 for rectal DIE4.
- TRUS has sensitivity of 97% and specificity of 96% and TVS has sensitivity of 99.3% and specificity of 87.2%.5

Vaginal DIE:

- Localized hypoechoic thickening of the vaginal wall with or without anechoic areas. (figure 2a,b)
- More clearly appreciated if probe is placed only superficially in the vaginal canal and the vaginal cavity is filled with gel (Gel Vagino-Sonography) or use 12ml (instead of 4ml routinely used) gel in condom or can fill the rectum with water.

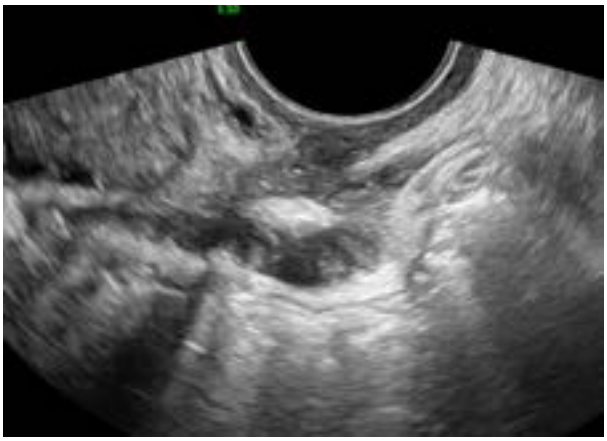


***Figure 1a**: bowel endometriosis- "Red Indian Head" sign as shown by the arrow*

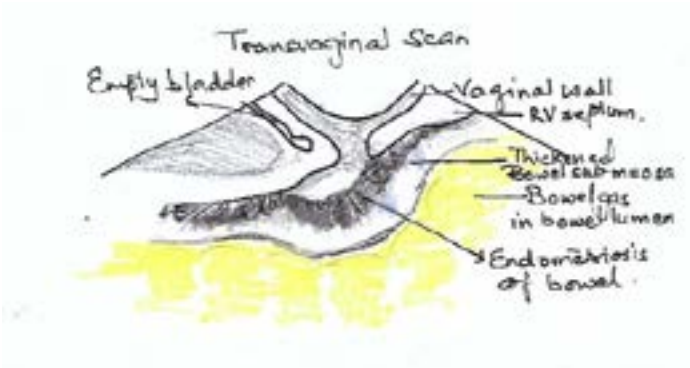


***Figure 1b:** Diagrammatic presentation of the bowel endometriosis- "Red Indian Head" sign*

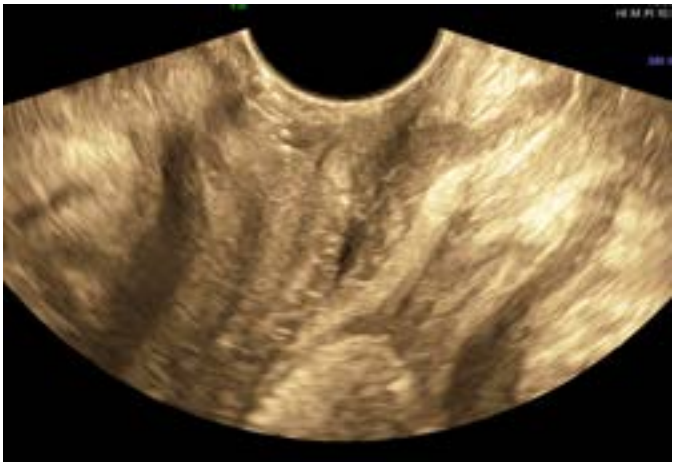


***Figure 2a:** Arrow showing irregular hypoechoic lesion involving the posterior vaginal wall and adjacent rectum- rectovaginal septum endometriosis (arrow)*

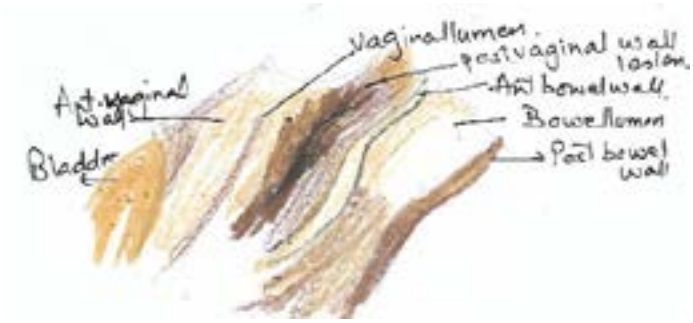


***Figure 2b:** diagrammatic representation of rectovaginal endometriosis*

Cervical DIE:

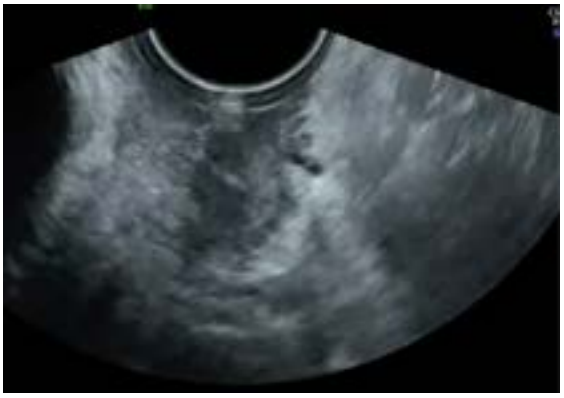
- Thick firm cervical wall appears as hypoechoic area on ultrasound. (Figure 3 a, b)
- ill-defined margins, at times associated with acoustic shadowing on gel Vagino-Sonography.

Uterosacral DIE:

- Thick (> 14mm) uterosacral ligament with hypoechoic, irregular soft tissue mass instead of a string-like structure on both sides of cervix.6
- TVS has sensitivity of 70.6% and specificity of 95.9% for uterosacral endometriosis5
- 3D rendering- endometriotic nodule of typical irregular contour
- Tomographic ultrasound imaging (TUI) to evaluate extension of nodule in rectovaginal septum
- Transrectal scan may be better route

Bladder DIE:

- Localized thickening of bladder wall with hypoechoic and hypovascular area (figure 4a, b) / solid projection on 2D ultrasound. (Figure 5a, b).
- Trigone is most commonly affected may also involve the ureteric insertion and may lead to obstruction and hydronephrosis
- Inflammation and fibrosis may to distortion of surrounding anatomy.



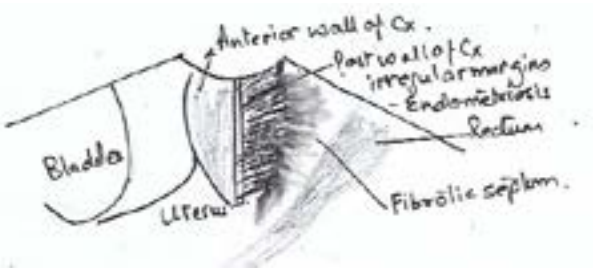
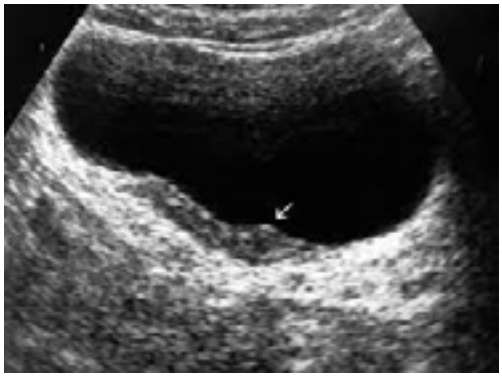


***Figure 3a**: irregular hypoechoic lesion involving posterior cervical lip with irregular margins, outlines by thick hyperechoic margin due to inflammatory hypertrophy surrounding the lesion*

***Figure 3b:** diagrammatic representation of cervical deep infiltrating endometriosis.*



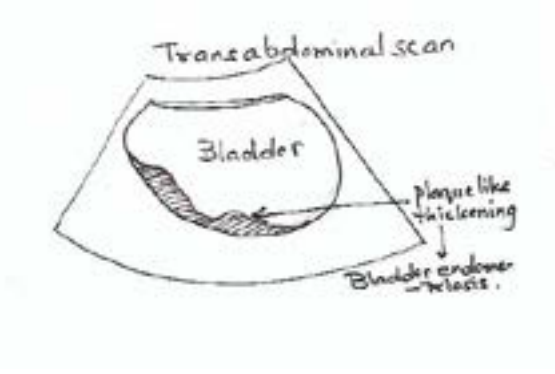
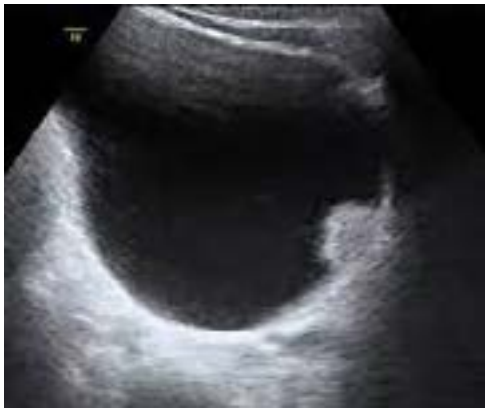


***Figure 4a, b:** Ultrasound image and diagrammatic presentation of plaque like lesion in the bladder- endometriotic patch.*



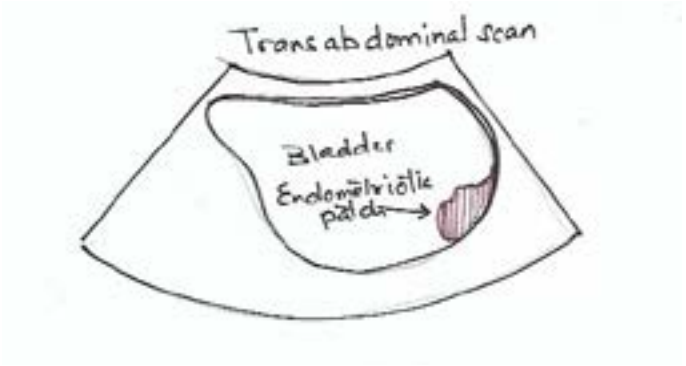


Figure 5a, b: *Ultrasound image and diagrammatic presentation of nodule like lesion in the bladder- endometriotic in origin.*

References:

1. O. Burney and L. C. Giudice, "Pathogenesis and pathophysiology of endometriosis," Fertility and Sterility, vol. 98, no. 3, pp. 511–519, 2012.
2. R. L. Gustofson, N. Kim, S. Liu, and P. Stratton, "Endometriosis and the appendix: a case series and comprehensive review of the literature," Fertility and Sterility, vol. 86, pp. 298–303, 2006.
3. Guerriero S, Condous G, van den Bosch T, et al. Systematic approach to sonographic evaluation of the pelvis in women with suspected endometriosis, including terms, definitions and measurements: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group. Ultrasound Obstet Gynecol. 2016;48:318-32.
4. Hudelist G, et al. Uterine sliding sign: a simple sonographic predictor for presence of deep infiltrating endometriosis of the rectum. Ultrasound Obstet Gynecol. 2013;41: 692-95.
5. Bazot M. Thomassin I, Hourani R, et al. Diagnostic accuracy of transvaginal sonography for deep pelvic endometriosis. Ultrasound Obstet Gynecol. 2004; 24:180-5.
6. Ohba T, Mizutani H, Maeda T, Matsuura K, Okamura H. Evaluation of endometriosis in uterosacral ligaments by transrectal ultrasonog- raphy. Hum Reprod 1996; 11:2014-17

In Chronic Pelvic Pain

℞ LUPRIDE DEPOT 1M 3M

Leuprolide Acetate Depot Inj. 3.75 mg / 11.25 mg

Suppresses Chronic Pelvic Pain & Improves Fertility

ACOG*and RCOG** support the empiric use of GnRH agonist in the diagnosis and management of CPP, even in the absence of confirmation of histology, after exclusion of other causes of pain[1]

ESHRE 2014 guideline: management of women with endometriosis[2]

Guideline development group (GDG), recommends GnRH agonists (Level A) as one of the options, as it reduces endometriosis-associated pain as against hormonal contraceptives (Level B)[2]

Six months of GnRH agonist therapy immediately following surgery

- Reduces the rate of symptom recurrence[4]
- Increases the length of time before symptoms recur[5]
- It is also more effective in managing endometriosis-related pain after surgery than using oral contraceptives[6]

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

1. Michele Morelli et.al Gynecol Endocrinol, 2013; 29(4): 305–308. 2. G.A.J. Dunselman, ESHRE guideline: management of women with endometriosis, Human Reproduction, Vol.0, No.0 pp. 1–13, 2014.
3. A. E. Schindler, Gynecol Endocrinol 2004;19:51–55. 4. Hemmings R. J Reprod Med 1998;43(3):316-320. 5. Schweppe K-W, Hummelshoj L. Recommendations on the use of GnRH in the management of endometriosis. In: Lunenfeld B (ed). GnRH Analogs in Human Reproduction. United Kingdom: Francis & Taylor, 2005:53-66. 6. Muzii L, Marana R, Caruana P, et al.. Am J Obstet Gynecol 2000;183:588-592

* American College of Obstetrics and Gynaecology. ** Royal College of Obstetrics and Gynaecology

Level A recommendation: Meta-analysis or multiple randomized trials (of high quality) Level B recommendation: Meta-analysis or multiple randomized trials (of moderate quality)

In Endometriosis associated Pelvic Pain

℞ EMERSA

Dienogest 2 mg Tablets

Effective Management of Endometriosis with Safety

Provides significantly greater reduction in endometriosis-associated pelvic pain (EAPP) than placebo in a 24-week[1]

Dienogest 2 mg once daily is

- Effective in the long-term management of EAPP in women with endometriosis[1]
- Progressive decreases in EAPP and bleeding irregularities during continued treatment[1]

Long term efficacy

- Highly effective in preventing recurrence after surgery[2]
- Reducing endometriosis-associated pain[2]
- Decreasing the size of recurrent endometrioma[2]

1. J Womens Health (Larchmt) 2019 Feb;28(2):170-177. doi: 10.1089/jwh.2018.7084. Epub 2018 Nov 21.
2. Clin Exp Reprod Med 2016;43(4):215-220.

Inca Life Sciences
a SUN PHARMA division

Alternate Therapies in Endometriosis

Nutritional approach for endometriosis

Dr. P. Raghavendra, Scientist - B, Division of Public Health Nutrition, ICMR - National Institute of Nutrition, Hyderabad.

Dr. Teena Dasi, Scientist - B, Division of Mother and Child Nutrition, ICMR - National Institute of Nutrition, Hyderabad.

Endometriosis is defined as the presence of functioning endometrium-like tissue outside the uterine cavity resulting in a chronic inflammatory condition driven by the hormones oestrogen and progesterone. Various studies conducted in Indian population have shown the incidence of endometriosis to range from 34% to 48% as diagnosed by laparoscopy.1The aetiology and pathogenesis of endometriosis are not yet fully understood.

However, copious evidence suggests that oxidative stress is involved both in the pathogenesis and the pathophysiology of endometriosis.2 Also immunological, endocrinal, genetic and environmental factors all appear to play a significant role in its pathogenesis. Among the environmental aspects, nutrition has been little studied, despite evidence showing its impact on the origin and progression of the disease3, 4.

Endometriosis can currently be treated pharmacologically and/or surgically. Because of the limited amount of success of treatment and because of the chronic character of endometriosis, it is worth exploring the literature to gather evidence on the nutritional approach for reducing the inflammation and pain associated with endometriosis. The current scientific evidence suggests that the diet and lifestyle may influence the presence of inflammation in the body, estrogen activity, menstrual cycle, and prostaglandin metabolism5

Pathophysiology of endometriosis:

In the typical lesions of the disease, the cells grow, differentiate out of the uterus, and retain their ability to respond to hormonal proliferative stimuli. Furthermore, excess estrogen stimulates the formation of large amounts of prostaglandins (from the even series), promoting inflammation and, consequently, a painful stimulus6, 7. During the progression of the disease, changes occur resulting in abnormal immunological antigen-antibody reactions, contributing to the increase of pro-inflammatory agents6. Women with endometriosis have a higher concentration of lipid peroxidation markers in the blood and peritoneal fluid, which promotes cell adhesion and activation of macrophages. These, in turn, release reactive oxygen and nitrogen species, leading to oxidative stress.8

Potential dietary strategies:

With the available literature, diets can be classified as the ones which will affect the occurrence of endometriosis (Preventive effect) and the diets which will affect the existing endometriosis (Therapeutic effect).

Diets which affect the occurrence of endometriosis:

Vegetables: Two studies have analysed the relation between servings/ week or day of green vegetables and fruit intake and risk of endometriosis3, 9 Green vegetable and fruit consumption were inversely associated with the risk of endometriosis3. Increased number of servings/ day of fruit was associated with increased disease risk (two or more versus one or less servings/day: OR 1.5, 95% CI 1.2–2.3, P trend = 0.04), but no association emerged with vegetables9

Fruit: Fruits contain antioxidants, which reduce oxygen free radicals thus having the potential to reduce inflammation (reduction in oxidative stress). This may, theoretically, also lower the risk of developing endometriosis. Fruits may contain organochlorines10 (due to the residual pesticides) which in turn have been positively associated with the risk of endometriosis11 Vitamins: Antioxidants (such as vitamins A, C, E and B 9 [folic acid]) reduce the amount of oxygen free radicals through effects on lipid peroxidation (LPO) and may thus have an anti-inflammatory effect.6, 9, 12. The antioxidant action exerted by vitamins may reduce the clinical consequences of endometriosis.

Fats: A diet that is high in fat is associated with various health effects, both positive and negative. Foods high in saturated fats like red meat and trans fats which are found in processed and deep fried foods are associated with higher risk of developing endometriosis. Whereas diets rich in monounsaturated fatty acids (olive oil, nuts and milk) and poly unsaturated fatty acids (fish, seaweed and nuts) have shown to be associated with low risk of developing endometriosis.

Saturated fats

Saturated fats may lead to higher plasma concentrations of oestradiol or steroid hormones and are therefore associated with the occurrence of oestrogen-dependent diseases 3. In 2018, within the Nurses' Health Study II, Yamamoto et al.13 were able to show that the consumption of red meat at > 2 portions/day was associated with a 56 per cent higher risk of developing endometriosis in comparison with women who only ate red meat once a week

Transfats

Transfats, which rarely occur naturally but can be found in processed and deep-fried foods, are generally categorised as being harmful to health. Trans fats are linked with higher levels of inflammation mediators such as TNF-alpha, interleukin 6 and C-reactive protein and, consequently, with increased inflammation.

Missmer et al.14 were able to show that women in the highest quintile for the consumption of trans fats were 48 per cent more likely to develop endometriosis as compared with women whose trans-fat consumption was in the lowest quintile

Monounsaturated fatty acids

Monounsaturated fatty acids, which occur in olive oil, nuts and milk, for example, have antioxidant properties and have an anti-inflammatory effect. Six studies3,6,9,12,14,15 considered the effect of the consumption of monounsaturated fatty acids on the risk of developing endometriosis. With regard to the potential effect on the risk of endometriosis, none of the cited studies were able to show any clear correlations.

Polyunsaturated fatty acids

Polyunsaturated fatty acids (such as omega-3 fatty acids and omega-6 fatty acids) primarily come from fish, seaweed and nuts. They have been proven to play a role in the regulation and reduction of inflammatory prostaglandins and cytokines (interleukins 1, 2 and 6, TNF-alpha). They were proven to reduce the proliferation of endometriosis lesions both in vivo and in vitro.16,17

Dairy products, vitamin D and magnesium

Kriegel et al.18 were also able to show that vitamin D deficiency could lead to an increased risk of inflammatory diseases. This could also apply to the occurrence of endometriosis. Vitamin D has been proven to stimulate immunosuppressive regulatory T-cells as well as the secretion of interleukin-10 and inhibits pro-inflammatory interleukin-17 and T-helper cells. Several studies19,20 have shown that magnesium leads to the relaxation of smooth muscle cells and can thus have an antispasmodic effect. This suggests that magnesium could influence the pathogenesis of endometriosis (retrograde menstruation) as well as on pain symptoms. Harris et al.21 were able to demonstrate that the consumption of magnesium was associated with a significantly lower risk of endometriosis.

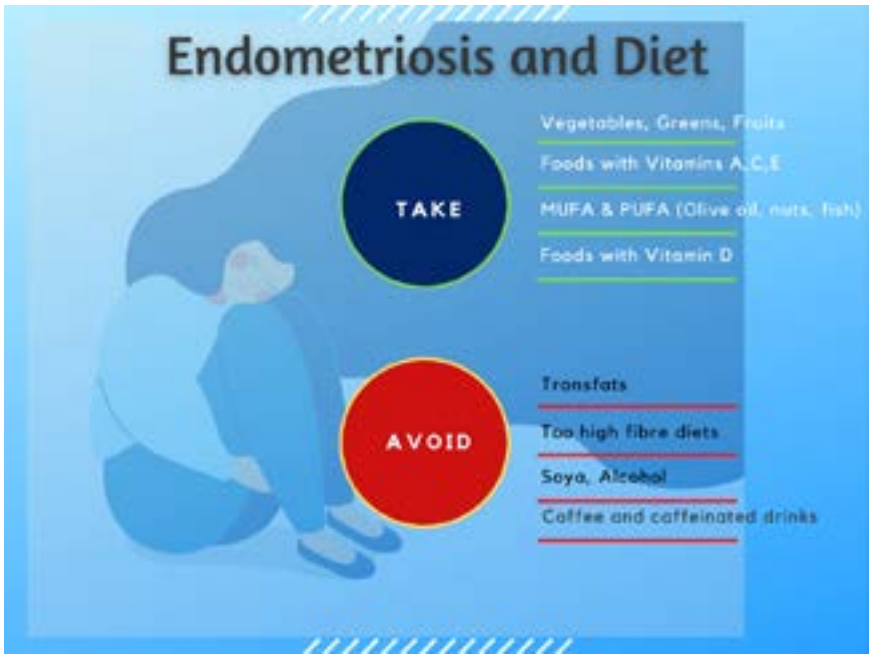
Fibre
A high-fibre diet is generally associated with health benefits. In this case, a high-fibre diet means one that is rich in complex carbohydrates with a low glycaemic index. Increased endometrial proliferation and thus a potentially elevated risk of endometriosis can occur as a result of simple carbohydrates (with a high glycaemic index).

Soya and phytoestrogens (isoflavones)
As a result of their oestrogenic effects, phytoestrogens, which primarily occur in soya, may be linked with the occurrence of endometriosis and other oestrogen-dependent diseases

Coffee and caffeine
According to the literature, the consumption of caffeinated beverages increases the availability of oestrogen and oestrones in the follicular phase as it is positively associated with sex hormone-binding globulin concentrations and inversely with bioavailable testosterone22 In three studies, an increased risk was reported in women reporting any versus no or infrequent coffee consumption.23-25 The association was statistically significant in two of them.

Alcohol
Alcohol is considered a risk factor for developing oestrogen-dependent diseases because it increases the activity of aromatase and thus the availability of oestrogen in the blood. Furthermore, there is a significant correlation between alcohol consumption and the occurrence of some chronic inflammatory diseases. According to a 2013 meta-analysis by Parazzini et al.3, there is a significant correlation between alcohol consumption and the occurrence of endometriosis

Diets which will affect the existing endometriosis:
The comprehensive review by Hansen et al26 showed that increased consumption of omega-3 fatty acids led to lower pain intensity, lower pain duration and lower painkiller use.
Sesti et al.27 investigated the effects of hormone therapy vs. diet-related measures vs. placebo in a randomised study in women having undergone surgery with more severe endometriosis (rASRM grades III and IV)
Women receiving hormone suppressants after surgery or receiving diet-related treatment showed significant pain reductions in all three categories ($p < 0.001$), as well as higher quality of life ($p < 0.001$) as compared with the placebo group.



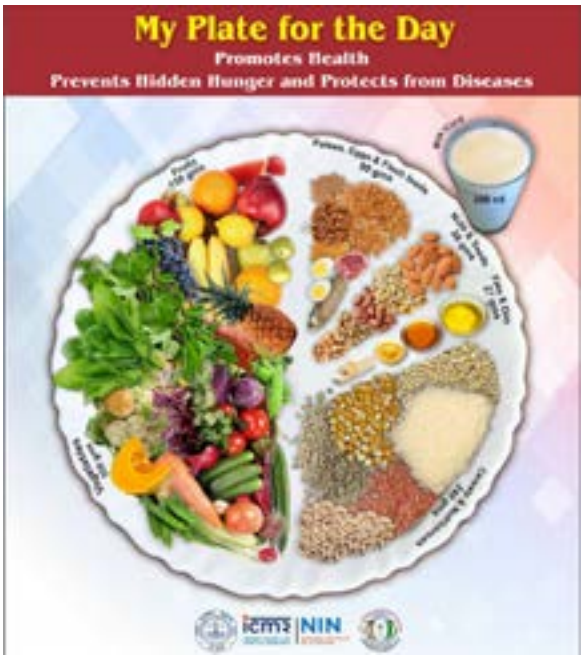
The following table provides insights to the role of diet in occurrence and progression of endometriosis:

Author	Study design	Dietary factor	Effect
Parazzini et al.[28], 2004	Case control study with experimental group (n = 504) consisted of women aged 20-65 years with confirmed endometriosis and the control group (n = 504) consisted of women aged 20–61 years with no gynecological disorders	Vegetables Fruits fats, fish oils, PUFA Red meat Vitamin – D	↓ ↓ ⇔ ⇧ ⇔
Trabert et al.[9], 2010	Case control study with experimental group (n = 284) consisted of women aged 20–65 years diagnosed with endometriosis and the control group (n = 660) consisted of healthy women	Vegetables Fruits fats, fish oils, PUFA Red meat Vitamin D	⇔ ⇧ ↓ ⇔ ↓
Savaris and Amara 6, 2011	Case control study with experimental group (n = 25) consisted of women with stage I–IV endometriosis and the control group (n = 20) consisted of women with no gynecological disorders	Fibre fats, fish oils, PUFA	⇧ ↓
Britton et al.[12], 2000	Case control study with subjects belonging to age:18–74 years, the experimental group (n = 393) – women with benign ovarian tumors, (n = 280) women with endometrial tumors; Control group (n = 351) - women with no diagnosed ovarian tumor or endometrial tumor	fats, fish oils, PUFA	⇧
Missmer et al.[14], 2010	Prospective study with experimental group consisted of n = 1,199 women aged 25–42 years diagnosed with endometriosis and the control group consisted of n = 69,510 healthy women	Omega – 3 FA Trans fatty acids	↓ ⇧
Harris et al.[21], 2013	Prospective cohort study with experimental group (n = 705.56) consisted of women aged 25–42 years including (n = 1.385) women diagnosed with endometriosis and the control group consisted of the healthy women	Vitamin D	↓
Khanaki et al.[29], 2012	Case control study with experimental group (n = 46) women diagnosed with stage I–IV endometriosis, and the control group (n = 74) consisted of women with no gynecological disorders	fats, fish oils, PUFA	⇔
Sesti et al.[27], 2009	RCT with Women diagnosed with endometriosis divided into four groups: placebo group (n = 65), GnRH-a therapy group (n = 65), group treated by continual low doses of the monophasic oral contraceptives, supplements (vitamins, mineral salts, lactic acid, cod liver oil) (n = 65)	fats, fish oils, PUFA	⇔
Heilier et al.[15], 2006	Case control study with experimental group (n = 176) consisted of women with diagnosed endometriosis and endometrial nodules and the control group (n = 88) healthy women	fats, fish oils, PUFA Red meat Vitamin D	⇔ ⇔ ⇔

↓ = decreased risk; ⇧ = increased risk; ⇔ = no influence

Conclusion:

With the available literature, we can conclude that there is evidence that diets influence the pathogenesis and progression of endometriosis. Though hormone therapy is the main mode of the available treatments, often with many side-effects, our focus on diets which lower the risk of developing and progressing endometriosis seems to be a sustainable approach along with regular exercise and weight loss. However, endometriosis being a complex and multifactorial disease, it is difficult to qualify or quantify the diet to be taken for women suffering with this condition. Therefore, the general recommendations for a balanced and varied diet in line with the guidelines of the NIN (My plate for a day) apply good even for endometriosis. In future, we can consider developing individual nutrition plans to ease the progression of endometriosis which requires not only epidemiological studies but also experimental studies to establish the extent to which individual nutrients affect the progression of endometriosis.



References:

1. Rajeshwari M, Ramanidevi T, Kadalmani B. Cohort study of endometriosis in south Indian district. Int J Reprod Contracept Obstet Gynecol. 2016; 5(11):3883–88
2. Augoulea A, Alexandrou A, Creatsa M, Vrachnis N, Lambrinoudaki I. Pathogenesis of endometriosis: the role of genetics, inflammation and oxidative stress. Arch Gynecol Obstet. 2012 Jul;286(1):99-103. doi: 10.1007/s00404-012-2357-8. Epub 2012 May 1. PMID: 22546953.
3. Parazzini F, Viganò P, Candiani M, Felede L. Diet and endometriosis risk: a literature review. Reprod BioMed Online. 2013, 26:323-36.
4. Paris K, Aris A. [Hypothetical link between endometriosis and accumulation of xenobiotics associated with genetically modified foods]. Gynecol Obstet Fertil. 2010; 38:747-53.
5. Jurkiewicz-Przondziono J, Lemm M, Kwiatkowska-Pamuła A, Ziółko E, Wójtowicz MK. Influence of diet on the risk of developing endometriosis. Ginekol Pol. 2017;88(2):96-102. doi: 10.5603/GP.a2017.0017. PMID: 28326519.
6. Savaris, A.L., do Amaral, V.F., 2011. Nutrient intake, anthropometric data and correlations with the systemic antioxidant capacity of women with pelvic endometriosis. Eur. J. Obstet. Gynecol. Reprod. Biol. 158, 314–318.
7. Bulun SE. Endometriosis. N Engl J Med. 2009; 360:368-797
8. Mier-Cabrera J, Aburto-Soto T, Burrola-Méndez S, Jiménez-Zamudio L, Tolentino MC, Casanueva E, et al. Women with endometriosis improved their peripheral antioxidant markers after the application of a high antioxidant diet. Reprod Biol Endocrinol. 2009; 7:54.
9. Trabert, B., De Roos, A.J., Schwartz, S.M., Peters, U., Scholes, D., Barr, D.B., Holt, V.L., 2010. Non-dioxin-like polychlorinated biphenyls and risk of endometriosis. Environ. Health Perspect. 118, 1280–1285.
10. Grassi, P., Fattore, E., Generoso, C., Fanelli, R., Arvati, M., Zuccato, E., 2010. Polychlorobiphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) in fruit and vegetables from an industrial area in northern Italy. Chemosphere 79, 292–298.
11. Buck Louis, G.M., Chen, Z., Peterson, C.M., Hediger, M.L., Croughan, M.S., Sundaram, R., Stanford, J.B., Varner, M.W., Fujimoto, V.Y., Giudice, L.C., Trumble, A., Parsons, P.J., Kannan, K., 2012. Persistent lipophilic environmental chemicals and endometriosis: the ENDO Study. Environ. Health Perspect. 120, 811–816.
12. Britton, J.A., Westhoff, C., Howe, G., Gammon, M.-D., 2000. Diet and benign ovarian tumors (United States). Cancer Causes Control. 11, 389–401.
13. Yamamoto A, Harris H R, Vitonis A F. A prospective cohort study of meat and fish consumption and endometriosis risk. Am J Obstet Gynecol. 2018;219:1780–1.78E12
14. Missmer, S.A., Chavarro, J.E., Malspeis, S., Bertone-Johnson, E.R., Hornstein, M.D., Spiegelman, D., Barbieri, R.L., Willett, W.C., Hankinson, S.E., 2010. A prospective study of dietary fat consumption and endometriosis risk. Hum. Reprod. 25, 1528–1535.
15. Heilier JF, Donnez J, Nackers F, et al. Environmental and host-associated risk factors in endometriosis and deep endometriotic nodules: a matched case-control study. Environ Res. 2007; 103(1): 121–129, doi: 10.1016/j.envres.2006.04.004, indexed in Pubmed: 16781705.
16. Calder P C. N-3 polyunsaturated fatty acids and inflammation: from molecular biology to the clinic. Lipids. 2003;38:343–352. [Europe PMC free article]
17. Gazvani M R, Smith L, Haggarty P. High omega-3:omega-6 fatty acid ratios in culture medium reduce endometrial-cell survival in combined endometrial gland and stromal cell cultures from women with and without endometriosis. Fertil Steril. 2001;76:717–722.
18. Kriegel M A, Manson J E, Costenbader K H. Does vitamin D affect risk of developing autoimmune disease? : a systematic review. Semin Arthritis Rheum. 2011; 40:512–5.31E10.
19. Altura B T, Altura B M. Endothelium-dependent relaxation in coronary arteries requires magnesium ions. Br J Pharmacol. 1987;91:449–451. intracellular Ca2+ without changing intracellular Mg2+ J Clin Invest. 1992;89:1988–1994.

20. D'Angelo E K, Singer H A, Rembold C M. Magnesium relaxes arterial smooth muscle by decreasing intra cellular Ca2+ without changing intracellular Mg2+ J Clin Invest. 1992;89:1988–1994.
21. Harris HR, Chavarro JE, Malspeis S, et al. Dairy-food, calcium, magnesium, and vitamin D intake and endometriosis: a prospective cohort study. Am J Epidemiol. 2013; 177(5): 420–430, doi: 10.1093/aje/kws247, indexed in Pubmed: 23380045.
22. Homan, G.F., Davies, M., Norman, R., 2007. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. Hum. Reprod. Update 13, 209–223.
23. Grodstein, F., Goldman, M.B., Ryan, L., Cramer, D.W., 1993. Relation of female infertility to consumption of caffeinated beverages. Am. J. Epidemiol. 137, 1353–1360.
24. Berube, S., Marcoux, S., Maheux, R., 1998. Characteristics related to the prevalence of minimal or mild en dometriosis in infertile women. Canadian Collaborative Group on Endometriosis. Epidemiology 9, 504–510.
25. Matalliotakis, I.M., Cakmak, H., Fragouli, Y.G., Goumenou, A.G., Mahutte, N.G., Arici, A., 2008. Epide miological characteristics in women with and without endometriosis in the Yale series. Arch. Gynecol. Obstet. 277, 389–393.
26. Hansen, S. O., & Knudsen, U. B. (2013). Endometriosis, dysmenorrhoea and diet. European Journal of Obstetrics & Gynecology and Reproductive Biology, 169(2), 162-171.
27. Sesti F, Capozzolo T, Pietropolli A, et al. Recurrence rate of endometrioma after laparoscopic cystectomy: a comparative randomized trial between post-operative hormonal suppression treatment or dietary therapy vs. placebo. Eur J Obstet Gynecol Reprod Biol. 2009; 147(1): 72–77, doi: 10.1016/j.ejogrb.2009.07.003, indexed in Pubmed: 19665279.
28. Parazzini, F., Chiaffarino, F., Surace, M., Chatenoud, L., Cipriani, S., Chiantera, V., Benzi, G., Fedele, L., 2004. Selected food intake and risk of endometriosis. Hum. Reprod. 19, 1755–1759.
29. Khanaki K, Nouri M, Ardekani AM, et al. Evaluation of the relationship between endometriosis and omega-3 and omega-6 polyunsaturated fatty acids. Iran Biomed J. 2012; 16(1): 38–43, indexed in Pubmed: 22562031.

Journal Scan

Dr. Saswati Sanyal Choudary

MD FICMCH FICOG FIAOG
Professor Dept of O&G. Gauhati Medical College
Vice President ISOPARB
President ISOPARB Assam chapter
Chairperson Medical Education Committee FOGSI.

'Does Cabergoline Help in Decreasing Chronic Pelvic Pain Due to Endometriosis Compared to Medroxyprogesterone Acetate?'
A Prospective Randomized Study

Kyal A, Pal A, Mukhopadhyay A, Mukhopadhyay P. J South Asian Feder Obst Gynae 2018;10(3):167-169.

ABSTRACT

Aims & objectives: The study aims to assess the safety and efficacy of cabergoline with respect to medroxyprogesterone acetate in treatment of chronic pelvic pain (CPP) due to endometriosis. Materials and methods: This study was conducted in Medical College, Kolkata from June 2015 to June 2016. Eighty patients of chronic pelvic pain due to endometriosis (diagnosed by USG and laparoscopy) were randomly assigned into two groups of 40 each receiving either medroxyprogesterone acetate (10 mg TDS) or cabergoline (0.5 mg twice weekly) for 12 weeks. Response for pain was measured on a visual analog scale (VAS) of 0–10 scale at the beginning of treatment and at intervals of 1, 3, 4 and 6 months.

Results: The study shows that the decrease in pain scores at various time points was statistically significant in both the groups. However, when the two groups were compared among themselves the reduction in VAS score at various time points were not statistically significant. Patients receiving medroxyprogesterone acetate had more side effects (67.5%) compared to cabergoline (47.5%). The most common side effect in medroxyprogesterone acetate group was amenorrhea (25%) whereas, in the cabergoline group, it was nausea and vomiting (45%).

Conclusion: Cabergoline and medroxyprogesterone acetate are equally effective in decreasing chronic pelvic pain due to endometriosis. However, due to lesser side effects and less frequent dosing, cabergoline has a better acceptance and compliance than medroxyprogesterone acetate. Thus cabergoline can be a better alternative to medroxyprogesterone acetate.

Reviewer's comments:
Dopamine agonists are used mostly in cases of prolactinoma. Cabergoline is a dopamine receptor 2 agonist. Its use is wider than other dopamine agonists like bromocryptine, because of its lesser side effects and dose conveniences. Use of Medroxyprogesterone acetate in endometriosis is mostly symptomatic by making the patient amenorrhoeic and thereby reducing pain. Cabergoline is an anti-angiogenic substance and was found to reduce angiogenesis in endometrial lesion in mouse model. Patient's acceptance is more in drugs which does not cause amenorrhoea but at the same time reduces pain. Cabergoline is better choice for those patients who do not want to be amenorrhoeic as well as do not prefer injectable route of administration.

Does cabergoline help in decreasing endometrioma size compared to LHRH agonist? A prospective randomized study

Amr M Salaheldin Abdel Hamid 1, Wael A Ismail Madkour, Ashraf Moawad, Mohamed Abd Elzaher, Mary P Roberts. Arch Gynecol Obstet. 2014 Oct; 290(4):677-82.

Aim: The aim of this study was to compare the efficiency of dopamine agonist, Cabergoline, in decreasing the size of endometrioma, with that of luteinizing hormone releasing hormone (LHRH) agonist, triptorelin acetate.

Study: This was a prospective, randomized study.

Setting: The setting was in two private medical centers in the UAE, from January 2011 to February 2012.

Patients and methods: One hundred and forty patients complaining of endometrioma, and fulfilling the eligibility criteria, were chosen and divided into two groups as follows: Group I comprised 71 patients; all of them received Cabergoline tablets, 0.5 mg tablets, twice per week for 12 weeks. Group II comprised 69 patients; all of them received LHRH agonist, decapeptyl, 3.75 mg subcutaneous, single injection, once a month for 3 months. All patients underwent vaginal ultrasound before and after the treatment period to compare the change in the size of endometrioma by the same sonography team in each hospital that was blind to the treatment groups.

Outcome: The outcome was measured by the changes in the endometrioma size by vaginal ultrasound after completion of the 3 months' treatment period. The management line was considered to be significantly effective if the endometrioma size was reduced by more than 25 % of its original pretreatment size.

Results:
Group I: 46 out of the 71 patients (64.7 %) had significant decrease in endometrioma size.
Group II: 15 out of 69 patients (21.7 %) had significant decrease in endometrioma size. Paired t test to compare the means of the two groups was highly significant ($p < 0.05$)

Conclusion: Cabergoline (dostinex) yields better results in decreasing the size of endometrioma, compared to LHRH-agonist by exerting antiangiogenic effects through vascular endothelial growth factor receptor-2 (VEGFR-2) inactivation. It has no major side effects, easier to administer, and cheaper than LHRH agonist

Reviewer's Comments: GnRH analogue is an established medication for the conservative treatment of endometrioma. But long-term use results in anti-estrogenic effect with reduction of bone mineral density and needs add-back therapy. Recurrence of endometrioma is observed after the therapy is stopped. GnRH injections are expensive and may not be suitable for a majority of our patients. Neovascularization is seen in endometriosis tissues and cabergoline with its anti-angiogenic property appears to be a suitable option. Endometriosis develops neuronal tissue as shown with immunohistochemistry, Studies have shown that there is significant reduction in neuronal tissue following cabergoline therapy. Long term of implications of cabergoline for endometriosis use needs to be evaluated, however we have used this molecule for long term management of prolactinomas without much adverse events. I have personal experience of using this in a young girl with a small endometrioma for 3 months and the there was considerable decrease in size.

MEMBERSHIP FORM

Member type= LIFE MEMBERSHIP

(Doctors having post graduation (MD or DNB in any field of Medicine or Surgery)
(Membership fees -) 5000/-

Personal Details:

1. Date of Application:
2. Full name:
3. Address (including zip code):
4. Email:
5. Telephone number:
6. Date of birth:
7. Current position:
8. Affiliations with institutions/ organizations/ societies

Qualification Details:

1. University/ College/ Institution:
2. Year of completion of MD/ DNB:
3. Speciality:
4. Medical Registration Number:

Payment Details:

Payment type- Cheque/ DD details

Send DD or cheque addressed to ENDOMETRIOSIS SOCIETY INDIA

6A & 6F, Neelamber, 28B, Shakespeare Sarani, Kolkata – 700017, West Bengal, India
Phone: (91) (033) 22874463, 28650364

Payment type- Bank transfer:

Account Name: ENDOMETRIOSIS SOCIETY INDIA
Account Number: 0673010072605
Account Type: Savings
IFS Code: PUNB0067320

Bank Name : PUNJAB NATIONAL BANK

BRANCH ADDRESS: 28B SHAKESPEARE SARANI,

KOLKATA - 700017