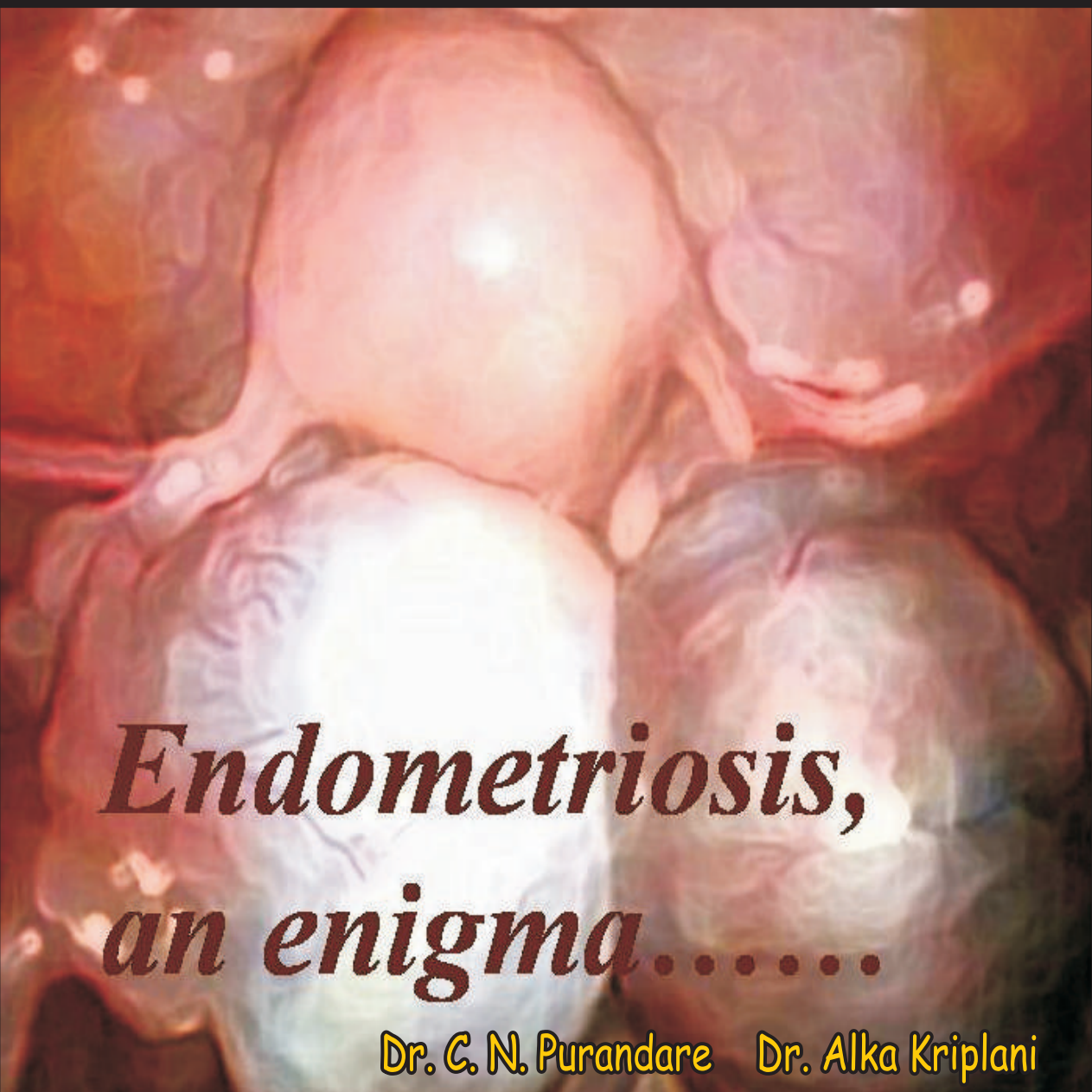
Fogsi Focus



Endometriosis, an enigma.....

Dr. C. N. Purandare Dr. Alka Kriplani

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FOGSI thanks Bharat Serum for supporting this issue

The President's Message

Dear FOGSIANS,

This issue of Fogsi Focus has been so aptly named Endometriosis- An enigma. Endometriosis is becoming commoner nowadays due to lifestyle changes and as women are also delaying the age at marriage and childbearing, this problem is present in a substantial proportion of patients presenting to the gynecologist.

This is an effort to unravel some of the mystery surrounding the disease and I sincerely hope that you all will enjoy reading this issue and use the knowledge to help patients who are in the prime of their lives but devastated by the relentless pain and inability to conceive.

I thank all the authors who have reviewed the subject extensively and our team members who have compiled the material in a beautiful and presentable manner.

Dr. C. N. Purandare
President, FOGSI

From The Vice Presidents and Chief Editors Pen

It gives me great pleasure to invite all of you to read this FOGI Focus "Endometriosis – An Enigma". Nowadays endometriosis is becoming commoner due to lifestyle changes, delay in child birth etc. This is commonly associated with infertility, pelvic pain and recurrence is common. This book deals with various aspects of endometriosis in detail. All the topics are prepared by experts in the field. Case discussion is also included to enhance students understanding of clinical situations and their management in day to day clinical practice. Special chapters like scar endometriosis, use of LNG-IUS and mifepristone in endometriosis are also included.

I hope the readers enjoy the book and find it a useful companion in the clinical practice. Your comments and suggestions are welcome.

Prof. Alka Kriplani
Editor FOGSI FOCUS
Second Vice President FOGSI

My Enemy

Creeping, crawling through my body, you leave me in a heap;
Biting, burning through my pelvis, burying yourself down deep.

I fight you hard, I dont give up but never seem to win;
Across my back I feel the pain, my hope just gets more dim.

The pain's so bad, I cant describe, I really just cant say;
How bad it feels to have you here all of every day.

The doctors look me up and down as if I am insane;
I ask for help, I plead with them "just take away the pain".

They cut me open, operate, "I'm better" is what they say;
A few months later I feel it back, have pain there every day.

"So try this hormone, stops the pain, you will be better with this";
And for a couple of wonderful weeks my life is complete bliss.

Well yes you guessed it, guess whats back, the minute that they stop;
My hope it crumbles, pain is back, my body seems to flop.

So what next, what do I do, should I have another test?
or live with the pain and put on a fake smile.

You give me pain, take away my life, there's nothing I can do;
but stay at home, make no plans, throw up, run to the loo;

I feel so sad with this disease and how it ruins my life;
takes away the joy that i had and replaces it with strife.

Other people dont understand what this does to us;
Other women just look on and think we make a fuss.

So as you read this very poem, understand and dont assume;
That we want attention, or like to talk of gloom.

We won't give up our fight, as we cannot just give in;
To let you win and just give up would be a total sin.

And so dear Endo, just to say the longer that you stay;
The harder that I will fight to make you go away.

....Written by a patient of endometriosis

Dear doctors,
With your patients,

Smile a bit – gain confidence
Listen long – get the diagnosis

Communicate more – give cure
Treat honestly – give satisfaction

The Patient – The most important visitor
The patient is not dependent on us,
we are dependent on them...
The patient is not an interruption of our work but the purpose of our work...

The patient is not an outsider but part of our profession...
The patient is not inept but a source of knowledge for us...

We are not doing a fovor by serving our patients...
They are doing us a favor by giving an opportunity to do so!

The pain of feminity
To be a female is a great pain
As a fetus: pain of female feticide
As a child: pain of discrimination
As a girl: pain of menstruation
As a wife: pain of parent's separation
As a mother: pain of parturition
But the greatest pain occurs when she has not felt the pain of motherhood

Those who are blessed with children may at times find them a pain in the neck...
But those who do not have them carry pain in their hearts!

..... Written by Dr. Nutan Agarwal

The '100% Human' Monoclonal Anti-D

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MONOCLONAL ANTI-Rho (D) IMMUNOGLOBULIN 300 mcg / 150 mcg

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CONTENTS

Etiopathogenesis of Endometriosis

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Endometriosis is defined as presence of ectopic deposits of endometrial tissue (glands & stroma) outside the uterus. It remains one of the most enigmatic diseases in gynecology and its exact pathogenesis still remains elusive. Various explanations have been given for its occurrence like mechanical, hormonal, immunological, environmental and genetic factors, but none of these provide conclusive explanations. Endometriosis can occur at any site and has been reported almost everywhere. No single theory can account for all ectopic locations of endometrium leading to endometriosis. Various theories that have been proposed for pathogenesis are:

1. Metastatic theory
2. Metaplastic theory
3. Induction theory
4. Infection hypothesis
5. Other factors

1) Metastatic theory : Metastasis of endometrial tissue to its ectopic location leads to endometriosis.
It explains most cases.

This metastasis can occur by

- Sampsons's theory : Passage of menstrual endometrium by transtubal regurgitation, supported by presence of endometrial cells in peritoneal fluid in 59-79% women during menses or early follicular phase.
- Dissemination of refluxed menstrual endometrium from peritoneal cavity through diaphragmatic defects or lymphatics or both may explain pleural & other extrapelvic sites of endometriosis.
- Intraoperative implantation
- Haematogenous/lymphatic dissemination and implantation

Following observations support menstrual implantation hypothesis (1)

- Endometriosis is more common closest to tubal ostia and occurs in a distribution that appears dependent on gravity and uterine position
- It is more common in women with early menarche, heavy and long flow, frequent cycles
- Its more common in females with congenital obstruction for menstrual flow
- Menstrual endometrium is viable, capable of tissue culture and growth after subcutaneous & intrapelvic injection
- Endometriosis may follow surgery on uterus
- Chance of episiotomy scar endometriosis is higher if curettage is performed immediately after delivery than in patients without post delivery curettage (1)
- Distant site endometriosis is explained by haematogenous or lymphatic dissemination of endometriotic tissue

2) **Metaplastic theory :** Coelomic epithelium has the capacity to change into other tissues. It is another widely accepted hypothesis that metaplastic development of coelomic epithelium into endometrial tissue at ectopic sites leads to endometriosis. It accounts for occasional cases in which metastatic spread is

unlikely / impossible. Pathways to initiation of coelomic metaplasia remain unclear, though it might be due to inflammation or genetic factors. Observations(1) in support of this theory are:

- Demonstration of endometriosis in Turners or pure gonadal dysgenesis who are amenorrheic and have hypoplastic uterus

- Juxtaposition of endometriosis with other putative metaplastic lesions of peritoneum such as diffuse peritoneal leiomatosis

3) **Induction theory :** which proposes that an endogenous (undefined) biochemical factor can induce undifferentiated peritoneal cells to develop into endometrial tissue.

4) **Infection hypothesis :** Recently a study has hypothesized the role of infection by Shigella or shigella-like organisms in triggering initiation of immunological changes in pelvic peritoneum causing endometriosis. In this study, mRNA was isolated from confirmed cases of endometriosis and subjected to differential display reverse transcriptase PCR(DD-RT-PCR). A unique band was found in ectopic endometrial tissue which had 96% homology with shigella DNA(2) Shigella is known to invade the mucosa of the colon through the feco-oral route causing inflammation, ulceration, hemorrhage, tissue destruction and fibrosis of the colonic mucosa, resulting in abdominal pain and diarrhea/dysentery, which is similar to the pathogenesis of endometriosis. The bacteria travel across the colon wall to reach the outer peritoneal surface of the colon, which is in close proximity to the posterior uterine surface in the Pouch of Douglas, the site which incidentally happens to be the commonest site of early endometriosis.

5. **Other etiologic factors** which explains why only a minority is affected despite common occurrence of retrograde menstruation is unknown. Some potential etiological factors that play a role in sustaining endometrial cells implanted at ectopic sites are

- **Genetic predisposition :** Risk of endometriosis in first degree relatives is 7 folds. Genetic studies suggest polygenic mode of inheritance (influenced by several different genes) or one that is multifactorial (a result of interaction between genetic and environmental factors). 75% incidence has been reported in homozygotic twins of patients with endometriosis(1)

- Hormonal: Endometriosis occurs exclusively in reproductive age. Increases estrogen in peritoneal fluid has been observed suggesting that estrogens are important for growth and maintenance of endometriosis(3) Mechanism has been explained in figure 1. Aromatase inhibitors are one of the treatment options for endometriosis.

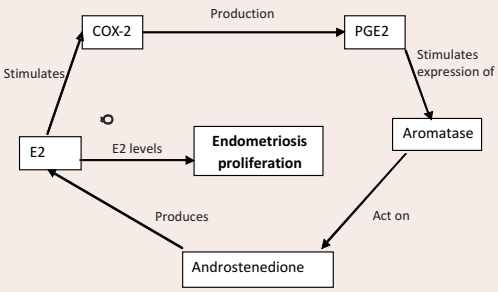


Figure 1: Role of estrogen in etiopathogenesis of endometriosis

This is also evidenced by rare example of endometriosis in phenotypic female with gonadal dysgenesis with exogenous estrogens. Similarly smoking and exercise that are inversely correlated with endogenous estrogen levels appear to be protective factors for development of endometriosis.

Progesterones inhibit development of endometriosis. Progestational milieu of pregnancy inhibits development of endometriosis, it is more common in delayed pregnancy and lesser in multiparous females and is less likely in females who have used oral contraceptives.

Some studies have found that increased frequency of luteinized unruptured follicular

syndrome (LUFS) in endometriotic patients(4) Normally ruptured corpus luteum releases progesterone rich fluid into peritoneal cavity which may inhibit implantation and growth of refluxed endometrial fragments at the time of menstruation. In LUFS, corpus luteum forms, but not ruptured, so decreased luteal phase progesterone allows endometriotic cells to implant. Other studies have not demonstrated such differences.

Immune factors: Altered immune responsiveness explains why some women develop endometriosis, whereas others do not(5). Moreover, several studies have found that the immunological components in the peritoneal fluid (PF) play an essential role in the pathogenesis and progression of the disease

i) Impaired cellular immune response to autologous endometrial antigen allows translocated endometrial cells to implant at ectopic sites(6). On the contrary, certain studies have shown that activated macrophages may stimulate growth of endometriosis.

ii) One study suggests inherent resistance of endometrial cells to apoptosis and immune mediated elimination(7).

iii) Cytokines serve as immunomodulators, angiogenic factors, or agents promoting endometrial cell growth. Various cytokines have been implicated in the pathogenesis.
IL-6 is a T cell derived cytokine. Its secretion is increased by peritoneal macrophages in endometriosis and by stromal cells of ectopic endometrium(8,9). The levels correlates with number and extent of red peritoneal endometriosis.

IL-8 facilitate attachment of endometrial cells to peritoneal surface, invasion of the extracellular matrix, local angiogenesis and endometrial proliferation, while simultaneously augmenting local immune responses.

Interleukin (IL)-15 : increased levels in endometriosis are inversely correlated with the depth of invasion and disease stage suggesting a possible role in early pathogenesis.

Tumor necrosis factor TNF-α is secreted by activated macrophages and has potent inflammatory, cytotoxic and angiogenic properties. TNF-α levels are increased markedly in the PF of women with endometriosis(10). However other studies had conflicting results which might be due to: differences in the techniques used to assess TNF, variations in the definition of the studied populations; and the heterogeneity of the endometriosis disease itself.

Peritoneal fluid Leptin: Proinflammatory and neoangiogenic action of leptin may contribute to the pathogenesis of endometriosis due to infiltration of CD4+ T helper cells. Leptin positively correlates with stage of endometriosis and may play a role in endometriosis-associated pain(11,12).

iv) Organochlorines (polychlorinated biphenyls and dioxin-like compounds) are immune-toxicants which cause alteration in immune system and appear associated with deep nodular form of endometriosis, though there is no association between peritoneal endometriosis and organochlorines(13).
Monocyte chemotactic protein-1(MCP-1) is produced by T cells, monocytes and endometrial cells and plays important role in recruitment of monocytes and macrophages to peritoneal cavity in endometriosis. In endometriosis, levels increase in serum and peritoneum(9,14).

v) Reactive oxygen species (ROS) have been detected in the PF of endometriosis patients(15) though their role in the disease progression has yet to be determined. These ROS are produced by erythrocytes, apoptotic endometrioma cells and activated

macrophages. Role of ROS in endometriosis is depicted in figure-2.

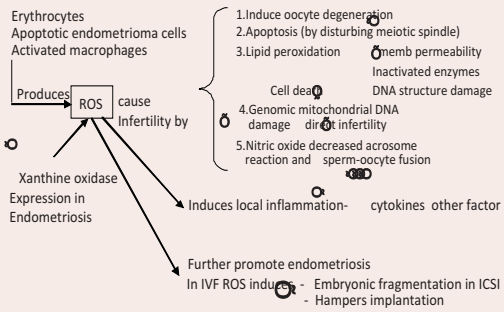


Figure 2 : Role of oxidative stress in endometriosis

Endometriosis-related protein, identified by comparative proteomics :

- E-cadherin - Decrease concentrations have been found in sera and peritoneal fluids in women with endometriosis.

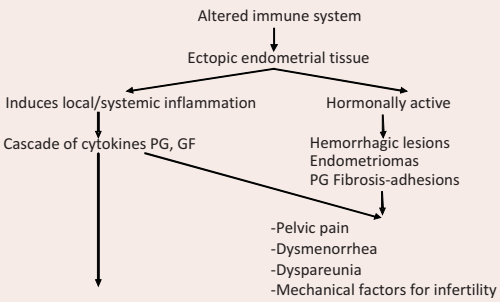
- Claudin superfamily – are membrane proteins and important components of cellular tight and adherens junctions. Their downregulation may contribute to endometrial cell detachment and increase the number of cells invading pelvic organs(16)

- Annexin-1 is an endogenous anti-inflammatory mediator which is overexpressed in eutopic endometrium of endometriosis and presents in the peritoneal fluids in endometriosis, and may play a role in the pathogenesis of endometriosis(17)

- Cathepsin D – is an aspartyl acid protease that initiates proteolytic events causing degradation of basement membrane and extracellular components.

Genomics : Recent studies have documented association of endometriosis with estrogen receptor gene polymorphisms, various exon-deleted progesterone-receptor mRNAs, aneuploidy for chromosomes 11, 16 and 17, loss of heterozygosity or an allelic imbalance. Another study had evidence for genetic linkage to chromosomes 7 and 10, but the genes (or variants) in these regions contributing to disease risk have yet to be identified(18). Genes with convincing evidence for association with endometriosis are likely to be identified in large genome-wide studies. This will provide a better understanding for this debilitating disease.

Endometriosis is a puzzling disorder with obscure pathogenesis. Further research in new proteomic and genomic technologies could help to clarify the etiology of endometriosis in future.



Causes infertility by

- Altered folliculogenesis due to altered immunologic function in follicular fluid
- Poor oocyte quality
- Ovulatory dysfunction
- Luteal phase defects
- Reduced fertilization
- Abnormal embryogenesis
- Reduced implantation rates
- Altered granulosa cell kinetics
  - ↓ number of granulosa cells in G2/M phase
  - ↑ number of granulosa cells in Sphase
  - ↑ granulosa cells apoptosis

Figure 3 : Etiopathogenesis of infertility in endometriosis

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Imaging in Endometriosis

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Endometriosis is a common and debilitating condition occurring up to 10% of women. Though laparoscopy is the gold standard for diagnosis of endometriosis, but recent advances in imaging technology have improved non-operative diagnosis. Endometrioma are relatively easy to detect but small peritoneal deposits presents as a challenge.

IMAGING MODALITIES

ULTRASOUND

Ultrasound is the first line investigation. Three techniques are available – transabdominal, transvaginal & endorectal scanning. Transvaginal scanning gives better resolution and image quality than transabdominal technique. Lesions on ultrasound are defined in terms of echogenicity with echogenic lesions appearing bright and hypo-echoic lesions appearing dark. High resolution images may be obtained via transvaginal using 7.5Mhz probe. The main focus is to visualize the ovaries and characterize cystic lesions in terms of internal echogenicity and wall morphology. Compared with laparoscopy, transvaginal ultrasound has limited value in diagnosing peritoneal endometriosis but it is a useful tool both to make and to exclude the diagnosis of an ovarian endometrioma (level A evidence) (1)

Detection of endometrioma using ultrasound is excellent with 83% sensitivity and 98% specificity (2). Sensitivity in detection of focal endometrial implants is poor. There is a broad range of ultrasound appearances of endometrioma. The classical appearance is homogenous, hypoechoic mass within the ovary with diffuse low level internal echoes with hyperechoic foci within the wall (fig 1). 95% of endometriomas display low level internal echoes (3). Wall nodularity should be differentiated from hyperechoic foci within the wall. The pathological basis for these hyperechoic foci has not been clearly known but may relate to cholesterol deposits. Patel et al found 35% of endometriomas had hyperechoic foci and this was the single highest predictor for endometrioma (3).Lesions can be unilocular or multilocular with either thin or thick septa. 20% of endometriomas display wall nodularity, which is a feature more usually associated with malignancy.

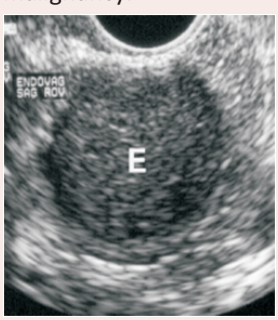

Fig 1: Endovaginal ultrasound scan of an endometrioma. Note the characteristic diffuse, low-level echoes of the endometrioma (E) giving a solid appearance.

The differential diagnosis of an endometrioma includes dermoid cyst, hemorrhagic cyst and cystic neoplasm. Dermoid cyst may contain acoustic shadowing (calcium) or echogenic lesions (fat). Hemorrhagic cyst demonstrates high level internal echoes with thin walled cyst and lesions resolve with time. If a cyst has soft tissue components then a malignant lesion must be excluded.

Transrectal ultrasound is performed to look at sigmoid for endometriosis infiltration. The advantage is better resolution and diagnostic accuracy but the field of visualization is quite restricted and only the distal bowel is imaged. Endometriotic deposits appear as rounded or triangular hypoechoic deposits. Infiltration of bowel wall is seen as thickening of muscularis propria. Chapron et al reported sensitivity and specificity of 97% and 89% respectively for transrectal ultrasound , and it was superior to MRI for diagnosis of rectal involvement in patients with endometriosis (4).

DOPPLER

Endometriomas are better studied in late follicular phase and early luteal phase. Diagnostic accuracy of endometrioma may be enhanced by doppler flow studies where blood flow in endometrioma is usually pericystic with RI more than 0.45 (5).

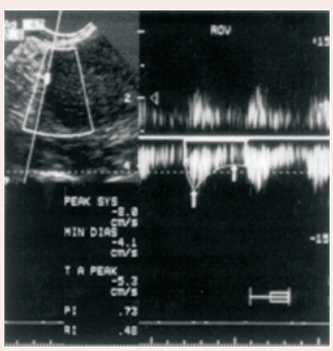

Fig 2 : Duplex ultrasound scan of an endometrioma. Note the resistive index of 0.48, indicating a low-resistance waveform. This value can also be seen with an ovarian neoplasm, yielding false-positive results.

MAGNETIC RESONANCE IMAGING (MRI)

MRI has the advantage of imaging entire pelvis in multiple planes – axial, coronal or sagital with sagital plane particularly useful for evaluating rectum and cul-de-sac. Standard sequences include T1 (where water is dark and fat and fresh hemorrhage are bright), T2 (where water is very bright and fat is quite bright). Pigmented lesions appear hyperdense on T1 images and hypodense on T2. Acute hemorrhage appears hypodense on T1 and T2 sequences. Old hemorrhages appear hyperdense on T1 and T2 sequences. Takahashi et al(6) have shown the density (chronicity) of cyst contents to be directly proportional to the iron concentration, with a corresponding decrease in the T2 relaxation time as the concentration of iron and the viscosity of cyst fluid increase.

Sensitivity and specificity of MRI for detection of endometrioma is 90% and 98% respectively (7). Endometrial implants by MRI have poor sensitivity (27%). The sensitivity can be increased by fat suppressed images to 61% (8). The major role is to help visualize laparoscopic blind spots such as retroperitoneal space and lesions obscured by dense adhesions or atypical lesions.

The appearance of endometriomas on magnetic resonance images are variable and depends on the concentration of iron and protein in the fluid, products of blood degradation. Most endometriomas have the gross appearance of chocolate cysts, representing highly concentrated blood products. MRI demonstrates these endometriomas as cystic masses with very high signal intensity on T1-weighted images

(fig3) and very low signal intensity on T2-weighted images (fig4). This low signal intensity on the T2-weighted images is termed shading and occasionally occurs in a gradient from higher to lower signal intensity. This pattern of signal intensities results from the high iron concentration in the endometrioma and is rarely seen in other masses.

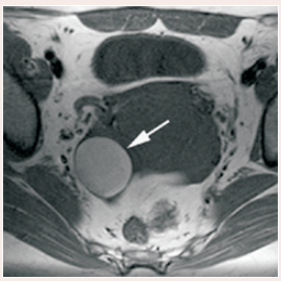

Fig 3: T1-weighted MRI of an endometrioma. Note characteristic high signal intensity (similar to that of fat) of this right-sided adnexal endometrioma (arrow).

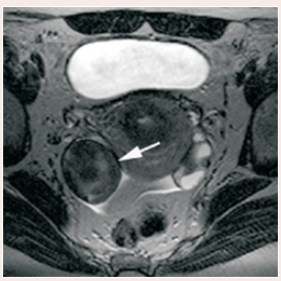

Fig 4: T2- MRI of an adnexal endometrioma (arrow). Note characteristic low T2-weighted signal, the result of the high iron concentration

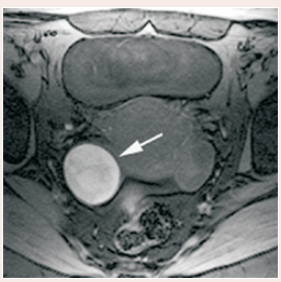

Fig 5 : Fat-saturated T1-weighted magnetic resonance image of an endometrioma. In this right adnexal endometrioma (same lesion as in Image above), fat saturation has been applied. Note that the endometrioma's (arrow) signal intensity does not decrease. This signal characteristic differentiates endometriomas from fatty adnexal masses, such as dermoids.

Diagnosis of dermoid cysts is easier to detect due to the presence of fat in these lesions which on fat-suppressed sequences loses signal (becomes dark) and in endometrioma signal intensity does not decrease (fig 5). The differentiation of hemorrhagic cysts from endometrioma can be difficult on MRI as both contain blood products.

Endometrial nodules found in rectovaginal septum, uterine ligament and muscular wall of pelvis are seen as low intermediate signal on T1 with punctate areas of high signal on T2.

Dilated fallopian tubes may demonstrate high signal on T1 and T2 (fig 6).

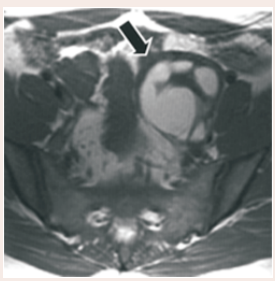

Fig 6 : Endometriosis of left fallopian tube – T2 weighted sequence shows dilated left fallopian tube with high signal intensity.

Involvement of bowel appears as low signal, irregular thickening on MRI . Chaperon et al reported senstivity and specificity of 76% and 97% respectively although sensitivity is lower than endorectal ultrasound (4)

Role of imaging in diagnosis of adhesions is rather limited.

20% of patients of endometriosis may have gentio-urinary syatem involved. The bladder is affected in 84% of cases. Hypodense mass with areas of hyperintensity is identified on the dome of bladder typically . Ureteral involvement is less frequent and is well visualized on coronal imaging although findings are non

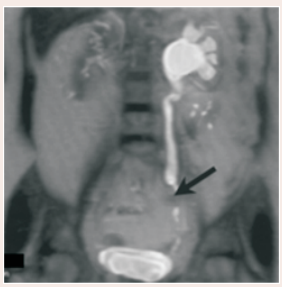

Fig 7 : Coronal T2-weighted single-shot fast spin-echo MR image shows left ureteral obstruction (arrow) causing hydronephrosis

Deep Pelvic Endometriosis (DPE) is presence of endometrial implants, fibrosis and muscular hyperplasia below the peritoneum. It can occur in uterosacral ligament, rectosigmoid colon, vagina and bladder.

Endorectalultrasound and MRI are recommended to diagnose and locate DPE.

OTHER IMAGING MODALITIES

Other techniques are CT scan, barium enema and Intravenous Urography (IVU).

CT scan : Owing to poor specificity, relative lack of resolution in visualization of ovaries and tubes and also due to high radiation exposure, use of CT in evaluation of pelvic endometriosis is less.

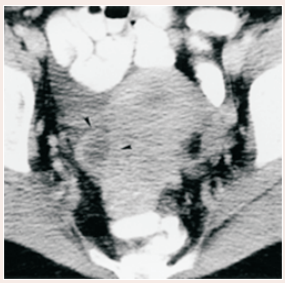

Fig 8 : Oral and IV contrast CT scan showing partly cystic and partly solid ovarian endometrioma posterior to the uterus.

INTRAVENOUS UROGRAPHY (IVU) : Serosal deposits are seen at dome of bladder. Involvement of ureters is seen as short or medium length tapering stricture which can cause secondary hydronephrosis

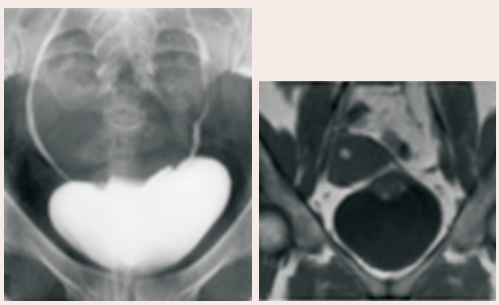

Fig 9: Bladder endometriosis. (a) Bladder view from an intravenous urography examination showing irregularity of the dome of the bladder. (b) Coronal T1 weighted spin echo image of the same patient showing an endometrial implant in the wall of the bladder dome containing foci of high signal intensity

BARIUM ENEMA : Typically, deposits are serosal causing thickening and fibrosis of muscularis propria which is demonstrated as asymmetric narrowing or eccentric intramural filling defect (9). The differential diagnosis is metastatic deposits or colon cancer.

CONCLUSION

Finally, the diagnosis of endometriosis is by laparoscopy and histopathology, however, imaging plays important role in diagnosis and follow up. The major advantage of diagnostic imaging is that it is non-invasive. Ultrasound is first line investigation with selected cases for MRI. The addition of fat saturated T1 weighted imaging has improved diagnostic accuracy in evaluation of both endometriomas and peritoneal disease. TVS and MRI are useful in evaluating recurrence and response to treatment in patients with known disease.

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Guidelines (EHARE) on management of Endometriosis

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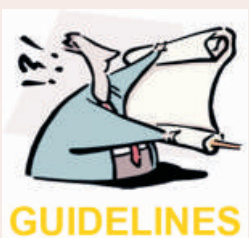
Diagnosis
Definitive diagnosis of endometriosis : visual inspection of the pelvis at laparoscopy is the gold standard investigation, unless disease is visible in the vagina or elsewhere.

Laparoscopy
Good surgical practice is to use an instrument such as a grasper, via secondary port, to mobilize the pelvic organs and to palpate lesions which can help determine their nodularity. It is also important to document in detail the type, location and extent of all lesions and adhesions in the operative notes; ideal practice is to record the findings on video or DVD.

Timing the laparoscopy: no specific time in menstrual cycle but it should not be performed during or within three months of hormonal treatment to avoid under-diagnosis (E vers,1987)

Histology
Positive histology confirms the diagnosis of endometriosis; negative histology does not exclude it. Visual inspection is usually adequate but histological confirmation of at least one lesion is ideal. In cases of ovarian endometrioma (>4 cm in diameter) & in deeply infiltrating disease, histology should be obtained to identify endometriosis and or exclude rare instances of malignancy. Because chocolate like fluid may also be found in other types of ovarian cysts, such as hemorrhagic corpus luteal or neoplastic cysts, biopsy and preferably removal of the cyst for histological confirmation is recommended if the cyst is >3 cm diameter. Ovarian endometriosis as a single finding occurs in < 1% of endometriosis patients, the rest having mostly pelvic and/or intestinal endometriosis as well (Redwine,1999).



Investigations

Ultrasound
Trans-vaginal ultrasound has no value in diagnosing peritoneal endometriosis, but it is useful tool both to make and to exclude the diagnosis of an ovarian endometrioma (Moore et al., 2002). TVS may have a role in the diagnosis of disease involving the bladder or rectum.

Magnetic resonance imaging
Insufficient evidence to indicate MRI is a useful test

Blood tests

Serum CA-125 levels has no value as a diagnostic tool (Mol et al.,1998).

Investigations to assess disease extent

If there is clinical evidence of deeply infiltrating endometriosis, ureteral, bladder, and bowel involvement should be assessed by MRI or ultrasound (trans-rectal and/or transvaginal and/or renal),with or without IVP and barium enema studies depending upon the individual circumstances, to map the extent of disease present, which may be multi-focal.

Classification systems

All classification systems for endometriosis are subjective and correlate poorly with pain symptoms, but may be of value in infertility prognosis and management (Chapron et al.,2003b; D'Hooghe et al.,2003)

Treatment of Pain

Non-steroidal anti-inflammatory drugs

Endometriosis-related pain is nociceptive (Bajaj et al.,2003), but persistent nociceptive input from endometriotic lesions leads to central sensitization manifested by somatic hyperalgesia and increased referred pain areas. The positive clinical experience of NSAIDs for reduction of endometriosis related pain may be explained by both a local anti-nociceptive effect and a reduced central sensitization besides the anti-inflammatory effect.

Hormonal treatment

Suppression of ovarian function for 6 months reduces endometriosis associated pain. The hormonal drugs investigated - COCs, danazol, gestrinone, medroxyprogesterone, acetate and GnRH agonists - are equally effective but their side-effect and cost profiles differ (Davis et al., 2007; Prentice et al.,1999;Prentice et al.,2000;Selak et al.,2007).The levonorgestrel intra-uterine system (LNG IUS) reduces endometriosis associated pain.

Treatment for 3 months with a GnRH agonist may be as effective as 6 months in terms of pain relief (Hornstein et al.,1995). Treatment for up to 2 years with combined estrogen and progestagen 'add-back' appears to be effective and safe in terms of pain relief and bone density protection; progestagen only 'add-back' is not protective (Sagsveen et al., 2003). However, careful consideration should be given to the use of GnRH agonists in women who may not have reached their maximum bone density.

Hormone replacement therapy

Hormone replacement therapy (HRT) is recommended after bilateral oophorectomy in young women given the overall health benefits and small risk of recurrent disease while taking HRT (Matorras et al., 2002). The ideal regimen is unclear: adding a progestagen after hysterectomy is unnecessary but should protect against the unopposed action of estrogen on any residual disease. However, the theoretical benefit of avoiding disease reactivation and malignant transformation should be balanced against the increase in breast cancer risk reported to be associated with combined estrogen and progestagen HRT and tibolone (Beral and Million Women Study Collaborators,2003).

Medical treatment

Progestagens

first choice for the treatment because they are as effective in reducing AFS scores and pain as danazol or GnRH analogues and have a lower cost and a lower incidence of side effects than danazol or GnRH analogues (Vercellini et

al.,1997). Medroxyprogesterone acetate (MPA) has been the most studied agent and is effective in relieving pain starting at a dose of 30 mg/day and increasing the dose based on the clinical response and bleeding patterns (Moghissi and Boyce,1976; Luciano et al.,1988). Pain was reduced significantly during luteal phase treatment with 60 mg dydrogesterone and this improvement still was evident at 12-month follow-up (Overton et al.,1994). Other progestagens, such as desogestrel, are now being looked at as alternative treatments (Razzi et al.,2006).

Local progesterone treatment of endometriosis-associated dysmenorrhea with a levonorgestrel-releasing intrauterine system during 12 months resulted in a significant reduction in dysmenorrhea, pelvic pain and Dyspareunia, a high degree of patient satisfaction (Vercellini et al.,1999b; Vercellini et al.,2005; Lockhat et al.,2005; Petta et al.,2005; Varma et al., 2005, Gomes et al. 1231-34) and a significant reduction in volume of rectovaginal endometriotic nodules (Fedele et al.,2001).

Depot preparation of Medroxyprogesterone acetate (DMPA-SC 104) demonstrates that pain reduction is as effective as that observed withGnRH analogues (Crosignani et al.,2006). Limited data also exists on the use of another depot preparation (Implanon – Etonogestrel) in the management of endometriosis (Yisa et al., 2004; Yisa et al.,2005).

Combined oral contraceptives

Any low-dose combination oral contraceptive pill containing 30-35 mg of ethinyl estradiol used continuously (to achieve amenorrhea) can be effective in the management of endometriosis (Moghissi,1999). Symptomatic relief of dysmenorrhea and pelvic pain is reported in 60-95% of patients. Following a first-year recurrence rate of 17-18%, a 5-10% annual recurrence rate has been observed. Oral contraceptives are less costly than other treatment modalities and may be helpful in the management of endometriosis with potential long-term benefits in some women (Moore et al.,1997).

Danazol

Doses of 800 mg/day are frequently used in North America, whereas 600 mg/day is commonly Prescribed in Europe and Australia. It appears that the absence of menstruation is a better Indicator of response than drug dose. A practical strategy for the use of danazol is to start treatment with 400 mg daily (200 mg twice a day) and increase the dose, if necessary, to achieve amenorrhea and relieve symptoms (Wingfield and Healy,1993).

Aromatase inhibitors

Theoretically aromatase inhibitors may have a role to play in the medical management of endometriosis, particularly in postmenopausal women (Attar and Bulun, 2006; Bulun et al., 2000; D'Hooghe, 2003b)

Surgical treatment

Depending upon the severity of disease found, ideal practice is to diagnose and remove endometriosis surgically at the same time, provided that preoperative adequate consent has been obtained (Abbott et al.,2003; Chapron et al.,2003b; Fedele et al.,2004a; Redwine and Wright,2001).

Ablation of endometriotic lesions plus laparoscopic uterine nerve ablation (LUNA) in minimal-moderate disease reduces endometriosis associated pain (Jacobson et al.,2001). However, there is no evidence that LUNA is a necessary component (Sutton et al., 2001), and LUNA by itself has no effect on dysmenorrhea associated with endometriosis

(Vercellini et al.,2003a).

There are no data supporting the use of uterine suspension but, in certain cases, there may be a role for pre-sacral neurectomy especially in severe dysmenorrhea (Soysal et al.,2003).

Endometriosis associated pain can be reduced by removing the entire lesions in severe and deeply infiltrating disease. If a hysterectomy is performed, all visible endometriotic tissue should be removed at the same time (Lefebvre et al.,2002). Bilateral salpingo-oophorectomy may result in improved pain relief and a reduced chance of future surgery (Namnoum et al., 1995).

Post-operative treatment

As endometriosis is a chronic estrogen-dependent disease, further hormonal treatment is often needed in many women. In a small RCT, the LNG IUS, inserted after laparoscopic surgery for endometriosis associated pain, reduced the risk of recurrent moderate-severe dysmenorrhea at 1 year follow-up (Vercellini et al.,2003c)

Peritoneal endometriosis

Endometriosis lesions can be removed during laparoscopy by excision, coagulation or vaporization by laser (carbon dioxide laser, potassium-titanyl-phosphate laser or argon laser). No controlled evidence is available demonstrating that one laser technique is better than the other. The effectiveness of surgical treatment by laparotomy has not been investigated by a RCT. The many observational studies that have been published claim a high percentage of success.

Ovarian endometriosis

Superficial ovarian lesions can be coagulated or vaporized. The primary indication for extirpation of an endometrioma is to ensure it is not malignant. Small ovarian endometrioma (< 3 cm diameter) can be aspirated, irrigated, and inspected for intracystic lesions. Their interior wall can be coagulated or vaporized to destroy the mucosal lining. Ovarian endometrioma >3 cm should be removed completely (Chapron et al.,2002b). In cases where excision is technically difficult without removing a large part of the ovary, a two-step procedure (marsupialisation and rinsing followed by hormonal treatment and surgery 3 months later) should be considered (Donnez et al.,1996). Although as little as one-tenth of an ovary may be enough to preserve function and fertility, at least for a while, there is increasing concern that ovarian cystectomy with concomitant removal or destruction of normal ovarian tissue may reduce ovarian follicle reserve and reduce fertility (Loh et al.,1999). Therefore, it has been proposed to replace cystectomy by fenestration and coagulation of the inner cyst wall (Hemmings et al.,1998) but a case-control study (Saleh and Tulandi,1999) and a randomized controlled trial (Beretta et al., 1998) have demonstrated that pain and subfertility, related to ovarian endometriomas, were improved more by cystectomy than by fenestration/coagulation. Therefore, based on the current evidence, ovarian cystectomy seems to be the method of choice (Chapron et al.,2002) with a significantly decreased risk of cyst recurrence (Vercellini et al.,2003b).

Adhesiolysis

If the endometriosis-related adhesions are part of an inflammatory fibrosis, they should be removed carefully. So far there is no evidence from randomized controlled trials that routine use of pharmacological or liquid agents prevent postoperative adhesions after fertility surgery (Watson et al.,2000).

Deep rectovaginal and rectosigmoidal endometriosis : Surgical management is only for symptomatic deeply infiltrating endometriosis. Asymptomatic patients must not be operated upon. Progression of the disease and appearance of specific symptoms rarely occurred in patients with asymptomatic rectovaginal endometriosis (Fedele et al.,2004b). When surgical treatment is decided the treatment must be radical with excision of all deep lesions.

Oophorectomy and hysterectomy
Radical procedures such as oophorectomy or total hysterectomy are indicated only in severe cases. If a hysterectomy is performed, the cervix should be extirpated as persistent pain in a remaining cervix is common due to endometriosis in the cervix or endometriosis in the utero-sacral ligaments.

Treatment of endometriosis associated infertility
Suppression of ovarian function to improve fertility in minimal-mild endometriosis is not effective and should not be offered for this indication alone (Hughes et al.,2007). The published evidence does not comment on more severe disease.

Surgical Treatment
Ablation of endometriotic lesions plus adhesiolysis to improve fertility in minimal-mild endometriosis is effective compared to diagnostic laparoscopy alone (Jacobson et al.,2002). No RCTs or meta-analyses are available to answer the question whether surgical excision of moderate to severe endometriosis enhances pregnancy rate. Laparoscopic cystectomy for ovarian endometriomas >4 cm diameter improves fertility compared to drainage and coagulation (Beretta et al.,1998; Chapron et al.,2002). Coagulation or laser vaporization of endometriomas without excision of the pseudo-capsule is associated with a significantly increased risk of cyst recurrence (Vercellini et al.,2003b; Hart et al.,2005).

Assisted Reproduction

Intra-uterine insemination
Treatment with intra-uterine insemination (IUI) improves fertility in minimal-mild endometriosis: IUI with ovarian stimulation is effective but the role of unstimulated IUI is uncertain (Tummon et al.,1997).

In vitro fertilization
In vitro fertilization (IVF) is appropriate treatment especially if tubal function is compromised, if there is also male factor infertility, and/or other treatments have failed. IVF pregnancy rates are lower in patients with endometriosis than in those with tubal infertility (Barnhart et al.,2002)

Treatment with a GnRH agonist for 3-6 months before IVF or ICSI should be considered in women with endometriosis as it increases the odds of clinical pregnancy fourfold. However the authors of the Cochrane review stressed that the recommendation is based on only one properly randomized study and called for further research, particularly on the mechanism of action (Sallam et al.,2006)

These guidelines are based on the ESHRE GUIDELINES for endometriosis management.

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Overview of Medical Management of Endometriosis

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Introduction :

Endometriosis is an enigmatic and debilitating disease, which occurs up to 15% of all women of reproductive age (1). The exact mode of development of endometriosis is unclear but it is evident that endometriosis occurs due to the dissemination of endometrium to ectopic sites and the subsequent establishment of deposits of ectopic endometrium, Endometriosis causes dysmenorrhea, dysparunia, chronic abdominal pain and infertility.

Treatment :

The treatment of women with endometriosis is a challenge. Treatment strategies must be tailored to the individual symptoms, age and desire for fertility. The most common approaches consist of medical treatment, laparoscopic surgery and major surgical management.

Medical Treatment :

It has been observed that endometriosis is rarely seen in the hypo-estrogenic postmenopausal women which led to the concept of medical treatment by suppression of ovarian steroids and induction of a hypo-estrogenic state that causes atrophy of ectopic endometrium(2). However, the medical treatment has limited value in patients with infertility because it inhibits ovulation.

Standard medical therapies include analgesics (non steroidal anti-inflammatory drugs - NSAIDs) oral contraceptive pills (OCPS), androgenic agents (danazol), progesterone, gonadotropins releasing hormone analogues (GnRH analogue) and antiprogestogens (gestrinone).

I) Non-steroidal anti-inflammatory drug (NSAIDs)

Endometriosis is a chronic inflammatory disease. As an empirical treatment, non-steroidal anti-inflammatory drugs have been reported to be effective in reducing endometriosis associated pain.

Endometriosis related pain is nociceptive and persistent nociceptive stimulus from endometriotic lesions leads to central sensitization which is manifested by somatic hyperalgesia and increased referred pain.(3) NSAIDs, apart from the anti-inflammatory effect reduce endometriosis related pain by local antinociceptive effect and by reducing Central Sensitization. Hence, NSAIDs, has been used extensively and as first line therapy for reduction of endometriosis related pain. In one small, double-blind, placebo controlled, four period, cross over clinical study has reported complete or substantial pain relief of endometriosis related dysmenorrhea in 83% of cases treated with naproxen compared with 41% in cases treated with placebo(4). However, NSAIDs cause significant side effects like gastric ulceration and inhibition of ovulation by antiprostaglandin action.

II) Hormonal Medical Treatment

Endometriosis is an estrogen dependent disease hence, hormonal study has been designed to suppress estrogen synthesis, thereby inducing atrophy of ectopic endometrial implants or interrupting the cycle of stimulation and bleeding. Hormonal therapy is not curative, hence it requires to be administered for years or until woman desires a pregnancy. It has been observed that the various hormonal therapies studies have similar efficacy (5). Therefore, based on a more favorable profile in terms of safety, tolerability and cost, combined oral contraceptives and progestins should be considered as the first line option, both as an alternative to surgery and as a postoperative adjuvant measure. Gonadotrophin releasing hormone analogues, danazol and gestrinone should be used when there is failure of progestins and oral contraceptives or are not tolerated or are contraindicated.

Oral Contraceptives (OCPs) :

OCPs suppress LH & FSH and prevent ovulation. They can be taken continuously or cyclically. The continuous use of low dose monophasic contraceptive pill (one pill per day for 6 to 12 months) induces pseudopregnancy caused by the resultant amenorrhea and decidualization of endometrial tissues in the treatment of endometriosis.

The decidualization of endometrial implants along with reduced reflux related to lower menstrual flow with cyclical OCPs are the probable mechanisms in reducing pain with OCPs and thus making them comparable to other hormonal treatment.

Low dose OCPs containing 30 to 35 µg of ethinyl estradiol when used continuously for 6 to 12 months, symptomatic relief of dysmenorrhea and pelvic pain was reported in 60 to 95% of patients. Recurrence rates after first year and annual recurrence rate were reported as 17% to 18% and 5% to 10% respectively(6).

The OCPs can be discontinued after 6 to 12 months or continued indefinitely till patient's satisfaction and desirability of pregnancy.

Progestins :

Progestins cause antiendometriotic effect by initial decidualization of endometrial tissues followed by atrophy. They are as effective as danazol or GnRH analogues and have lower cost and a lower incidence of side effects compared to these agents. After 3 to 6 months of evaluation Medroxy progesterone acetate was found to do effective in relieving pain when started at a dose of 30 mg/day and increased the dose based on the clinical response and bleeding patterns(7). Medroxy progesterone acetate 150 mg given intramuscularly every 3 months is also

effective for relief of pain associated with endometriosis. Orally norethidrone 5 mg / day increased maximum to 15 mg / day, Megestrol acetate 40mg/day, Lynestrenol 10 mg/day and dydrogesterone 20 to 30 mg / day either continuous or cyclical are also effective in relieving pain associated with endometriosis. If effective, these agents can be used safely for longer periods of time. The levonorgestrel releasing intrauterine device has been reported very effective at relieving pain associated with endometriosis especially relieving dysmenorrhea and pain due to rectovaginal endometriosis(8). Progestins are associated with more adverse effects than OCPs. Side effects include nausea, weight gain, fluid retention, breakthrough bleeding and delayed return of fertility after the cessation of treatment.

Danazol :

Danazol is a synthetic androgen that suppresses gonadotrophin secretion resulting into direct inhibition of steroidogenesis. It also causes increased metabolic clearance of estradiol and progesterone, direct antagonistic and agnostic interaction with endometrial androgen and progesterone receptors. The multiple effects of danazol cause a high androgen and low estrogen levels, which does not support the growth of endometriosis. Moreover, danazol induced amenorrhea prevents new seeding of implants from the uterus into the peritoneal cavity.

The immunological effects of danazol include a decrease in serum immunoglobulins a serum C3, a rise in serum C4 levels, decrease in serum autoantibodies levels against various phospholipid antigens and decrease in serum CA 125 level. It inhibits interleukin 1 and TNF production by monocytes in dose dependent manner and suppresses macrophage and monocyte mediated cytotoxicity of susceptible target cells. These immunological effects of danazol also help in suppression of endometriosis.

The initial dose of danazol is 400 mg/day orally (200 mg twice a day) which is increased to maximum 800 mg. per day to achieve amenorrhea and pain relief. Treatment duration is six months but can be extended to nine months in severe cases. The overall response is reported to be 84 to 92% with beneficial effects lasting up to six months after cessation of treatment(9).

Adverse effects due to estrogen deficiencies include headache, flushing, sweating and atrophic vaginitis. Androgenic side effects include acne, edema, and hirsutism, deepening of voice and weight gain.

Gestrinone :

Gestrinone is a 19- nortestosterone derivative with androgenic, antiprogestogenic, antiestrogenic and antigonadotropic properties. Gestrinone causes cellular in activation and degeneration of endometriotic implants. Amenorrhea occurs in 50% to 100% of women and is dose dependent. A randomized trial demonstrated that 2.5 mg gestrinone twice weekly for 24 weeks is more effective and has a better effect on bone mass compared to 1.25 mg. Gestrinone given twice a week for 24 weeks(10). Side effects are dose dependent and are similar to danazol but less intense.

Gonadotropin Releasing Hormone Agonists (GnRH Agonists) : GnRH Agonists bind to pituitary GnRH receptors and stimulate LH & FSH synthesis and release. However, the agonists have much longer biologic half life i.e. 3 to 8 hours than endogenous GnRH (3-5 minutes) resulting in the continuous exposure

of GnRH receptors to GnRH agonist activity. This exposure results into loss of pituitary receptors and down regulation of GnRH activity with low FSH and LH levels. Thus, ovarian steroid production is suppressed giving rise to state of pseudomenopause.

Various GnRH agonists available for treatment of endometriosis are leuprolide, buserelin, nafarelin, histrelin, goserelin, deslorelin and triptorelin. It has been reported that treatment with GnRH Agonists for 3 months is effective in improving pain for 6 months(11). Inj. leuprolide in a single monthly 3.75 mg depot injection is given intramuscularly while Gosarelin 3.6 mg. subcutaneously every 28 days and nafarelin as a nasal spray given twice a day. About 90 percent of patient experience pain relief. Prolonged pretreatment with GnRH analogue before IVF has been reported to improve clinical pregnancy rates in infertile women with endometriosis(12).

Side effects caused by hypoestrogenism include hot flushes, vaginal dryness, osteoporosis and reduce libido. Because of concerned about osteoporosis, 'add back' therapy with progestins only (norethisterone 1.2 mg / daily) or estrogen progesterone combination (conjugated estrogen 0.625 mg + Medroxy progesterone 2.5 mg.) or Tibolone (2.5 mg/day) are recommended.

Progesterone Antagonists :
Without the risk of hypoestrogenism or bone loss that occurs with GnRH Agonists treatment, progesterone antagonists and progesterone receptor modulators suppress endometriosis based on their proliferative effects on the endometrium.

Mifepristone (RU-486) is potent antiprogestrogen with a direct inhibitory effect on endometrial cells and with high doses it has antiglucocorticoid action. It has been observed that mifepristone in dose of 50 to 100 mg / day reduced pelvic pain and induced 55% regression of endometriosis without significant side effects (13).

Other progesterone Antagonists under research are onapristone, ZK 230211, and ZK 137316.

Aromatase inhibitors and selective estrogen receptor modulators : Aromatase inhibitors have characteristics of inhibiting estrogen production selectively in endometriotic lesions without affecting ovarian functions. This also allows conception during treatment. The clinical role of these drugs in the treatment of endometriosis is under evaluation.

Conclusion :
Current medical treatment of endometriosis depends on drugs that suppress ovarian steroids and induce a hypoestrogenic state that causes atrophy of ectopic endometrium

This hypoestrogenism also induces many unpleasant side effects as well as causes recurrence with discontinuation of treatment. These and other shortcomings of current drug therapies emphasize their limitations and the necessity for the development of novel endometriosis treatments. Recent research shows a very promising role for new hormonal medication (aromatase inhibitors, estrogen and progesterone receptor modulators) and anti inflammatory drugs (Tumor necrosis factor – alpha inhibitors, matrix metalloproteinase inhibitors, cycloxygenase – 2 inhibitors) in the management of endometriosis which may prevent or eradicate endometriosis and also allow the conception during treatment rather than merely relieving the symptoms.

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Endometriosis and Infertility: Current Surgical Management

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Introduction

Endometriosis is one of the most common gynaecologic disorders affecting 10% of women in the general population, 40% of women with infertility and 60% of women with chronic pelvic pain(1). Infertility and pain are the two major presenting complaints of endometriosis. Various medical and surgical modalities of treatment are available for the management of endometriosis. Yet endometriosis is a challenge to the gynecologist as there is considerable confusion regarding the optimal method of management.

Management options for endometriosis associated infertility

Endometriosis-related infertility is often treated successfully with surgical destruction of the disease. Medical therapies rely upon interruption of normal cyclic, ovarian hormone production resulting in an environment which is unfavourable not only for growth of endometriosis but also for pregnancy. Suppressive medical treatment of endometriosis does not benefit fertility and should not be used for this indication alone.

Current therapy for endometriosis has three main objectives: (1) To reduce pain; (2) To increase the possibility of pregnancy; and (3) To delay recurrence for as long as possible. Effective, evidence-based treatments of endometriosis-associated infertility include conservative surgical therapy and assisted reproductive technologies.

Controlled ovarian hyperstimulation with intrauterine insemination is recommended in early-stage and surgically corrected advanced stage endometriosis after the pelvic anatomy is restored. In advanced cases, in vitro fertilization is a good option, and its success may be augmented with prolonged gonadotropin-releasing hormone analog treatment(2).

For a definitive diagnosis of endometriosis, visual inspection of the pelvis at laparoscopy is the gold standard investigation. Positive histology confirms the diagnosis of endometriosis but a negative histology does not exclude it. For peritoneal disease, visual inspection is usually adequate but histological confirmation of at least one lesion is ideal. In cases of ovarian endometrioma (greater than 3 cm in diameter) and in deeply infiltrating disease, histology should be obtained to identify endometriosis and to exclude rare instances of malignancy(3)

Detailed history and a thorough clinical examination is an important part of patient

management, followed by a transvaginal ultrasound. Care is taken to detect any rectal involvement or deeply infiltrating disease as more extensive surgery may be needed and patient needs to be prepared and counseled accordingly.

Surgical Management of Endometriosis Associated Infertility

The Cochrane reviews and the RCOG guidelines(3) are in agreement that there is a definite improvement in infertility associated with endometriosis with laparoscopic surgery(4). In addition, laparoscopic surgery for minimal, mild and moderate endometriosis results in a significant degree of pain relief at six months compared to expectant management (Cochrane Database of Systematic Reviews 2001)(5).

Surgery versus Expectant management in endometriosis

Ablation of endometriotic lesions plus adhesiolysis to improve fertility in minimal–mild endometriosis is more effective compared with diagnostic laparoscopy alone(3). So whenever endometriotic deposits are found at diagnostic laparoscopy, they should be ablated.

Principles of surgery

Surgical therapy can be performed concurrently with diagnostic laparoscopy and may include removal (excision) or destruction (ablation) of endometriotic tissue, division of adhesions and restoring normal pelvic anatomy. Care is taken to preserve normal ovarian tissue. Good surgical technique and meticulous hemostasis are important in reducing adhesion formation. Care is taken not to damage the tubes during surgery. Tubal flushing appears to improve pregnancy rates in women with endometriosis-associated infertility(3).

Surgical procedure:

The actual surgical procedure performed depends on the severity of disease, size of the endometriotic cyst, availability of equipment and experience of the operator.

1. Minimal/ mild endometriosis:

Although it is clear that superficial endometriotic lesions observed by laparoscopy have to be treated, the actual surgical procedure remains controversial. They may be cauterized with bipolar forceps or excised. Excision is preferred in deep lesions as cautery may not destroy them completely.

2. Moderate/ severe endometriosis:

In moderate and severe disease more extensive surgery in the form of endometriotic cystectomy and destruction of all implants, adhesiolysis and restoration of pelvic anatomy is required. Although there is enough clinical experience that surgery does help such patients and improve their conception rates, there are no randomized controlled trials or meta-analyses available on the role of surgery in improving pregnancy rates for moderate-severe disease(3).

Laparoscopy versus Laparotomy

Advantages of laparoscopy include minimally invasive procedure and smaller incision associated with reduced post operative pain and analgesic requirement, reduced duration of hospitalization and reduced chance of adhesion formation. The disadvantages include need for expensive equipment, operator skill, long learning curve apart from a lack of 3D perception and inability to palpate. Laparotomy may be required in “extensive disease” or involvement of rectum, ureter etc. This again is relative and depends on the experience & skill of the operator.

Excision versus Ablation:

The greentop guidelines clearly state that laparoscopic cystectomy for ovarian endometriomas is better than drainage and coagulation(3). According to a recent

Cochrane review, there is good evidence that excisional surgery for endometriomata provides for a more favourable outcome than drainage and ablation with regard to the recurrence of the endometrioma, recurrence of pain symptoms, and in women who were previously subfertile. Consequently this approach should be the favoured surgical approach (Cochrane Database of Systematic Reviews 2008) (6). Excisional surgeries also have the advantage of providing tissue for histopathology. But there is a risk of loss of normal ovarian tissue and decrease in ovarian reserve.

Coagulation or laser vaporization of endometriomas without excision of the pseudocapsule seems to be associated with a significant increase in risk of cyst recurrence. Ablation may be performed if cyst wall cannot be excised. For cysts larger than 4cm, excision is preferred(7). Hence ablation should be done only if excision could not be done due to small cyst size or technical problems.

Finer details of surgery

Some of the factors that go a long way in optimizing patient outcome in terms of both fertility outcome and pain relief include attention to the finer details of surgery like operating in the right planes, minimal use of cautery and gentle tissue handling, especially the tubes. Hemostasis must also be ensured as blood clots can lead to infection and adhesion formation.

Endometrioma formation is associated with invasion of ovarian capsule and formation of adhesions. There is no need to give a separate incision over the endometrioma during cystectomy. By means of blunt dissection, the ovary is to be separated from the uterosacral ligaments. This results in drainage of the endometrioma. The stoma from which the endometrioma drained is enlarged and cyst wall is stripped off in-toto from the normal ovarian tissue. In case the distinction between the normal ovarian tissue and cyst lining is not clear, the edge is freshened with the help of scissors.

Adhesion prevention

Apart from careful surgical technique and following the principles of microsurgery, certain agents have been used in an attempt to reduce adhesion formation. A recent cochrane review has concluded that the current evidence for the use of fluid and pharmacological agents (steroids, icodextrin 4%, SprayGel and dextran) for the prevention of adhesions is limited. There is no evidence on any benefit for improving pregnancy outcomes when pharmacological and fluid agents are used as an adjunct during pelvic surgery. However there is some evidence that hyaluronic acid agents may decrease the proportion of adhesions and prevent the deterioration of pre existing adhesions but due to the limited number of studies available, this evidence should be interpreted with caution and further studies are needed.(Cochrane Database of Systematic Reviews 2006 (8).

Role of medical management pre/post surgery:

1. Role of pre-operative hormonal treatment: Theoretical advantages of using medical supression pre-operatively include a possible reduction in pelvic vascularity and size of implants, thereby reducing blood loss at surgery. The possible benefit should be weighed in the context of the adverse effects and costs of these therapies. Although hormonal therapy prior to surgery improves the revised American Fertility Society classification system scores, there is insufficient evidence of any effect on outcome measures such as pain relief or conception rates to justify its usage(3). (Cochrane Database of Systematic Reviews 2004)(9).

2. Role of post-operative hormonal treatment: Post-operative suppression was used with the idea of treating any residual disease and reducing recurrence. But there is no evidence of significant fertility enhancement and further fertility therapy is unnecessarily delayed. It has been shown that compared with surgery alone postoperative hormonal treatment does not produce a significant reduction in pain recurrence at 12 or 24 months and has no effect on pregnancy rates or disease recurrence(3). (Cochrane Database of Systematic Reviews 2004). Also, the best chances of pregnancy in an infertile patient operated for endometriosis are immediately after surgery. If GnRH analogues are given at this time period, the patient will not be unable to conceive. Some patients develop prolonged amenorrhea after GnRH analogues and the dose of gonadotrophins required for ovulation induction may be increased. The patients also experience a lot of psychological problems from infertility and they may not want to wait for so long to start trying for conception.

To conclude, there is insufficient evidence of benefit to justify the routine use of preoperative or postoperative hormonal treatment.

Two Stage surgery:
Two-step operative laparoscopy with interval pituitary suppression by means of gonadotrophin-releasing hormone analogues has been found to reduce the extent of endometriosis, as classified by the American Fertility Association, and appears to be a promising method of achieving optimal cytoreduction and facilitating complicated surgery in severe endometriosis, while protecting the ovary from unnecessary trauma(10).

Repeat surgery:
Repeat surgery is commonly practiced if a patient fails to conceive after the first surgery in endometriosis. This is a good option especially if there was incomplete clearance in first surgery. Repeated surgeries may lead to loss of ovarian reserve especially if the first surgery was extensive and patient is elderly. In such cases IVF may be a good option.

Ovarian reserve after conservative surgery
There have been concerns about decrease in ovarian reserve following surgery for endometriosis but there is no conclusive evidence to prove that it affects fertility outcome negatively. In one study, the mean percentage of reduction of dominant follicles, oocytes, embryos, and high-quality embryos was 60%, 53%, 55% and 52% respectively in the operated gonad. Fertilization rate and rate of good-quality embryos were similar. The authors concluded that laparoscopic excision of endometriomas is associated with a quantitative but not a qualitative damage to ovarian reserve(11).

After surgery…
Best chances of conception are immediately after surgery and this should be explained to the patient. She must be advised to try for conception, and if there is a long duration of infertility ovulation induction with or without IUI after surgery is a good option.

Role of IVF in endometriosis:
IVF is appropriate treatment for endometriosis when tubal function is compromised, if there is also male factor infertility and/or other treatments have failed(3).

Pregnancy rates for IVF in endometriosis:
The presence of endometriosis has a negative effect on the pregnancy rate after ART. It is unclear if surgical treatment prior to ART may increase the pregnancy rate after ART. It is also unclear if ART is a risk factor for recurrence or progression of endometriosis.

Role of GnRH agonists before IVF:
The administration of GnRH agonists for a period of three to six months prior to IVF or ICSI in women with endometriosis increases the odds of clinical pregnancy by fourfold. Data regarding adverse effects of this therapy on the mother or fetus are not available at present(3). (Cochrane Database of Systematic Reviews 2006(12).

Role of surgery before IVF:
There are no randomised controlled trials comparing laparoscopic excision with no treatment before IVF. However, laparoscopic ovarian cystectomy is recommended if an ovarian endometriomas ≥4 cm in diameter is present to confirm the diagnosis histologically; reduce the risk of infection; improve access to follicles, and possibly improve ovarian response and prevent endometriosis progression. The woman should be counselled regarding the risks of reduced ovarian function after surgery. The decision should be reconsidered if she has had previous ovarian surgery(3).

Laparoscopy after IVF failure:
Laparoscopy and endometriotic cystectomy and adhesiolysis may still be a viable option after IVF failure especially if the patient has severe disease. Laparoscopy may be followed by ovulation induction and IUI or IVF.

In one study, of 29 patients with prior IVF failures, 22 conceived after laparoscopic treatment of endometriosis, including 15 non-IVF pregnancies and 7 IVF pregnancies. The authors concluded that in the absence of tubal occlusion or severe male factor infertility, laparoscopy may still be considered for the treatment of endometriosis even after multiple IVF failures(13).

Surgery fails, ivf fails, and patient has pain and is desperate for relief…….management options???
Conventionally such patients were managed by hysterectomy and bilateral salphingo-ovariotomy and removal of all pelvic disease for pain relief after they were reconciled to the fact that they were unlikely to conceive as all options have failed.

Now we have less radical options to offer these patients. LNG-IUCD insertion relieves pain effectively and in case there are large cysts, they may be aspirated before LNG-IUCD insertion. This treatment modality does not cause permanent loss of fertility.

Levonorgestrel impregnated IUCD:
It reduces dysmenorrhea associated with endometriosis when used alone or in combination with USG guided cyst aspiration/ conservative laparoscopic surgery in case of ovarian endometriotic cysts. It is a good alternative to panhysterectomy. The advantages are that it is noninvasive, there is no hypoestrogenism (as compared to panhysterectomy) and hence no need for HRT.

In a small randomised controlled trial, the LNG-IUS inserted after conservative laparoscopic surgery for endometriosis associated pain significantly reduced the risk of recurrent moderate–severe dysmenorrhoea at 1 year follow-up(14).

Role of cyst aspiration in endometriosis :
Cyst aspiration in endometriosis is not to be done as a routine as the material is thick and often incompletely aspirated, spill may lead to inflammation and adhesion formation. The cyst usually refills after aspiration as the cyst wall is still there and hemorrhage occurs every month from the lining. It has a limited role when used along with some form of suppression (LNG-IUCD or Mifepristone) in patients who have recurrence after multiple surgeries as a alternative to panhysterectomy.

Conclusion:
Endometriosis is an enigmatic disease and a leading cause of infertility and its incidence is

rising. The management is a challenge to the gynecologist. Medical management has no role in the management of infertile patients with endometriosis. Surgical management with removal of all endometriotic implants and restoration of pelvic anatomy is the treatment of choice for moderate to severe disease. In minimal/ mild disease, ovulation induction with IUI is effective therapy. But if diagnostic laparoscopy has been done and minimal/ mild disease has been found, destruction of the implants is associated with a better fertility outcome compared with diagnostic laparoscopy alone. If surgical management fails, IVF may be offered to these patients.

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Recto Vaginal Endometriosis

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Introduction

Endometriosis is a disease which continues to be poorly understood & improperly treated. An enigmatous, perplexing disease adds more confusion especially for Rectovaginal endometriosis. Drugs are still used to treat advanced disease when there is absolutely no evidence for their efficacy. Hysterectomy is still performed for a disease that by definition is "extra-uterine". Myths and false concepts are carried from one textbook to the next.

In the pelvis, three different forms of endometriosis must be considered: 1) peritoneal endometriosis, 2) ovarian endometriosis, 3) rectovaginal septum endometriosis.

The deep-infiltrating endometriotic nodule in the recto-vaginal septum was studied by Koninckx (1). These authors described three subtypes of deep endometriosis depending on the depth of infiltration. The recto-vaginal septum endometriotic nodule was considered as the deepest form of endometriosis and a result of the natural evolution of peritoneal endometriosis in some women. Other authors (2,3) have suggested that the recto-vaginal endometriotic nodule is an adenomyotic nodule whose histopathogenesis is probably not related to the implantation of regurgitated endometrial cells but to the metaplasia of Mullerian remnants.

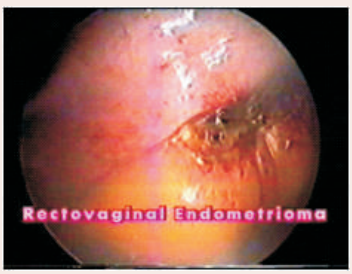
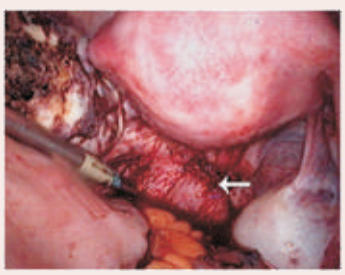


Fig 1 : (a) Rectovaginal endometrioma



(b) Rectovaginal endometrioma

Clinical presentation

Patients present with symptoms of deep rectal pain, often worsened with bowel movements or exacerbated at the time of menstruation. Disturbance of bowel habit manifesting as alternating diarrhea and constipation is common and with more advanced disease tenesmus or a feeling of incomplete rectal emptying may occur. Rectal bleeding may be noticed, commonly occurring at the time of menstruation. Occasionally they are asymptomatic.

On clinical examination apart from per vaginal, per rectal examination is more important to diagnose & evaluate the extent & involvement of rectal muscularis, fixity etc.

Histology of deep endometriosis

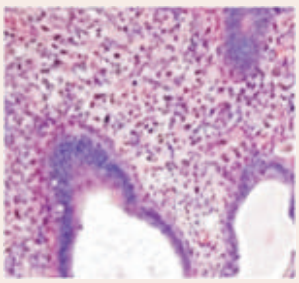


Fig 2: Histology picture of rectovaginal endometriosis

Deep vaginal endometriosis associated with pelvic endometriosis can take the form of nodular or polypoid masses involving the posterior vaginal fornix. It has been called an "adenomyotic nodule of the recto-vaginal septum" (4).

Histologically, scanty endometrial-type stroma and glandular epithelium is disseminated in muscular tissue proliferation. Indeed, in all cases, hyper plastic smooth muscle was observed surrounding the endometriotic tissue. This smooth muscle proliferation is probably a reaction to the presence of endometriotic foci in the recto-vaginal septum.

A circumscribed nodular aggregate of smooth muscle, endometrial glands, and usually, endometrial stroma thus represents the typical histological confirmation of a recto-vaginal endometriotic nodule. This histological description, similar to the histological description of adenomyosis, led to suggest that the so-called endometriotic nodule of the recto-vaginal septum is, in fact, an adenomyoma or an adenomyotic nodule.

Hypothesis of pathogenesis

Cullen in 1908 proposed that rectovaginal disease occurred as a result of direct extension of lower uterine adenomyosis

Koninckx and Martin (1) suggested that the "endometriotic" nodule is the consequence of deep infiltration by active disease and that three types of "deep-infiltrating endometriosis" can be distinguished according to the depth of infiltration. According to their histological findings, the presence of loose connective tissue permits infiltration.

Nissole & Donnez (3) believed that embryonic remnants into the rectovaginal septum undergo metaplastic change to endometrial like tissue & by proliferation become surrounded by hyperplastic smooth muscle representing a typical adenomyotic nodule deep in the rectovaginal septum.

It has been proved (5) that Müllerian rest cells are able, after a long period of quiescence, to proliferate and differentiate, explaining the development of uterine adenomyosis. There is no reason why this hypothesis cannot be extended to explain the development of the recto-vaginal adenomyotic nodule.

Hyperplasia of the smooth muscle in the septum provokes a perivisceritis through an inflammatory process followed by secondary retraction. This perivisceritis is not an endometriotic rectal lesion or an invasion of the rectal wall by the endometriotic process, as has been suggested by many authors (1,6,7) but only the consequence of serosal retraction due to the inflammatory process and fibrosis on the anterior wall of the rectum.

Vercellini (8) approached this debate by measuring the Pouch of Douglas (POD) depth and volume of women with and without recto-vaginal endometriosis. He found that women with deep endometriosis had POD depth measurements on average 1/3 less than those without deep disease, and therefore believed that this was a primary peritoneal disease, extending into a pseudo-recto-vaginal septum.

Rectal endometriosis often arises from infiltrative utero-sacral disease, with involvement of the lateral rectal wall. It seems equally likely that peritoneal POD disease causes the majority of anterior rectal disease with rearrangement of POD anatomy by adhesion formation.

Principles of Management

These principles depend upon an understanding of the pathophysiology of recto vaginal endometriosis. Growth cycles induce recurrent inflammatory response and ultimately fibrosis. Even surface peritoneal disease often involves much thicker fibrotic peritoneum than first assessment would suggest. Inflamed peritoneal surfaces lead to adhesion formation in some patients. Dissect from normal tissue separating the endometriotic nodule, safe from the rectum. For rectovaginal endometriotic nodule surgery a consent for diverting colostomy is not easy to get in India. Fortunately the incidence of rectovaginal endometrioma are less in India compared to western countries.

Classification

The revised AFS classification for endometriosis is not useful in categorizing deep endometriosis for pain. This is mainly because of loading of the scores by ovarian and tubal adhesions, and ovarian endometrioma. For comparability in ongoing research an accurate anatomical description of the location and infiltration of deep endometriosis is more valuable.

CONTROVERSIES IN TREATMENT MODALITIES:

Treatment approaches to advanced endometriosis in recent times have been most illogical. No amount of progestogen and no degree of oestrogen suppression will permanently eradicate the endometrium, so how could we expect such hormonal approaches to eradicate endometriosis. Temporary suppression is the only outcome, and while symptomatic improvement may occur, recurrence of symptoms following cessation of treatment is almost invariable. No effect on the associated fibrosis occurs, and no drug of any class will eradicate scar. This probably accounts for the fact that a percentage of women with deep fibrotic endometriosis fail to experience even temporary symptom relief with hormonal suppressive therapies.

In order to avoid treating just the "tip of the iceberg", the only logical approach must surely be surgical removal or excision of disease. Disease overlying the ureter dictates that the ureter be dissected free and retracted from the surgical site. Disease overlying or involving the bowel dictates that this organ be mobilized, and dissected free from the disease. Herein lies a problem. Certainly in our country, the surgical training of most Gynecologists has not equipped them for such dissections. So patients continue to be treated with surface ablation for deep disease, avoiding the danger sites, with resulting treatment haphazard at best. Even worse they are subjected to multiple courses of hormonal therapies that are known to be ineffective, interspersed with multiple laparoscopies to "see how the disease is going". These are the only patients who do not need a laparoscopy to diagnose endometriosis.

In desperation, hysterectomy and bilateral oophorectomy is often recommended to relatively young women with advanced endometriosis. This is often performed leaving deep disease remaining. Not surprisingly such women often remain symptomatic.

Laparoscopic treatment of deep endometriosis:

Conservative excision of deep endometriosis is almost always possible to achieve as a laparoscopic procedure, with the advantages of faster patient recovery, less post-operative adhesion formation, and most importantly improved identification and access to deep disease. The disadvantage of course is the

more prolonged operating time. Furthermore there is no doubt that this is complex and difficult surgery, and certainly not without risk of serious operative morbidity.

Let us assume a patient with pelvic side wall disease, invasive uterosacral disease and a deep rectovaginal nodule with bowel tethered centrally to the posterior cervix. There is no ovarian involvement.

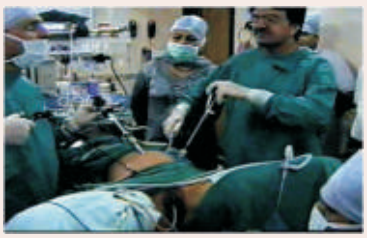


Fig 3: Port Placement

A 1 cm intra-umbilical incision for the primary port and two 5mm incisions in both iliac fossa (at the junction of the medial 2/3rd and lateral 1/3rd of the anterior superior spino-umbilical line, lateral to the deep inferior epigastric artery are made for the auxiliary ports. 3rd auxiliary (left upper port) is placed as shown in the fig.3

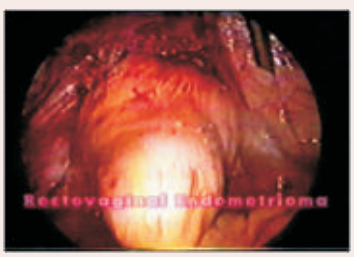


Fig 4 : Pre laser treatment rectovaginal endometriosis (Rectal probe)

Ancillary ports are introduced under vision. Two grasping forceps (one toothed), a pair of laparoscopic scissors through which unipolar current can be delivered, a suction irrigation probe with an irrigation pressure generator connected via wide bore tubing and a bipolar coagulating forceps are needed.

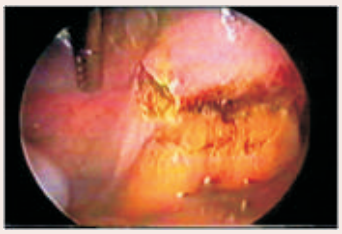
The first principle is to commence dissection in an area of normality. The second principle is to use constant tissue traction during dissection and the third is to use a combination of high power density cut (unmodulated) current and sharp scissor dissection. For this reason we prefer to deliver electrosurgical current through the laparoscopic scissors. The electrosurgical generator is set at 100W pure unmodulated current and coagulation effect can be achieved by varying power density by altering the amount of electrode in contact with the tissue. The bipolar output is set to 30W, and similarly delivers unmodulated current automatically.

The ureter is identified through the peritoneum high on the pelvic sidewall and the peritoneum opened linearly above it. The ureter can then be swept off the peritoneum in an area where it is healthy and non-adherent. The peritoneum is then retracted medially while dissection around all areas of disease occurs with about a 0.5cm margin. Particular care need be taken where overlying peritoneum is adherent to the ureter, but it is virtually always possible to shave the ureter free from overlying disease. The peritoneum is always found to be thicker and more fibrotic than expected, reinforcing my belief that excision of disease is the only logical approach. As one proceeds towards the side of the uterus, vascular injury becomes of increasing concern. The uterine artery will usually become apparent in its tortuous course over the top of the ureter, and the uterine veins lateral to the insertion of the utero-sacral ligaments become particularly prone to injury. The ureter at this point lies more laterally and is less susceptible to injury.

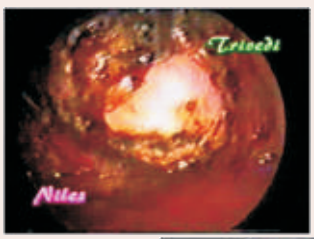
Another modality of treatment is CO2 Laser or a combination of high power density cut (unmodulated) current. They are dangerous, but can be used precisely by some experts. Many endoscopists prefer scissors to any energy modality since it gives an indirect palpation and tissue feeling when it is dissected and cut.

Fig 5: Laser treatment of rectovaginal endometrioma.

(a) CO2 laser



(b) Rectovaginal-Nodule



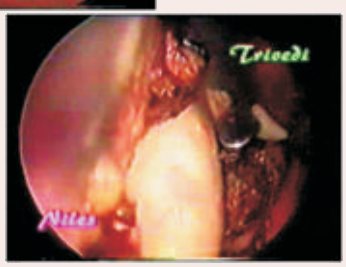


FIG. 6 Nodule excision by laser (a & b)

Next the para-rectal spaces must be opened. An uninvolved area of rectosigmoid is chosen, and the peritoneum opened on the medial side of the utero-sacral ligament. This space may be safely opened quite deeply although bleeding from para-rectal vessels will always be encountered. This bleeding can be controlled with the application of electrosurgical energy through bipolar forceps. Bleeding from the rectal sidewall can also be controlled with bipolar energy although it is frequently prudent to use "liga-clips" to minimise inadvertent thermal injury to the rectal wall.

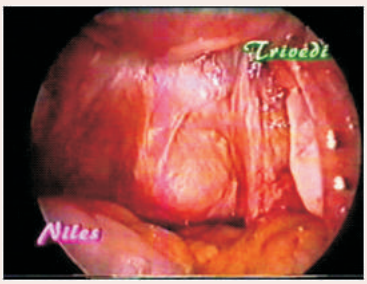
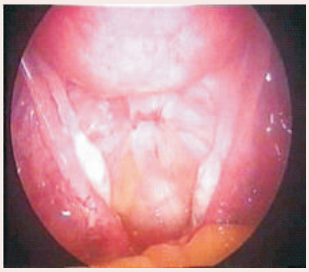


Fig 7: Post Laser effect

Once the rectum has been mobilised laterally, the most difficult part of the surgery commences. It is necessary to mobilise the rectum from the posterior cervix until the areolar tissue of the normal recto-vaginal septum is reached. It may be possible to find a tissue plane between the nodule and the posterior cervix / vagina, and it may be possible to find a plane between the nodule and the rectum. More commonly the dissection proceeds through the nodule, leaving disease both on the posterior cervix / vagina, and on the anterior rectal wall.

With these spaces opened, it is now possible to excise uterosacral disease to whatever depth necessary to achieve eradication. Much reliance is placed upon trans-laparoscopic palpation of tissues to confirm that all uterosacral disease has been removed.

Residual rectal disease must now be removed. It is usually possible to shave such disease from the anterior rectal wall, but in cases of deep muscularis involvement a disc excision may be required.



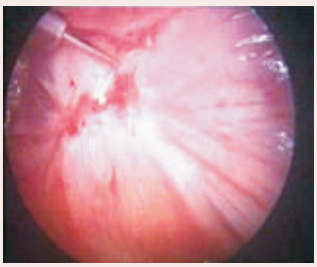


Fig 8 : Rectovaginal nodule with posterior fornicial nodule in case of dyspareunia

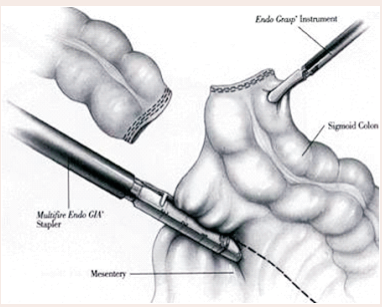


Fig 9: ENDO GIA multifire stapling device

Occasionally, with the greatest of care the rectum may be inadvertently opened. Only when there is rectal stricture formation from fibrosis, or extensive endometriotic disease involving more than 1/3 of the rectal circumference would anterior segmental resection be considered. In this instance, complete mobilisation of the rectum, resection of the involved segment and either trans-anal staple anastomosis or mini-laparotomy for a hand-sewn anastomosis is undertaken.

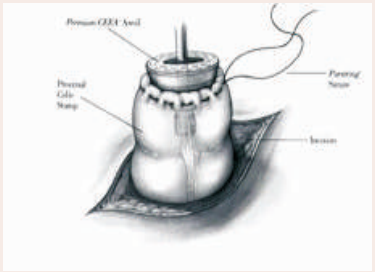


Fig 10: Showing the Anvil

Regarding repair of a rectal defect, any hole greater than 1cm should be closed in a transverse direction. This prevents hourglass stricturing of the rectum that could lead to significant functional disturbance.

Rectal defects may be closed by single layer interrupted sutures or larger defects may be closed quickly with an ENDO GIA multifire stapling device. The articulating head stapling devices are particularly suitable for this, as they facilitate the desired transverse closure.

Finally, any residual disease on the posterior cervix / vagina must be removed. This may be shaved laparoscopically, or with deeply invasive disease may be more efficiently removed via a vaginal approach. Excision of a segment of vaginal wall may be required with primary vaginal closure.

If a defect in the bowel wall has been repaired, leave a Penrose drain from the site of repair, exiting through one of the lower lateral port sites. This should be left for 5-7 days.

Before removing the ports, the pelvic and peritoneal cavity should be copiously irrigated with saline and haemostasis checked. It is wise to finally check haemostasis after deflation of the pneumoperitoneum for a period of time. The pneumoperitoneum pressure may otherwise tamponade venous bleeding sites that only become apparent after release of this pressure.

This outlines the approach to excision of advanced endometriotic disease. This is often long and complex surgery, but symptomatic response to this surgery is most rewarding. Redwine and Perez (9) have reported a series of more than 500 cases of excisional surgery for advanced endometriosis. These patients have been followed for up to four years with significant and sustained improvement in symptoms.

In conclusion, we suggest calling this disease "recto-vaginal adenomyosis" as the lesion originates from the recto-vaginal septum tissue and consists essentially of smooth muscle with active glandular epithelium and scanty stroma. In last 15 years out of 18,000 laparoscopic surgeries, 2000 cases of endometriosis we have encountered only 12-13 cases of rectovaginal nodule. Though the incidence of rectovaginal endometriosis is less in India as compared with western countries more so because many times it is difficult to obtain the consent for colostomy. The ideal treatment in rectovaginal endometriosis is considered to be using ENDO GIA multifire stapling device in western countries which is yet to be practiced in India. Multiple treatments by multiple gynecologists often lead to inadequate treatment for rectovaginal endometriosis. This should be best handled by an expert laparoscopic gynaecologist along with colorectal surgeon.

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Surgical Management of Adenomyosis

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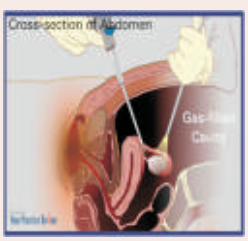
Introduction:

Adenomyosis, partly understood, is called 'elusive' or 'enigmatic' because of difficulty in diagnosis, controversy in definition, and because of the vague and ill-defined pattern of symptoms. Patients experience troublesome, heavy menstrual bleeding, dysmenorrhoea, infertility, bad obstetric history and sometimes a tender uterus. The association of adenomyosis with other pelvic pathologies (Fibroids, Endometriosis, Rectovaginal Endometriosis etc.) confuses the understanding of related symptoms. There is no specific combination of symptoms which can be attributed specifically to adenomyosis. Now that moderate to severe degrees of adenomyosis is diagnosed by ultrasound or magnetic resonance imaging (MRI), there is an urgent need for multicentric collaboration to prospectively define symptomatology uniformly, and relate it with findings on imaging (also with surgical and pathological findings).

Mechanism of origin:

When the myometrium is invaded by endometrium from within, the condition is called uterine endometriosis or adenomyosis.



Microscopic invasion of the muscle by basal endometrium is normal, and this is exaggerated when the endometrium is hyperplasic. The possibility of adenocarcinoma or other malignant disease in an island of endometriosis is well known. Adenomyosis involves the corpus, in its wall or its part. Rarely, it is found in the cervix. When adenomyosis is local it is most likely to be situated in the posterior wall of the uterus.

Clinical features :

The symptoms are menorrhagia & dysmenorrhoea in majority of cases, few are asymptomatic. Dysmenorrhea is gradually progressive in some years and is caused by enlargement of the uterine cavity (bleeding area) and an increased blood supply. Other causes for the menorrhagia are impaired contractility of the myometrium, and associated endometrial hyperplasia. Dysmenorrhoea is more likely when the myometrium is deeply penetrated and is due to disturbed uterine contractions rather than by tarry cyst formation. The increased size of the uterus causes diurnal frequency, a sensation of weight in the pelvis, and abdominal mass. The patient may also have Infertility. The enlargement of the uterus is detected on bimanual examination. The organ is mobile and there is usually no evidence of extra uterine endometriosis. The symptoms are similar so it is impossible to distinguish clinically between adenomyosis and Myoma. Adenomyosis tends to occur at older age; it rarely enlarges the uterus more than 12-14 weeks size and it causes a regular rather than a nodular uterine enlargement

Fibroid	Adenomyosis
Age 25-35 years	Age : 35-45 years
Menorrhagia	Menorrhagia + Dysmenorrohea
Associated endometriosis : rare	Associated endometriosis :Common
Localized bosses over uterus	Generalized enlargement of uterine wall
Well circumscribed capsule	No evidence of capsule
Cut surface smooth	Cut surface irregular & tarry small cyst
Dissection easy with myoma screw	Dissection not possible with myoma screw
Fibroid removal as a treatment	End result Hysterectomy for continued symptoms
HPE : Typical finding	HPE : Presence of endometrial glands + stroma

Why Adenomyosis & Infertility are so significant today?

Uterine adenomyosis is frequent and debilitating and its incidence and association with infertility is increasing. Incidence of Adenomyosis rises in mid-thirties. Moreover, when women delay their first pregnancy until thirties or forties, adenomyosis is encountered in the fertility clinic during diagnostic work-up. By recent advances in the non-invasive diagnosis of the condition, non-surgical treatment options for infertile patients with adenomyosis arise but need to be confirmed in larger series(1)

Preoperative Diagnosis:

Non-invasive imaging techniques (USG & MRI):

Both MRI and sonography diagnose adenomyosis so that treatment may be instituted specific to the disease process. The muscular hyperplasia with heterotopic endometrial tissue actually produces the typical gross appearance of adenomyosis and corresponds to areas of decreased echogenicity or signal intensity on ultrasound and magnetic resonance imaging respectively and, these changes are detected with increasing frequency(2), including the presence of myometrial nodules, linear striation, poor definition and nodularity of the endo-myometrial junction, pseudo widening of the endometrium, and myometrial cysts or hemorrhagic foci, without well defined capsule seen in typical fibroid scan. ***Patient with fibroid & dysmenorrhea must be scanned for the possibility of adenomyosis before surgery. Patient should be counseled about this possibility before laparoscopic fibroid surgery especially if patient had dysmenorrhea.***

Spectrum of MRI features in adenomyosis:

MRI is a precise, non-invasive method for diagnosing adenomyosis. Typical MRI features(3) include either diffuse or focal thickening of the junctional zone or an ill-defined area of low signal intensity in the myometrium on T2-weighted MR images. The islands of ectopic endometrial tissue are identified as punctate foci of high signal intensity. Adenomyosis present as a well-circumscribed form known as adenomyoma, adenomyotic cyst characterized by the presence of haemorrhagic cyst, or adenomyomatous polyp protruding into the uterine cavity. The MR appearances of adenomyosis may occasionally fluctuate in response to hormonal stimulation and treatment. MR imaging is helpful not only in monitoring the treatment effect of hormonal therapy, but also in predicting therapeutic effect. In cases of endometrial cancer in the uterus with adenomyosis, evaluation of myometrial invasion may become difficult. Rarely, endometrial cancer may arise directly from adenomyosis resulting from malignant transformation of endometrial glands, creating diagnostic challenges & and they should be carefully differentiated from

adenomyosis by identifying typical clinical and MR features in these lesions.

Pre-operative Biopsy:
Patients with dysmenorrhoea and menorrhagia refractory to medical treatment were diagnosed as Adenomyosis. Diagnosis of adenomyosis is improved by use of vaginal ultrasound and percutaneous or transcervical myometrial biopsy(4) :-Conservative surgical procedures including endometrial resection and myometrial reduction or excision may reduce the need for hysterectomy in the presence of adenomyosis.

Decision Making during Laparoscopy / open surgery:
Surgeon must evaluate carefully for evidence of Endometriosis around pelvic organs in all the cases of surgery for Fibroid. Usually adenomyosis produces a diffuse enlargement of the uterus in contrast to the well circumscribed bosses characteristic of fibroids. After incision on the uterus it shows typical picture of irregular cut surface with multiple small tarry cysts with no specific capsule anywhere.

Look for localized adenomyoma or involvement of all the walls of uterus with adenomyotic changes in advance, as continuing surgery with diffuse adenomyosis involving uterus walls, may result in opening the uterine cavity & very difficult suturing of the defect or hysterectomy. This may be disaster for an infertile patient, especially if consent for Hysterectomy is not taken.

Hormonal/Medical treatment for Adenomyosis:
Like endometriosis and uterine myomas, adenomyosis presents typical characteristics of estrogen-dependent diseases. The medical treatment of adenomyosis is based on the hormonal dependency of the disease and its strongly debated similarities with endometriosis. In fact, despite the evident differences between the two conditions, the therapies that treat endometriosis effectively have also been successful for the treatment of adenomyosis. Although the two diseases have distinct epidemiological features, they have the same 'target tissue' for hormonal therapy, namely ectopic endometrium. Recognized approaches are systemic hormonal treatments, which are generally used for endometriosis and are capable of suppressing the estrogenic induction of the disease, and local hormonal treatment that targets the ectopic endometrium directly. Gonadotropin-releasing hormone agonists, danazol and intrauterine levonorgestrel- or danazol-releasing devices are used in the treatment of adenomyosis. Despite the base for its hormonal treatment, few studies are performed on medical therapy for adenomyosis (5).

Non-invasive treatment modalities for conservative treatment for Adenomyosis :
A. Uterine Artery embolization:
Uterine Artery embolization(6) is a promising nonsurgical alternative for patients with menorrhagia and adenomyosis. There is significant improvement in presenting symptoms and in quality of life with decrease in uterine size and junctional zone thickness. Need further studies for safety/efficacy for patients with adenomyosis.

B. Magnetic resonance-guided focused ultrasound surgery (MRgFUS):
MRI is better than TVUSG to diagnose focal adenomyosis. Magnetic resonance-guided focused ultrasound surgery (MRgFUS) destroys a significant part of the tumor. One author reported that following an uncomplicated MRgFUS(7) treatment, after 6 weeks, the patient experienced a significant reduction in menometrorrhagia and about 50% decrease in tumor size. She conceived and, gave birth at term to a healthy infant via normal vaginal delivery. Further studies are needed to assess the overall safety and long-

term effectiveness of MRgFUS for the non-invasive treatment of adenomyosis.

Conservative Surgical modalities for Adenomyosis:
Laparoscopic Adenomyosis Resection : (Author's technique)
Selection Criteria:

(1) Localized Adenomyoma can be excised better and likely to give better result.
(2) Generalized Adenomyosis with uniform enlargement of uterus of >12-14 size case is not favorable for Adenomyosis resection.
(3) Patient should be counseled about very poor fertility result after adenomyoma resection surgery.
(4) Laparoscopic surgeon must do meticulous suturing of myometrial defect after adenomyoma resection otherwise patient may develop rupture uterus when she becomes pregnant.

Laparoscopic Technique:

Part of uterus with maximum bulge is incised with scissor or Monopolar needle or spatula followed by excision of adenomyotic tissues. Haemostasis is controlled during surgery with bipolar desiccation. Adenomyotic tissue is grasped with 5 mm claw forcep and pulled and gradually excised till normal healthy myometrium is reached. One should be careful that cavity is not opened and large defect is not formed and then it becomes very much difficult to approximate the defect and suture adequately. Uterine defect should be closed with No.1 Vicryl and by extra-corporeal knot technique or intracorporeal suturing with slipped knot technique or figure of "8 stitch using extra port for strapping while applying second knot.

Author's result:
I have operated 15 cases of localized adenomyoma and given post operative Luperide depot. Symptomatic relief (i.e. dysmenorrhoea) is achieved in majority of the cases, but fertility result is achieved only in one case. My personal experience indicates very poor fertility result after adenomyoma resection. Facts must be shared & counseled with patient and her relatives.

Another study of Laparoscopic excision of localize adenomyoma was performed & in most of the patients, dysmenorrhea(8) was relived postoperatively.

Another technique of Laparoscopic bipolar coagulation of adenomyomata(9) for Conservative treatment obviated the need for major surgery in 90% of women with adenomyoma, but further evaluation of this technique in large series is necessary to confirm this.

Few Fertility results after conservative surgery for adenomyosis:
Few other studies e.g. Laparoscopic Excision(10) of adenomyoma with intraoperative peculiarities involving difficulties in their dissection and manipulation but it appears to be safe and feasible with good follow-up results and limited recurrence rates and Live birth(11) have been reported after conservative surgery for severe adenomyosis following diagnosis by MRI and therapy with GnRh-a & excision.

Essentially, data are from case reports or small case series. However, there is no agreed imaging definition of adenomyosis, and so therapies that do not excise the uterus have unfair comparison. Since the techniques presented here are new, they need further scrutiny and discussion for general acceptance. Until now the only certain diagnoses have been made by histopathologists on uteri removed at surgery, but recently accurate techniques allow diagnosis on the uterus in situ. With these methods, it's possible to obtain correct

information on the epidemiologic characteristics of adenomyosis to clarify whether it has a pathogenic role in unexplained ovulatory menorrhagia and juvenile dysmenorrhoea.

Conclusions:

Investigations are indicated in women with continuous menstrual pain or menorrhagia not responding to drug or conservative surgery. There are (5) three approaches to hysterectomy for benign disease like Adenomyosis - abdominal hysterectomy (AH), vaginal hysterectomy (VH) and laparoscopic hysterectomy (LH)(12). Significantly improved outcomes suggest VH should be performed in preference to AH where possible. Where VH is not possible, LH may avoid the need for AH, however the length of the surgery increases as the extent of the surgery performed laparoscopically increases, particularly when the uterine arteries are divided laparoscopically and laparoscopic approaches require greater surgical expertise. The surgical approach to hysterectomy should be decided by a woman in discussion with her surgeon in light of the relative benefits and hazards.

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Pelvic Pain in Endometriosis

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Endometriosis still remains a disease of uncertain etiology and non-specific treatment and even now, for many patients it is associated with tragically chronic prolonged course. It is the presence of functioning endometriotic glands and stroma outside the uterine cavity in the form of ectopic lesions. It is becoming one of the most common gynecological disorders and is found to be associated with approximately 70% of patients with chronic pelvic pain(1).

Pain in endometriosis is found in varied forms such as dysmenorrhoea, dyspareunia and most importantly chronic pain in the pelvic region. Dysmenorrhoea is characteristically of congestive type, beginning prior to onset of menses and continuing during the bleeding phase as well. Dyspareunia is attributed to presence of endometriotic lesions over the uterosacrals and also due to presence of dense adhesions in cul-de-sac making the uterus retroverted with restricted mobility.

Mechanism of pain in endometriosis:
While there is no established relationship between the extent of disease and symptoms, the location and type of the disease can impact pelvic pain. The intensity of pain associated with infiltrative disease has been correlated with the depth of lesions. It has been studied that the lesions with depth of 6mm or more are associated with severe pain(2). Perineural inflammation and direct infiltration of nerves by endometriosis have been observed.

Most commonly suggested mechanisms for pain in endometriosis are:

1. Production of substances such as cytokines and growth factors by the activated macrophages associated with endometriotic implants.
2. Effects of bleeding from the ectopic implants causing peritoneal irritation and fibrosis.
3. Invasion of the pelvic nerves by the endometriotic implants.
4. Enhanced aromatase expression has been detected in the ectopic endometriotic lesions which causes local accumulation of estradiol and stimulates the growth of the tissue(3).

Pain measurement:
Assessing the level of pain in an individual can be difficult. Most clinical studies for pain have

used standardized methods such as Visual Analogue Scale (which rates pain from none to worst), McGrill Pain Questionnaire and Categorical scale. But these are rarely used in clinical practice.

Diagnosis:
As endometriosis is not the only cause of chronic pelvic pain, confirmation of diagnosis is of utmost importance. To do so, pelvic examination, ultrasound, MRI or Laparoscopy can be done. Pelvic examination is notoriously inaccurate in estimating the volume of endometriosis nor have the ultrasound or MRI techniques improved the diagnostic accuracy. Operative visualization of the lesions with laparoscopy is gold standard for diagnosis.

Treatment:
1. Symptomatic relief:
Can be achieved in some patients with NSAIDS like ibuprofen, mefenemic acid

2. Medical treatment:
Series of drugs have been used such as oral contraceptives, progestogens, danazol, GnRH agonists

The above mentioned preparations cause amenorrhoea and hence help in arresting the progress of disease and thus reducing the pain factor.

A study by Sandro et al on efficacy of vaginal danazol therapy has shown significant reduction in dysmenorrhoea, dyspareunia and chronic pelvic pain within 3 months of treatment in patients with deeply infiltrated endometriosis(4).

A meta analysis of randomised control trials(evidence-level 1a) has shown that Levonogestrol intrauterine system is proven to be effective in reducing endometriosis associated pain(5).

Treatment with GnRH agonist have shown significant reduction of endometriosis associated in most of the patients and it was found out to be more effective than the oral contraceptives for the relief of pain.

A new group called Aromatase inhibitors have been tried in proven case of endometriosis. There have been pilot studies involving small number of patients for the treatment of endometriosis and pelvic pain. However such treatment is still considered under investigation and is not yet considered as definitive therapy.

3. Surgical approach:
It has been studied that relief of pain following surgical treatment of endometriosis at one year follow up ranges between 50-95%. The proportion of patients with improved pain was significantly higher among those with mild to moderate endometriosis. Considering these facts, laparoscopic treatment of visible endometriosis does lead to pain relief and hence supports the recommendation to treat endometriotic lesions seen during diagnostic laparoscopy.

Surgical options include treatment of ectopic endometriotic lesions with cauterization, removal of ovarian endometriomas, adhesiolysis, and ablative techniques. Cauterization can be done by unipolar or bipolar cautery while ablative procedures done using KTP, CO2, ND-YAG laser. Removal of endometriotic lesions have also been associated with symptomatic relief from pain. Ovarian cyst exicision improves dysmenorrhoea and deep dyspareunia. As simple drainage of endometriomas have high recurrence, definitive treatment in form of cyst excision is preferable.

Role of LUNA: It is a technique designed to disrupt the efferent nerve fibres in uterosacral

ligaments to reduce pain. There is no evidence to support that LUNA is effective and an essential component to treat pain. Also a large number of randomized control trials have observed no relief of pain in patients who underwent the procedure. Hence it does not appear to offer any added benefits beyond those that can be achieved with conservative surgery alone(7).

Presacral neurectomy which is also said to reduce pain in endometriosis involves interrupting symptomatic innervations to the uterus at the level of superior hypogastric plexus. It was found that there was greater improvement in pain factor. However it is important to know that presacral neurectomy is technically challenging procedure associated with significant risk of bleeding from adjacent venous plexus.

The final resort or the definitive surgery for the relief of symptoms is total abdominal hysterectomy with bilateral oopherectomy. But this is reserved for women with debilitating symptoms who have completed their child bearing or in whom other therapies have failed.

No studies have directly compared medical vs the surgical treatment of endometriosis and hence there is no substantial evidence to establish the superiority of one approach over the other.

To sum up, endometriosis should be viewed as a chronic disease that most of the times requires a life long management plan with goal of maximizing the use of medical treatment and avoiding repeated surgical procedures.

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Endometriosis and Assisted Reproduction

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Endometriosis is a challenging disease observed in 20% - 40% subfertile women (1). Alterations of the immunologic milieu within the peritoneal cavity create a "hostile" environment in endometriosis that may impair gamete interaction and early embryo development (2, 3). Expectant management, surgical resection, medical therapy, and controlled ovarian hyperstimulation (COH) with assisted reproductive technologies (ART) may be applied for conception in these patients (4, 5).

Endometriosis is a condition characterized by endometrial tissue located outside of the uterus, most commonly on the ovary and peritoneum. Endometriosis is associated with dysmenorrhea, chronic pelvic pain, and infertility. The mechanisms by which endometriosis impairs fertility have not been completely determined but are likely varied. Severe endometriosis is associated with pelvic adhesions and a distortion of pelvic anatomy. However, it is probable that endometriosis, even in a mild stage, may have a direct negative effect on oocyte development, embryogenesis, or implantation. Postulated mediating factors include local paracrine action of interleukins or other cytokines, alteration in inflammatory response, or autoimmune factors (6,7, 8).

Although both surgical and medical management of endometriosis have been associated with a reduction in symptoms, both have resulted in only a minimal increase in fertility (9, 10). In vitro fertilization offers the highest pregnancy rates of assisted reproductive technologies and is often used to treat women with infertility associated with endometriosis. The question of whether the presence of endometriosis affects the outcome of women undergoing IVF has not been resolved, with some authors noting negative associations and others noting no association (11-14). If endometriosis is associated with poor IVF outcome, by evaluating each component, it may be possible to determine the specific effects of endometriosis on reproductive outcome.
Although IVF – ET was initially developed as a treatment for tubal-factor infertility (15), it has become a successful treatment for patients with infertility for many indications, including male-factor and unexplained infertility (16). Patients with moderate or severe endometriosis may have anatomic distortion of the fallopian tube and ovary which may necessitate the use of IVF. However, even mild stages of endometriosis may have negative effects on oocytes

development, embryogenesis, or implantation (17, 18, 19, 20, 21).

In vitro fertilization may improve conception rates in endometriosis-associated infertility, although some studies report equal pregnancy rates (PR) but lower fertilization or implantation rates in endometriosis compared to tubal or unexplained infertility (4, 22, 23). Decreased numbers of retrieved oocytes are observed in patients with endometriosis undergoing intracytoplasmic sperm injection (ICSI) due to severe male infertility with similar fertilization rates, implantation rates, and PRs in comparison to those without endometriosis (24, 25).

The impact of endometriosis on assisted reproductive technology (ART) outcomes is controversial. Several early studies suggested that pregnancy rates after IVF were significantly lower in women with severe endometriosis than in those with minimal or mild endometriosis. However, more recent larger studies have shown no difference in IVF pregnancy rates for women with stage III or IV disease (26, 27, 28).

Although pregnancy rates after surgery for endometriomas are satisfactory, there is concern that the mechanical removal of the pseudo-capsule may impair ovarian reserve (31). Moreover, laparoscopic cystectomy before commencing controlled ovarian hyperstimulation (COH) does not appear to improve fertility outcomes compared with proceeding directly to IVF – ET. In fact, proceeding directly to IVF – ET in women with asymptomatic ovarian endometriomas may reduce the time to pregnancy, the costs of treatment, and the risk of surgical complications.

Directly visualization of the pelvis through a laparoscopic examination is essential for the diagnosis of peritoneal implants and adhesions. However, endometriotic ovarian cysts can be reliably identified by transvaginal ultrasound. A trained sonographer can easily distinguish endometriomas from other ovarian cysts according to their characteristic echogenic appearance. Sensitivity and specificity of the transvaginal ultrasound for the detection of endometrioma are 84% - 100% and 90%, respectively (28% - 33%). The possibility of identifying endometriotic ovarian cyst without laparoscopic removal and histologic confirmation and the development of IVF techniques have led to new therapeutic scenarios. Hence, aspiration of endometrioma before IVF – ICSI cycles offers a nonsurgical approach (33).

A debated and still unsolved topic is whether endometriomas should be treated before undergoing IVF cycles because of these risks. According to the studies opposing the surgical management of endometrioma before IVF, excision of endometriosis ovarian cysts is associated with a significant reduction in ovarian reserve and nonsurgical treatment is a better option to avoid reduction of the ovarian response in infertile patients (31). New medical therapies, such as use of GnRH antagonists, are potential candidate drugs for improving IVF outcome in endometriosis because their mechanism of action may be beneficial for a limited cohort of follicles in patients with advanced stages of endometriosis and patients who have undergone resection of endometrioma.

Individualized IVF protocols, according to various stages of endometriosis and according to management of endometrioma, may improve clinical outcomes of IVF in patients with endometriosis. To the best of the knowledge, there are no prospective studies in literature comparing the outcomes of COH with GnRH-a and GnRH antagonist protocols in patients with different stages of endometriosis.

Gonadotropin – releasing hormone agonists (GnRH-a) in ovarian stimulation protocols are used to prevent possible deleterious effects of premature LH surges in ART. The IVF-embryo transfer outcomes after a long protocol with

GnRH-a and stimulation with hMG/hCH in patients with stage I – II endometriosis demonstrate similar outcomes of IVF-embryo transfer as in those of the patients with tubal infertility (29). Recently developed GnRH antagonists cause immediate suppression of gonadotropin secretion by competitively blocking pituitary GnRH receptors and prevent premature LH surges during ovarian stimulation (30). These features constitute the GnRH antagonist as a reasonable choice for poor responder patients in IVF cycles. The use of GnRH antagonist may be rational for IVF cycles in patients with decreased ovarian reserve due to ovarian endometrioma and after its surgical treatment.

Endometriosis may have adverse effects on various aspects of reproductive physiology including folliculogenesis, ovulation, sperm, embryo quality, and fertilization. A recent meta-analysis demonstrates that patients with endometriosis-associated infertility undergoing IVF have a 36% reduction of PR compared to women with other indications for IVF. Moreover, the severity of endometriosis is likely to affect the outcome of assisted reproduction, women with stage III and IV disease having fewer numbers of oocytes retrieved, lower peaks of E2, lower fertilization and implantation rates compared with those in stage I and II. Impaired fertilization and implantation in endometriosis may be traced directly to the defects in the oocyte. Some altered factors involved in the process of oocyte activation in endometriosis patients could be overcome by the ICSI procedure and similar fertilization, implantation, and clinical PRs could be obtained in patients with endometrioma. Such data indirectly suggest that ICSI may be a useful technique to overcome fertilization defects in selected women with endometriosis (32).

Cryopreserved embryos offer another chance at pregnancy to patients who either did not conceive during the fresh IVF cycle or want another pregnancy. It is suggested that the advantage of cryopreserved embryo transfer in women with endometriosis was even more apparent, because ovarian hyperstimulation, which might activate the endometriosis, was not required.

Despite the availability of a large amount of literature aimed at determining the influence of endometriosis on IVF outcome, evidence regarding the compliance of affected women with this treatment is extremely scanty. The precise proportion of infertile women with endometriosis who are referred for IVF is actually unknown. The scarce attention paid to this aspect is surprising considering that adhesion to a treatment strategy plays a critical role in determining its overall effectiveness. Fedele et al. documented an overall frequency of IVF use among women operated for endometriomas and attempting to become pregnant as 36% (41 out of 114 women).

The overall frequency of IVF use in women failing to become spontaneously pregnant was 51% (41 out of 80), and the proportion of women achieving pregnancy was 37% (15 out of 41) (34). Cheekadhanaraks reports that only 24 out of 157 infertile women (15%) who were operated on for stage III-IV endometriosis subsequently underwent IVF (35).

The observation that infertile women with endometriosis do not systematically undergo IVF is of the highest clinical relevance. This point is surprising considering that there is a general consensus on the effectiveness of this technique, and it has to be kept clearly in mind when deciding on a therapeutic strategy with the patient. The attitude of the women in regard to IVF has to be carefully evaluated. The possibility of alternative, even if less effective, therapeutic approaches must be considered. Of relevance here is that recent studies have supported possible benefits of second-line surgery.

It is commonly believed that IVF represents an emotional and physical burden. The women may be frightened by the procedure. Indirect

evidence supporting this possibility has been recently provided by studies investigating the drop out rate from IVF treatment cycles. It has been shown that 30% - 50% of patients do not complete a standard program of three cycles.

Of note, we can not exclude that personal beliefs regarding IVF of the gynecologists who were managing the patients and who are generally not engaged in this field may have adversely influenced referral. A higher rate of referral may be expected if women are informed more adequately. On the other hand, this is a situation that presumably occurs in the vast majority of clinical contexts. Conversely, the financial aspects of IVF have not presumably influenced referral. Women with endometriosis may be frightened about the possible detrimental effects of IVF in the progression of their disease. Information in the literature on this topic is scanty. Five cases of harmful progression of deep endometriotic nodules have been reported. In contrast, D' Hooghe et al. evaluated the long-term recurrence rate of the disease in a cohort of 50 women with stage III-IV endometriosis and showed that the procedure is generally safe.

IVF is currently considered an effective treatment in women with endometriosis. There is a general consensus that IVF should be recommended in infertile women who fail to get pregnant after surgical treatment.

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Perimenopausal Endometriosis and HRT issues in endometriosis

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Endometriosis is a benign, proliferative, sex steroid dependent disease of women which commonly affects the reproductive organs. It has an unclear etiology and its pathogenesis is not yet completely understood. The hormonal dependence of endometriosis is evident, as the disease is rarely seen before menarche, after menopause or during pregnancy and it regresses during medical treatments that induce hypoestrogenemia. Endometriosis occurs in approximately 10 % of the women of reproductive age. Women diagnosed to have endometriosis in the postmenopausal period are estimated to be only 2 – 4 % of the disease population. The wide range of presentation of this disease allows a variety of treatment options to be considered. This enables individualization based on age, presenting symptoms, reproductive status, stage and previous response of the patient to treatment. The main goals of treatment are to relieve symptoms by removing or inducing resolution of implants and limiting progression of the disease as well as delaying recurrence.

Management depends upon whether or not the disease is symptomatic. Accidently discovered asymptomatic endometriosis should be left alone. Medical, surgical or combination of both modalities are the available management options for symptomatic patients. The perimenopausal patients who do not desire future fertility and having Stage I and II disease, diagnostic laproscopy can be extended to thermocoagulation, adhesiolysis and resection of implants and residual fibrosis. Thereafter, follow-up is directed to recurrence, which then indicates an additional hormonal regimen. In Stage II and III, a 3 to 6 month course of danazol or gonadotrophin-releasing hormone agonists (GnRH-a) should follow endoscopic surgery, if required. In Stage IV, the procedure for women under 45 years is identical to that for stage III. In patients over 45 years, oophorectomy with or without hysterectomy is still a frequently chosen therapeutic option in women with extensive, infiltrating or recurrent pelvic endometriosis. In such patients foci of endometriosis are often left in deep pelvic sites or on other organs such as the bowel, ureters and bladder. In fact, the difficulty of eradicating these lesions completely is the

main reason for performing definitive surgery.

The commonly used medical treatment options for endometriosis are danazol, gestrinone, GnRH-a and GnRH-a with "add-back" therapy –usually hormone replacement therapy (HRT) or tibolone. If a GnRH agonist is considered the treatment of choice, then HRT should be used in combination. Add-back HRT can alleviate the undesirable hypo-estrogenic effects of the GnRH agonists, which include hot flushes, sweating, vaginal dryness, breast atrophy, dyspareunia and loss of libido and loss of bone mineral density (BMD). There have been three recently published European studies investigating the combination of GnRH agonist plus add-back HRT in the treatment of endometriosis. The loss of bone mineral density was significantly diminished in a study using 25 micrograms oestradiol patches combined with continuous medroxyprogesterone acetate (5 mg). Neither this low oestrogen dose nor a full bone-sparing dose of oral oestradiol (2 mg daily) reduced the efficacy of GnRH-a (goserelin acetate) in patients with endometriosis. The ESHRE guideline 2008 states that treatment for up to 2 years with combined oestrogen and progestagen add-back appears to be effective and safe in terms of pain relief and bone density protection; progestagen only add-back is not protective. However, careful consideration should be given to the use of GnRH agonists in women who may not have reached their maximum bone density.

Tibolone is also used as "add back" therapy with GnRH-a. Tibolone is a synthetic steroid with estrogenic, progestogenic and androgenic properties due to its tissue specific effects. Because of its progestogenic activity in the endometrium, it results in endometrial atrophy but in the vagina, the estrogen-like effects results in improvement in vaginal dryness which may be advantageous in patients with endometriosis. Furthermore, in a small open study the gonadomimetic tibolone totally prevented the loss of bone structure during GnRH agonist therapy. It has been reported that the discontinuation rate with tibolone is lower than with HRT preparations.

Perimenopausal women who suffer from menopausal symptoms may need to be put on HRT. The question of whether HRT is a safe and helpful option for postmenopausal women with endometriosis is of great concern to both women and her treating physician. Only a few studies have addressed this problem. There is no agreement on whether estrogen administration in postmenopausal women with previous endometriosis is appropriate. Many physicians are of the opinion that women with a history of endometriosis can be offered HRT for menopausal symptoms, using the lowest effective dose of estrogen therapy. After radical surgery for severe endometriosis, women often have much to gain from HRT, particularly in the early years. Benefits of HRT in terms of control of menopausal symptoms, prevention of urogenital atrophy and loss of libido and bone protection are of particular importance. However, with the use of HRT, there is an increased, although undefined, risk of recurrence of endometriosis, especially in known severe cases and in obese patients. The possibility of recurrence or malignant transformation has been the limiting factor for the use of HRT in these patients, even after complete removal of all endometriotic tissue. This is because endometriotic cells can remain inactive for many years but become "activated" upon estrogenic administration. Unopposed estrogen appears to carry a higher risk than combined preparations. Delay in starting HRT after pelvic clearance is not of any benefit. The theoretical disadvantages of HRT must be weighed against its advantages particularly in younger women who face a prolonged period in the menopausal state. HRT adds to the quality of life in such young women whose ovaries are removed prematurely to prevent the extreme pain

associated with infiltrating endometrioses.

The Cochrane review 2009 studied two randomized controlled trials (Matorras et al, 2002 and Fedele et al, 1999) that looked into pain and disease recurrence in women with endometriosis who used HT for post-surgical menopause. Matorras R used sequential administration of estrogens (E) and progesterone (P) with two 1.5mg estradiol 22-cm^2 patches applied weekly to produce a controlled release of 0.05mg/day. Micronised progesterone was administered orally (200mg/day) for 14 days with a 16-day interval free of treatment. This intervention arm was compared to the control group which did not receive treatment. The mean follow-up time was 45 months. The number of patients who reported recurrence of pain was 3.5% (4/115) or 0.9% per year in the estrogen with or without progesterone arm compared with 0/57 women in the no-treatment arm. The result was not significant. If more than 3 cm peritoneal involvement was detected at the initial surgery, there was a 2.4% recurrence per year, and if there was incomplete surgery, there was a 22.2% recurrence. If HRT is indicated, patients should be informed of and accept this recurrence rate and following initiation of HRT, they should be monitored closely and if there is any suspicion of recurrence, HRT should be stopped. Fedele et al compared nonstop transdermal estradiol 50mg twice weekly combined with cyclic medroxy progesterone acetate (10mg per day) for 12 days per month in women with a conserved uterus with nonstop tibolone (2.5mg/day). The participants were followed up for 12 months. The number of women who reported recurrence of pain in the E & P arm was 4/10 compared with 1/11 in the tibolone arm. There was no significant difference between the two groups. Thus, there is some evidence from these two studies that HRT for women with endometriosis and post-surgical menopause may lead to pain and disease recurrence. The authors are of the opinion that the evidence in the literature is not strong enough to suggest depriving severely symptomatic patients from prescribing HRT in order to relieve their menopausal symptoms.

There is divided opinion on whether to use a combination of oestrogen and progesterone or estrogen alone for hysterectomised women with a history of endometriosis. In the absence of evidence from randomized studies, symptomatic endometriosis, or large residual volumes of endometriosis may be an indication for progestin therapy following hysterectomy, either as part of a continuous combined regimen or as progestin-only therapy. There is also no evidence that withholding HRT for 6 months following definitive surgery will reduce the risk of recurrence or malignancy. This remains a matter of clinical judgment and informed choice.

The Society of Obstetricians and Gynaecologists of Canada (SOGC) published a Clinical Practice Guideline on Menopause in 2006 which states that combined hormone therapy in standard doses does not appear to cause regrowth of endometriosis in postmenopausal women, nor in women receiving estrogen-progestin add-back therapy following medical oophorectomy with GnRH analogues. A small subgroup of women may experience recurring pain and other symptoms during unopposed estrogen therapy, particularly if residual disease remains following definitive surgery.

As per ESHRE and RCOG guidelines, HRT is recommended after bilateral oophorectomy in young women given the overall health benefits and small risk of recurrent disease while taking HRT. The ideal regimen is unclear: adding a progestagen after hysterectomy is unnecessary but should protect against the unopposed action of oestrogen on any residual disease. However, the theoretical benefit of avoiding disease reactivation and malignant transformation should be balanced against the increase in breast cancer risk

reported to be associated with combined oestrogen and progestagen HRT and tibolone. Hence in women at high risk of Breast Cancer, it would be advisable to use estrogen alone, without addition of progesterone.

In recent years the issue of whether endometriosis is associated with or indeed causes malignant disease has been raised in the scientific literature. Heaps et al (1990) have reported that endometriosis is not associated with an increased risk of cancer in general. However, the transformation of endometriosis to malignancy has been described but is extremely rare. There are case reports of endometrial cancer developing in residual endometriosis in women receiving unopposed estrogen therapy, as well as in obese women with high endogenous estrogens, following abdominal hysterectomy and BSO for endometriosis. Oxholm et al (2007) reviewed published literature using Medline search from 1950 to 2007 and found 32 case reports on postmenopausal endometriosis. The most common location was in the ovaries. The authors stated that postmenopausal endometriosis infers a risk of malignant transformation, the incidence being about 1%, with a peak incidence in patients over 45 years.

The best way of treating peri and post-menopausal women with endometriosis is still a very debatable issue and constantly poses challenges either in the form of rarities or controversies. A careful assessment of the literature will allow us to make evidence-based decisions in treating women with the debilitating symptoms of endometriosis.

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Problem of Recurrent Endometriosis

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Nothing is 'no problem' about endometriosis – definitely not for recurrent disease. Indeed I have discovered that writing about it is no less a problem than managing it in practice.

While drafting this write-up, I was intrigued to know that there is hardly any clear-cut definition of 'recurrence' of a disease. Nevertheless, it is suggested as a clinical or pathological recrudescence of a disease following remission, achieved either spontaneously or following some treatment. The basic pathophysiologic defect, however, persists at bio-molecular level and the disease burden re-accumulates over time to re-express itself. Recurrent endometriosis conforms to this natural history albeit few subtle differences. Spontaneous resolution is doubtful for advanced disease though this has been documented to the extent of 20% for stages I-II(1). Recurrence, therefore, nearly always means reappearance of the disease following treatment – medical and/or surgical. Even hysterectomy and bilateral adnexectomy is not absolutely recurrence-proof as traditionally believed. It is definite and not uncommon- mostly underreported and unrecognised.

In this context, endometriosis is quite akin to malignancy – both are abnormal tissue growths, invade locally, metastasise and bear the unpredictable potential to re-appear. There is one difference though- malignancy commonly kills the patients while endometriosis cripples them.

To raise a few questions at this point may not be unwise. After the primary treatment, how can we be sure that the pelvis is cleared off endometriosis? Do we always do a check laparoscopy after conservative surgery or medical treatment, or we rely on the symptomatic relief of the patient? Does symptomatic relief always imply that all pathological lesions are cleared? Is it always possible to clear the fibrotic or deeply infiltrating diseases completely by surgery and make the patient pain-free? Are we able to deal with all minute lesions through magnified and well-illuminated operative laparoscope, not to speak about open surgery?

Several puzzles are faced with as we storm our brains with these issues. The problem of recurrent endometriosis lies in its definition, incidence, recognition of symptoms and signs, diagnostic criteria, counseling, treatment and lastly prevention.

Definition:

It is difficult to differentiate between true recurrence and residual disease that could not be excised surgically or left out inadvertently. There is no consensus on defining recurrence – relapse of symptoms or reappearance of morbid lesions? Recurrence of endometriosis is a time-dependant event. Majority believes that persistence of symptoms or its reappearance within three months without any postoperative medical treatment implies residual disease. On the contrary, recurrent

disease seldom manifests before three months. Jee et al (2) defined recurrent endometrioma as cystic ovarian mass with diameter more than 1 cm and homogenous low-level echoes in TVS, regardless of patient's symptoms.

Incidence:

The incidence varies on multiple factors- age, natural history, stage and aggressiveness of the disease, treatment modality, extent of surgery, expertise of surgeon and use of fertility drugs(3). Recurrence of endometrioma after laparoscopic resection is 6-30%(4) whereas that after GnRH agonists (GnRHa) is 53.4% – 74.4% depending on severity of the disease(5). It is estimated that 4-year cumulative recurrence rate of ovarian and pelvic endometriosis after laparoscopic conservative surgery is 23.7% (6).

Recurrence is almost certain in all cases of advanced disease after medical therapy or conservative surgery, in some it is earlier than others.

It is unequivocally proved that hysterectomy with adnexectomy is not always a farewell to endometriosis. However, there are many factors, which dictate the recurrence - (1) technique of hysterectomy (2) peritoneal involvement and (3) estrogen replacement therapy after BSO. Recurrence of painful disease is up to 31% after simple extrafascial hysterectomy (7) while radical hysterectomy is almost recurrence-proof when post-operative transdermal estrogen was advised to both groups. Peritoneal endometriosis more than 3 cm is an additional independent risk factor(8).

Symptomatology:

The clinical features are similar to primary disease - dysmenorrhoea and chronic pelvic pain. The problem is often the attitude of her doctor who believes that the pain is due to some other cause like amoebic colitis or chronic urinary infection or it is 'all in her mind'. The patient's situation, on the other hand is – 'pain, pain everywhere and no one to believe'. The ultimate result is a delay in diagnosis that could have been avoided altogether. This problem has simple solutions- being recurrence-minded and readiness to acknowledge the facts.

Confirming the diagnosis

'When' and 'how' are frequently faced problems for diagnosing recurrence of endometriosis. Periodic clinical examination still remains as primary step to explore tender nodule in POD. TVS, which is able to identify endometrioma with 90%(9) sensitivity, is advised after six months routinely. Otherwise many will enter into advanced stage unnoticed. Sonography is advisable if symptoms reappear earlier. Clinical examination stands superior in comparison to TVS for diagnosing extra ovarian endometriosis. MRI with 84.8% sensitivity for detecting utero-sacral endometriosis(10) may be an alternative, which can delineate the lesions better than TVS.

Laparoscopy being the gold standard for diagnosing the primary disease is seldom used for recurrent disease. The reason is obvious, its invasiveness and cost. Nevertheless it is recommended when a corrective surgery is planned concommittently. The author advises routine check laparoscopy if patient fails to conceive by six months to one year after laparoscopic fertility promoting procedures for moderate-to-severe endometriosis. The reason is clear; asymptomatic recurrence may progress to distort the pelvic anatomy and function. Biochemical marker CA125 is of little help for its low specificity. However a raised

value can be additional information.

Therapeutic trial has an important role especially in post-hysterectomy patients, to confirm recurrence. Medroxyprogesterone acetate (MPA) or GnRHa can be used for 3 months. Relief of symptoms confirms diagnosis. This is of immense help to the gynaecologists practicing in rural areas where other investigative facilities are not readily available.

Counselling

Breaking the bad news of recurrence is always a sensitive issue. Initial reaction of the patient will be a state of extreme frustration in spite of being aware of its probability. She questions "why me"? Where did the things go wrong! Was it due to the disease, surgery or the surgeon! Could we have prevented it?

She is frightened to think of another course of medical therapy and or surgery. Is there any guarantee for permanent cure or do I have to again take the risk of re-recurrence or do I have to live with the disease? Depression takes the upper hand for infertile patients more as she begins to feel that her hope for pregnancy is fading away. The situation becomes worse if the disease recurs after hysterectomy and BSO, when she was promised a permanent cure. We, the clinicians, become indecisive and sometimes fail to give the definite answers to these questions. This calls for patient hearing, sympathetic explanation of the facts and figures of recurrence and assurance of a best possible management. Self-confidence and skill of the clinician is an important tool for counseling.

Treatment Options

As a physician I recall my dismay for not being able to offer anything more than repeat surgeries or hormones for the treatment of recurrent endometriosis. Most difficult cases are those where rectum, bladder or ureters are involved. If necessary, the patient can be advised to attend a dedicated Endo-clinic where treatment providers include multidisciplinary specialists. Medical therapy remains the first line of treatment.

Pain-killers

Most patients are upset with the return of pain, the treatment of which is difficult yet possible. For some women it will mean totally pain free, for others some reduction will be acceptable. Age-old medicines like aspirin, NSAIDs and narcotics can be used. Relatively recent addition in this list is 2nd generation COX-2 inhibitors with less gastrointestinal side effect and more efficacy. Local application of analgesic cream or heat also helps many women.

Hormones

Hormonal manipulation especially with MPA, GnRHa, danazol and combined oral contraceptives (COC) are definitely not justified for childless ladies because of their antifertility effect. However, a six months' course of dydrogesterone plus symptomatic treatment may be offered with a hope of spontaneous pregnancy. For women not concerned with fertility, a course of MPA or GnRHa with or without add-back therapy may be advised for six months or more. However, their side effects are sometimes unacceptable and therefore compliance is less.

I have many patients having oral MPA cyclically for more than 5 years and they are quite happy to continue.

Surgery

Surgery is indicated when medical treatment fails or contraindicated or there are unbearable side effects. The first hurdle to

repeat endometriosis surgery is convincing the patient. It is technically demanding too. The adhesions are often more dense, tough and fibrous, deposits may be more infiltrating; adjacent organs like pelvic colon and ureter are often involved. Injury to these structures is not rare. Literature shows a predilection of recurrent endometrioma to the left side(3) adjacent to the pelvic colon. This corroborates to my own experience. There is a higher chance (up to 39%) (11) of conversion of laparoscopy to laparotomy. Gut injury or deliberate excision may invite temporary colostomy. Unfortunately, even the ablest surgeon cannot guarantee that re-recurrence would not occur. Conservative surgery can be undertaken for infertile women who cannot afford IVF or for creating a better pelvic environment by removing chocolate cyst or damaged tube prior to IVF.

The question remains 'how many surgeries can a lady have before she has her womb out'? I have experiences to see ladies who underwent four or five conservative surgeries just to have a baby and eventually requested hysterectomy with desperation to lead a pain-free life.

Frequently clinicians are requested hysterectomy by women who have completed family and not interested to undergo repeated course of medicines. However for younger group it can be deferred with long-term medical therapy. One should remember that simple removal of uterus and adnexa is not enough. Excision of all the visible or palpable endometriosis implants is mandatory to avoid further recurrence.

Prevention

How can a disease be prevented when we do not know what causes it? However there are ways and means that can be tried. General measures like changing life style, getting control over Candida and allergies, avoiding toxic exposures and PVC, eating organic food and achieving pregnancy are believed to prevent endometriosis to some extent. For clinicians it goes beyond this boundary.

Pre-operative GnRHa to reduce the visible disease burden is often recommended. The counter-probability is that it hides the minutest lesions from the view of laparoscope and helps earlier recurrence once the effect of hormone is gone. Controversy exists regarding use of post-operative GnRHa. Recent studies(2) show that post-operative GnRHa for 4-6 months cannot prevent recurrence of endometrioma. However, I believe it delays recurrence giving at least some benefit to the women. Vercelleni et al(12) showed that regular post-operative use of COCP effectively prevents recurrence of endometrioma.

Most importantly we should remember that first surgery is the best chance to give the maximum benefit and prevent recurrence. Half-done surgery must be avoided. If the surgeon is not competent enough or is in the learning curve, an expert endometriosis surgeon should be called for in anticipated difficult cases. It is an accepted notion that in spite of our sincere effort it may not be possible to prevent in all the cases but we can definitely reduce the incidence. At present we are looking into the role of levonorgestrel intra-uterine system (LNG-IUS) in preventing recurrence after conservative surgery. So far studies show a promising result.

At this point I remember a quote.

"If a problem is too difficult to solve, one can not claim that it is solved by pointing at all the efforts made to solve it" (13)

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Levonorgesterol IUD and Endometriosis

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INTRODUCTION:

Endometriosis is a common gynaecologic disorder with varied clinical presentations depending on the disease severity, age group and extent of involvement of pelvic organs. It is a disease characterized by long course which extends throughout the reproductive life-span and frequent occurrence of recurrences. Dysmenorrhea, dyspareunia and infertility are the main presenting features.

Surgical management is the mainstay of treatment for endometriosis related infertility. Oral medications (NSAIDS/ hormonal) do not improve fertility but improve pain related to endometrosis whereas surgical management improves both pain and fertility. Medical management has the disadvantage of the need for the patient to take medication regularly and recurrence if patient stops the drug. Even after conservative surgery, pain ultimately recurs after a variable time period. For such patients, especially if fertility is not an issue, levonorgestrel containing intrauterine devices (LNG-IUCD) is a good option for prevention or treatment of recurrence.

CASE STUDY:

The course of one particular infertile patient who presented to us is reported here to highlight the importance of LNG-IUS. The patient was 34 years old, married for 15 years, with primary infertility. USG showed features of endometriosis for which laparoscopy and aspiration of endometriotic cyst was done 12 years ago. This was followed by ovulation induction with clomiphene citrate, but patient failed to conceive. She developed a recurrence after 4 years of the first surgery. She underwent a second laparoscopic surgery and endometriotic cystectomy. This was followed by several cycles of ovulation induction with letrazole as well as gonadotrophins along with intrauterine insemination (IUI) which failed to result in a pregnancy. She underwent two cycles of IVF which also failed. The patient was frustrated and gave up all hopes of conception.

She then developed recurrence of pain which further affected her quality of life. The patient was primarily interested in pain relief and not on conception, so she was advised a panhysterectomy by several doctors after which she reported to us. After extensive

counseling of the patient, we did an USG guided cyst aspiration (7X6 cm cyst in right ovary and 4X3 cm on the left ovary) and the fluid was sent for cytology (showed hemosiderin laden macrophages) along with LNG-IUCD insertion. Her pain gradually reduced over 3 months and after that, patient became pain free. She is on follow up for the past three and a half years and symptom free. There was also a drastic reduction in menstrual blood loss and she developed amenorrhea after 1 year of insertion.

DISCUSSION:

Endometriosis remains a challenge to the treating gynecologist and although there are a variety of treatment options (medical and surgical), long term relief is often evasive. The problem with oral medications is that compliance is a problem in the long term and symptom recurrence is common following discontinuation of drug. Surgical management may produce pain relief that is longer lasting but recurrence still occurs after conservative surgery. Repeated conservative surgeries run the risk of reduction in ovarian reserve, intra-operative complications and sometimes removal of ovary may become necessary.

Other options do exist like GnRH agonist but duration of therapy is limited (6 months) due to possible loss of up to 6% of bone mineral density in the first 6 months and the loss may not always be entirely reversible(1). Desperate patients even at a young age may be driven to the option of hysterectomy and bilateral salphingo-ovariotomy in order to get pain relief. LNG IUCD may be an alternate to hysterectomy in such patients.

LNG-IUCD results in direct drug distribution to pelvic tissues with a local concentration greater than plasma levels. This results in good effectiveness with limited adverse effects and increased patient compliance during long-term treatment. Levonorgestrel induces endometrial glandular atrophy and extensive decidual transformation of the stroma, downregulates endometrial cell proliferation, increases apoptotic activity, and has antiinflammatory and immunomodulatory effects. Although hormonal activity of LNG-IUCD is mainly local, a systemic effect secondary to uterine absorption of levonorgestrel is probable. It has proven effective in relieving pelvic pain symptoms caused by peritoneal and rectovaginal endometriosis. But it does not consistently inhibit ovulation(2).

Evidence suggests that the LNG-IUS reduces endometriosis-associated pain with symptom control maintained over 3 years(1,3). The LNG-IUCD may be used alone or in combination with USG guided cyst aspiration/ conservative surgery in case of ovarian endometriotic cysts. If there are no cysts or deposits in the pelvis, LNG-IUCD may suffice by itself for pain relief & avoid the need for surgery which may be risky in such patients.

In a small randomised controlled trial, the LNG-IUCD, inserted after conservative laparoscopic surgery for endometriosis associated pain, significantly reduced the risk of recurrent moderate–severe dysmenorrhoea at 1 year follow-up. A Total of 40 parous women with moderate or severe dysmenorrhea undergoing first-line operative laparoscopy for symptomatic endometriosis were randomized to immediate LNG-IUCD insertion or expectant management after laparoscopic treatment of endometriotic lesions. Moderate or severe dysmenorrhea recurred in 2 of 20 (10%) subjects in the postoperative LNG-IUCD group and 9/20 (45%) in the surgery-only group(4).

If young patients are subjected to hysterectomy and bilateral salphingo-ovariotomy, there arises the controversial problem of hormone replacement therapy. There are concerns about possible stimulatory effect of unopposed estrogen on any residual disease. Combination of estrogen and progesterone for HRT may reduce this risk, however, the theoretical benefit of avoiding disease reactivation or malignant transformation should be balanced against the increase in breast cancer risk associated with combined oestrogen- progestogen HRT. The ideal regimen for HRT after bilateral oophorectomy in endometriosis is unclear and should be discussed on an individual basis. The LNG-IUCD avoids this problem as it does not suppress ovarian cyclicity and hormone production but still suppresses the endometriotic tissue.

Although the LNG-IUCD has several advantages over other management options, it cannot improve fertility, in fact it acts as a contraceptive and so precludes pregnancy. It is best suited for those who have completed their family and pain relief is the main requirement. In some infertile patients also, it may be an option if conservative surgery followed by ovulation induction/ IVF fail and patient's main concern is pain relief rather than fertility.

CONCLUSION:

LNG-IUCD is a good option for pain relief in endometriosis when used alone or after USG guided cyst aspiration/ conservative laparoscopic surgery. It is a good option to prevent or treat recurrence in such patients. It avoids the need for removal of uterus & ovaries at a young age and the consequent need for hormone replacement therapy. However, it should be used in infertile patients only if all other measures fail as a method to avoid hysterectomy, and patient should be informed about the contraceptive effect of LNG-IUS.

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Aromatase Inhibitors for the treatment of Endometriosis

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In the last few years, our understanding of the pathogenesis of endometriosis at the cellular and molecular levels has improved significantly. This may give us the opportunity to use new, specific agents for the treatment of this disorder. Novel therapeutic strategies may improve our ability to eliminate endometriotic lesions when present and to prevent the recurrence of endometriosis after surgical treatment. The blockage of aromatase activity in endometriotic lesions with an aromatase inhibitor may represent a new step in the medical treatment of endometriosis. (1)

Mode of Action of Aromatase Inhibitors:
The adrenal gland, in a series of reactions beginning with cholesterol, synthesizes steroid hormones such as aldosterone, cortisol androgens and estrogens.

Aromatase, a cytochrome P450 dependent enzyme acts as the final step in the synthesis of estrogen, catalyzing the conversion of androgens to estrogens. (2) The conversion of androgen to estrogen occurs in the muscle, fat and liver (3)

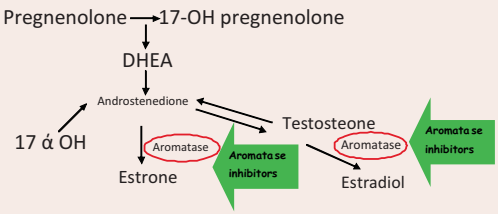

Figure 1: Mechanism of action of Aromatase Inhibitors

Zeev Shoham pg 523. Text book of ART. David K. Gardner

Aromatase inhibitors acts as competitive inhibitors of this aromatase enzyme system and inhibit the conversion of androgens to estrogens. These inhibit the aromatic enzyme by competitively binding to the heme of the aromatase, cytochrome, P450 sub unit of the enzyme, therefore reducing estrogen synthesis in all tissues where it is present.

Treatment with aromatase inhibitors greatly reduces serum estrone, estradiol and estrone sulphate. The maximum suppression is seen in 48 – 78 hours.

With improvements in formulation, third generation aromatase inhibitors are now available which have very few side effects. They can also be classified as Type I (Steroid analogs of androstenedione and type II Nonsteriodal)

Clinical use.

Letrozole was first used for ovulation induction by Mitwally and Casper (4). As a result of many further studies, letrozole is now being used regularly for ovulation induction, either alone or in combination with gonadotrophins.(5) Recently, aromatase overexpression has been detected in endometriotic tissue. Aromatase (p450arom) is responsible for conversion of C19 androgens to estrogen in several human tissues. Aromatase activity gives rise to local estrogen biosynthesis, which, in turn, stimulates prostaglandin E(2) production by upregulation of cyclooxygenase-2 (COX-2), thus establishing a positive feedback cycle. Another abnormality in endometriosis, i.e. the deficiency in 17 beta-hydroxysteroiddehydrogenase type-II (17 beta-HSD-Type-II) expression, impairs the inactivation of estradiol to estrone. In contrast to the eutopic endometrium, these molecular aberrations collectively favour accumulation of increasing amounts of local estradiol and prostaglandin E(2) in endometriosis. In several human cell lines, prostaglandin and estrogen concentrations are associated with proliferation, migration, angiogenesis, apoptosis resistance, and even invasiveness. Consequently, aromatase and COX-2 are promising new therapeutic targets. Specific aromatase inhibitors (such as Letrozole, Anastrozol or Exemestan) or selective COX-2 inhibitors (e.g. Celecoxib, Rofecoxib) are of great interest to be studied in clinical trials in premenopausal woman with endometriosis to increase the choice of currently available treatment options.

Drugs:

Letrozole is 4,4-(1H-1,2,4–triazole-1-Ylmethylene) dibenzonitrile. Its empirical formula is C17H11N5. Anastrozole has the molecular formula C17H11N5 These drugs have been approved for treatment of postmenopausal women with breast cancer. In India, they have also been approved for ovulation induction.

A very appealing area of interest is the possibility of treating endometriosis without suppressing ovarian function. Aromatase inhibitors might have such characteristics as they have been shown to inhibit oestrogen production selectively in endometriotic lesions, without affecting ovarian function. (6)

Ailawadi conducted a study where oral administration of letrozole (2.5 mg), the progestin norethindrone acetate (2.5 mg), calcium citrate (1,250 mg), and vitamin D (800 IU) was done daily for 6 months. The combination of letrozole and norethindrone acetate achieved marked reduction of laparoscopically visible and histologically confirmed endometriosis in all 10 patients and significant pain relief in nine out of 10 patients who had not responded previously to currently available treatments. On this basis, letrozole should be a candidate for the medical management of endometriosis. (7)

Remorgida V, etal (8) did a prospective study which evaluated the efficacy of letrozole 2.5 mg per day combined with norethisterone acetate (2.5mg/day) in the treatment of pain symptoms related to the presence of rectovaginal endometriosis. The treatment significantly decreased the intensity of symptoms, but pain recurred at 3-month follow-up.

A study of the effect of letrozole and progesterone only pill in stage 4 endometriosis using daily oral administration of letrozole 2.5 mg, desogestrel 75 microgm, elemental calcium 1000 mg and vitamin D 880

I.U. was done. The scheduled treatment period was six months.

The results showed that none of the women included in the study completed the six-month treatment because all patients developed ovarian cysts. All women reported significant improvements in dysmenorrhoea and dyspareunia. Pain symptoms quickly recurred at three-month follow up. There were no severe adverse effects of treatment; no significant change in the mineral bone density was observed during treatment. (8)

Pharmacokinetics:

These drugs can be given orally and have a half life of 48 hours, so once a day using is adequate. These drugs are metabolized in the liver and excreted mainly through the biliary (85%) and urinary systems (11%).

Adverse effects:

- Bone pain
- Hot flushes
- Back ache
- Nausea
- Dyspnoea

Conclusion:

Preliminary clinical studies have demonstrated the efficacy of third-generation nonsteroidal aromatase inhibitors (i.e. anastrozole and letrozole) in reducing the intensity of pain symptoms associated with the presence of endometriosis. The new selective progesterone receptor modulators may represent a valid hormonal treatment option. Therapeutic manipulation of the immune system through TNFalpha inhibitors may be beneficial in women with endometriosis. New pharmaceutical agents affecting inflammation, angiogenesis, and matrix metalloproteinase activity may prevent or inhibit the development of endometriosis. (1)

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Mifepristone in Endometriosis

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Abstract:
Mifepristone is an antiprogestin useful in many conditions. It has no anti estrogenic effect. Hence there is no bone loss, hot flushes and other menopausal symptoms. It is now emerging as a substitute for GnRH in the treatment of fibroids, endometriosis etc. Especially in recurrent endometriosis, after ultra sound guided aspiration, treatment with mifepristone at 10 – 25mg daily for 3 – 6 months helps in delaying the recollection and progress of disease and also provides symptomatic relief without any antiestrogenic side effects.

Introduction:
Mifepristone (RU 486) is an antiprogestin initially introduced as an abortificient. Now it has been found to have variable uses including treatment for endometriosis, fibroids, control of menorrhagia etc. The use of mifepristone in endometriosis is reviewed.

Case Report:
Mrs X, 30 years old P1 L1, presented with complaints of pain lower abdomen for six months duration. She also complained of inability to conceive since last three year. Her menstrual cycles were regular, but were associated with severe congestive dysmenorrhea. She had conceived spontaneously and had delivered a male child by LSCS seven years back. They had used barrier contraceptive since then for three years. Examination revealed a normal sized uterus, and bilateral adnexal masses. Ultrasound showed both ovaries enlarged to 10 x 10cm with multiple endometriotic cysts of size varying from 3 to 7cm. She underwent laparoscopic cystectomy and chromotubation. Intraoperatively, there were dense adhesions with the bowel. Adhesiolysis and cystectomy followed by ovarian reconstruction was done. Chromotubation revealed bilateral patent tubes. She was started on ovulation induction with chlomiphene and she conceived in her second cycle and delivered a fullterm female child by LSCS. Four years later she presented again with pain abdomen and congestive dysmenorrhea. Examination revealed bilateral adnexal masses of 7 x 7cms. Ultrasound showed right ovarian endometriotic cyst of 7 x 7cm and left ovarian cyst of 5 x 5cm. She was reluctant to undergo further surgery. Hence she underwent ultrasound guided cyst aspiration followed by T. mifepristone 10mg daily for a period of six months. She was asymptomatic and there was no recollection at the end of three months and six months. At nine months follow-up she is still asymptomatic and ultrasound shows no collection.

Review of Literature:

More than fifteen years have passed since the discovery of Mifepristone (RU-486)(1), and the interest in the antagonist effect of antiprogestins has revealed novel information about the molecular mechanisms of progesterone action. Mifepristone causes blockage of the progesterone receptors.

The effect of mifepristone on the expressions of estrogen and progesterone receptor in human eutopic and ectopic endometrium(2) was studied. Progesterone receptor expression in endometrial cells was significantly higher with endometriosis. Estrogen and Progesterone receptor expressions in endometriotic cells were significantly lower than those of endometrial cells during the proliferative phase and significantly higher during the late secretory phase. Mifepristone causes down-regulation of the expressions of E and P receptors, in both the eutopic and the ectopic endometrial cells. This may be one of the therapeutic mechanisms of mifepristone on endometriosis. The inhibitory effects on the secretion of IL-6 by ectopic and (or) eutopic endometrium may provide another of the cellular therapeutic mechanisms of mifepristone and progesterone on endometriosis(3).

Mifepristone has been shown to relieve pelvic pain associated with endometriosis and to decrease American Fertility Society endometriosis scores. Mifepristone side effects include hot flushes and transient increases in liver transaminases. Generalized cystic changes in the endometrium have been demonstrated consistent with a chronic unopposed estrogen effect.

Kettel et al studied the safety and efficacy of mifepristone in endometriosis(4), by a prospective clinical trial. Nine women with endometriosis were treated with mifepristone (50 mg/d) for 6 months. Daily symptom inventories and urinary steroid metabolites were assessed before, during, and after treatment. The extent of endometriosis, bone mineral density, circadian rhythm of cortisol, and LH pulsatility were determined before and after treatment. They found that pain and uterine cramping improved in all patients. Endometriosis regressed by 55%. All patients exhibited endocrine features of anovulatory amenorrhea without hypoestrogenism. A rise in serum LH and Testosterone levels was observed during the first month of treatment and one patient developed an elevation of liver transaminases during the last month of treatment. All other measurements were unchanged. They concluded that, mifepristone is effective in causing regression of endometriosis in the absence of significant side effects.

In another study using low dose of mifepristone, seven patients were given 5 mg daily(5) for 6 months. Pelvic pain improved in six of seven patients. Four of the seven patients had irregular bleeding. Hence 5 mg daily dose resulted in symptomatic improvement, but did not stabilize the endometrium.

In a study that evaluated the long-term effects(6) of 100 mg/day or approximately 2 mg/kg/day of mifepristone in patients with symptomatic pelvic endometriosis, all women became amenorrheic and acyclic. This ovarian inhibition was achieved without estrogen deprivation. However, ovarian suppression was incomplete. Serum concentrations of LH, androstenedione and testosterone increased in the first 3 weeks of treatment and then returned to baseline. Additionally, an

antiglucocorticoid effect was demonstrated. There was improvement in pelvic pain without significant changes in the extent of disease as evaluated by laparoscopy.

Zhao explored the factors that influence the recurrence of endometriosis(7) after surgery. They found that, higher the clinical stage of the endometriosis, the higher the recurrent rate ($P < 0.05$)and also that mifepristone could prolong the interval of recurrence after operation [(13 +/- 4) vs (7 +/- 3) months; $t = 4.575$, $P < 0.01$]. In a study that compared the efficacy and safety of mifepristone and danazol following conservative surgery for endometriosis(8), sixty-one patients were treated orally either with mifepristone 10 mg/d (n = 31) or danazol 200 mg 2-3 times/d (n = 30) for 3 months. Side effects like hot flushes, irregular vaginal bleeding, back pain, weight gain and acne, were less commonly seen with mifepristone. Also the FSH, LH and serum estradiol (E2) levels remained in normal range but declined to postmenopausal level with Danazol. There were no significant changes of biochemical parameters of bone metabolism before and at the end of treatment except significant increases of serum AKP and BGP with Danazol.

Conclusion : Daily use of mifepristone has been shown to provide symptomatic benefit especially for pain. Also short term use following surgery is a useful alternative in reducing the recurrence following the surgery.

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Scar Endometriosis

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Introduction:
Endometriosis was first described by Rokitansky in 1860 and was first described as the presence and proliferation of endometrium outside uterine cavity, most commonly in the pelvis. Scar endometriosis or cutaneous endometriosis is a subtype of extra pelvic endometriosis. It is a rare entity. The abdominal wall endometriosis may show deposit in the dermis, subcutaneous tissue, rectus abdominis muscle and rectus sheath.Various theories have been put forward to explain it, for example metaplasia, venous or lymphatic spread, metastasis and mechanical transplantation [1]. The probable etiology is transplantation of viable endometrial cells into the scar during surgery which subsequently proliferate or induce metaplasia under the influence of estrogen. Any surgery that involves contact with endometrial tissue is at risk of scar endometriosis. Most commonly it occurs in cesarean section, hysterotomy, hysterectomy, episiotomy, laparotomy, ectopic pregnancy and tubal ligation.

Incidence:
The actual incidence is difficult to determine as it remains under diagnosed, however it varies between 0.03 to 0.5percent [2]. Most often patients are referred to general surgeons and may thus be misdiagnosed. The incidence after hysterectomy is 1.08 – 2 percent whereas after cesarean section 0.03 -0.2 percent.

Clinical picture:
A recent review of 25 published cohorts from 1951 to 2006, on abdominal wall endometriosis (defined as endometrial tissue superficial to peritoneum) showed that the classical cyclical symptoms were present only in 57 percent women [3]. The most common presentation present in 96 percent was a mass over the scar. Pain was present in 87 percent women. The interval between surgery and development of symptoms was 3.6 years.

Clinical examination may reveal a painful and palpable nodule with maximum tenderness over the scar during menstruation in a patient with a previous history of gynecological or obstetrical surgery.

Differential diagnosis:
It is not an easy condition to diagnose, only half of them present with classical symptoms and may be confused with incision hernia, granule, lymphoma, neuroma, cyst, abscess or sarcoma[4]. There may be a considerable delay of upto 31.7 months in the diagnosis and initiation of treatment [5].

Diagnosis:
It is a difficult condition to diagnose. A high index of suspicion is recommended with post operative abdominal lump as well as in those where there is absence of classical symptoms. The presence of cyclical pain in an incision mass during menstruation is almost pathagnomonic. Some believe that when the diagnosis is made on clinical grounds no further investigation is necessary. However, some advocate the use of FNAC, color Doppler, CT Scan and MRI. Preoperative imaging is valuable in detecting the extent of the disease and planning an accurate excision [6]. FNAC is a simple procedure that not only helps diagnosis but also obviates the need for an invasive surgery [7]. Colour Doppler may be useful when there is a large lesion on the abdominal wall. MRI enables very small lesions to be detected and is better compared to CT Scanning detecting the planes between the muscle and subcutaneous tissue.

Histopathology:
The excised tissue shows endometrial glands in cellular stoma. Enhanced mitotic figures are seen along with some RBC and chronic inflammatory cells.

Treatment:
Management must be individualized according to the clinical presentation. Treatment is not required in an asymptomatic patient. If pain is the main complaint, it can be successfully controlled by GnRH analogues or Danazol for 9 – 12 months. It is associated with adverse symptoms like amenorrhea, weight gain, acne, osteoporosis as well as risk of recurrence after discontinuation. No medication has proved superior to the other [9]. Medical therapy offers only temporary relief of symptoms in women with endometriosis.

Treatment of choice is always surgical excision of the lesion. It is both diagnostic and curative. Polypropylene mesh repair may be required in larger defects.

Certain risk factors have been identified in operations of hysterectomy and Cesarean sections. Early hysterotomy (less than 22 weeks), heavy menstrual flow and alcohol consumption have been found to be associated with scar endometriosis [10]. Similarly, Caesarean section performed before spontaneous onset of labour, may increase the risk of cutaneous endometriosis [11]. It is recommended that the abdominal wound should be thoroughly cleaned, especially around the corners [12].

Risk of malignancy:
Malignant changes in scar endometriosis are rare [13]. It should be suspected in a long standing case with recurrence. Treatment is surgical excision with mesh replacement.

Conclusion:
Scar endometriosis continues to be a diagnostic challenge. In view of increasing cesarean rate and hysterectomy it is of utmost importance to modify practices at the time of surgery, to prevent the transplantation of endometrial tissue over the site of scar. An increased awareness and a high index of suspicion can lead to accurate diagnosis and management.

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Bladder Endometriosis

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Endometriosis of bladder is an uncommon lesion seen in < 1% of all cases of endometriosis(1) with 60% cases being associated with pelvic endometriosis. Fewer than 300 cases have been reported in the world wide literature. Other sites of urological endometriosis may be ureter, kidney and urethera. Ureteric and bladder endometriosis are independent entities(2) with ureteric endometriosis being part of severe advanced pelvic endometriosis.

Bladder endometriosis exists in two forms - primary and secondary. Primary form is generally a part of generalized pelvic disease. Exact pathogenesis is perplexing but may be same as other sites of pelvic endometriosis including retrograde menstruation, direct dissemination at surgery, lymphatic metastasis, coelomic metaplasia, origin from mullerian remnants and vascular dissemination.

Primary bladder endometriosis may also develop from extension of adenomyosis of anterior uterine wall by penetrating the bladder detrusor.

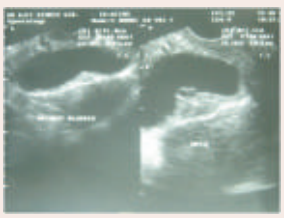

Fig 1 Bladder endometriosis on USG

Secondary endometriosis is iatrogenic that occurs exclusively after pelvic surgery like caesarean section or hysterectomy(3). The risk increases if adenomyosis exists in the uterus which can lead to direct dissemination of endometrial tissue at the surgery. When uterine cavity is opened during pelvic surgery, a meticulous surgical technique is required to avoid transplantation of endometriotic particles.

Clinical diagnosis: Diagnosis of bladder endometriosis is often difficult to make because of its non-specific symptoms(4).

Symptoms and signs: Most common symptoms of vesical endometriosis are vesical discomfort i.e. pain in hypogastrium, heaviness, cramps and sensation of pressure. Other common symptoms are urinary disturbances like dysuria, urgency, frequency and burning sensation. Both bladder

discomfort and urinary disturbances have cyclical character, coinciding with menstrual activity. Frequency and severity of dysuria is higher in basal endometriotic nodule than when the lesion is at bladder dome. Menstrual haematuria(menouria) due to invasion of bladder mucosa is pathognomonic of bladder endometriosis. Dysmenorrhea is usually a consistent feature in bladder endometriosis.

Dysmenorrhea is found in 100% cases, urinary discomfort in 80%, deep dyspareunia in 30% and menstrual haematuria in 30%. These symptoms tend to become chronic over time.5 On per vaginal examination, a tender nodule through anterior fornix may be palpable in 30-50% cases.

Diagnosis: Clinical features remain the mainstay of diagnosis. Catamenial onset of symptoms correlating with menstrual cycle is very characteristic(1) and menouria if present aids the diagnosis. Bladder endometriosis may mimic recurrent cystitis or interstitial cystitis(6). Benign lesions such as varices, angioma, papilloma, localized vesical inflammation or ulceration and malignant lesions such as infitrative and metastatic carcinoma, stromal endometriosis also form the differential diagnosis. Temporary relief of symptoms with anti-endometrial drug support may diagnose doubtful cases(7).

Investigations: Investigations are an adjunct to the clinical diagnosis. In few cases where clinical features are not very suggestive of bladder endometriosis, investigations may aid in reaching a diagnosis.

Imaging – Ultrasound is the most useful investigation. It may reveal bladder nodule (figure-1). Volume and location of lesion, degree of infiltration of detrusor and mucosa and relationship with concomitant adenomyosis of uterus can also be seen. Studies have shown that transvaginal ultrasound is more precise for diagnosis as well as for preoperative evaluation of bladder endometriosis than transabdominal ultrasound(8).

If ultrasound is inconclusive, CT and MRI may help in defining the size of lesion, detrusor infiltration, involvement of adjacent myometrium and uterovesical septum. MRI is excellent for evaluation of extravesical extension(9).

Cystoscopy, though an integral part of work-up for bladder endometriosis may visualize endometriotic foci on bladder mucosa as typical bluish nodules, which develop only in minority(30%) of cases(8). Besides cystoscopy findings may change according to the phase of menstrual cycle and repeat cystoscopy during menstruation is advisable to confirm the diagnosis(6). Biopsy can also be taken from the visible lesions during cystoscopy, histopathology of which may clinch the diagnosis even before surgery. However, it can not define the extent and relation with uterus. Urography is non specific for bladder endometriosis, but still useful to evaluate integrity of upper urinary tract and ureters. In certain cases, it may reveal a filling defect in bladder.

Histopathology of the lesion biopsy is the only definitive investigation as in endometriosis of other sites.

Management

The choice of management modality for bladder endometriosis depends on age, marital status, desire for future fertility, extent of vesical lesion, severity of symptoms, co-existing menstrual disorders and associated pelvic pathology.

Medical therapy is only palliative with recurrence being common on discontinuation. It can be instituted in patients with minimal symptoms who are poor surgical risks. Various options are GnRH, danazol, combined oral contraceptives, progesterones. Recently, few studies have evaluated antiprogesterone RU486 in endometriosis, but none has evaluated its role in bladder endometriosis.

Surgery - Surgery is the mainstay of managing bladder endometriosis which can be done by various approaches, the goal being complete resection of the disease(4).

Transurethral resection: Resection of lesion by transurethral approach is not an optimal treatment for bladder endometriosis(4) and can only be done if lesion is visible at cystoscopy. However, perforation of bladder, incomplete excision and recurrence are the risks involved(7).

Transabdominal approach- Abdominal approach is better over transurethral as deeply embedded nodule can be completely excised and associated endometriotic pelvic lesions can be simultaneously treated. It can be done by laparoscopy or laparotomy. Nowadays, with increased expertise in laparoscopic procedures, this approach is preferred. Principles of surgery and steps are same irrespective of the approach.

During surgery, the first and foremost step is the inspection of whole pelvis, followed by dissection of vesico-pelvic space to render the nodule/endometrioma completely mobile. If lesion is small and mobile, surgical excision of the bladder endometrioma after cystotomy is performed. Partial cystectomy may be required in some cases which may lead to decreased bladder capacity. Stabilization of lesion during surgery is very essential as nodule being very mobile, tends to move inside the bladder wall, rendering excision difficult. Mucosa can be spared if it is not involved. Bladder wall is usually opened for complete resection, hence proper cystotomy repair and sealing is essential. Sometimes, combined vaginal and laparoscopic approach may be needed if bladder lesion extends upto upper vagina.

Robotic assisted laparoscopic partial bladder resection has been described recently.(10,11) If future fertility is not desired, a hysterectomy without oopherectomy can be combined as there are high chances of associated adenomyosis.

CASE STUDY: We have reported a case who was repeatedly treated for recurrent PID and UTI before reporting to us 4 years after onset of symptoms(12). She did not have catamenial symptoms or menouria and her cystoscopy was normal, thus deferring an early diagnosis. A diagnosis of bladder endometriosis was suspected due to history of lower segment caesarean, extensive dysmenorrhea increasing over time, a nodule being felt through anterior fornix, USG and MRI showing some growth. One month treatment with danazol resulted in partial relief. This response to anti-endometriotic treatment ultimately helped in making the diagnosis of bladder endometriosis. Since symptoms recurred on stopping danazol treatment after 6 months and again after 3 doses of GnRH analog as well as dehydrogesterone given for 3 months, surgery was planned. Exploration laparotomy with cystotomy and bladder endometrioma excision with cystotomy repair along with total abdominal hystyerectomy was done. Patient fared well after the surgery.

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Distant Endometriosis

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Endometriosis is defined as the presence of endometrial tissue outside the uterus.The most frequent sites of implantation are the pelvic viscera and the peritoneum.

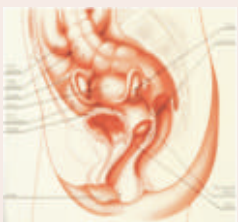


Fig 1: Endometriosis – common sites

Symptoms - Their frequency and Intensity:
Cyclic changes in endometriotic lesions (described above) are responsible for symptoms of the disease such as: ·

- Painful menstrual periods
- Pain during or after urination
- Pelvic pain unrelated to menstruation
- Heavy, prolonged menstrual periods
- Pain during and after sexual intercourse
- Infertility
- Pain during or after bowel movements

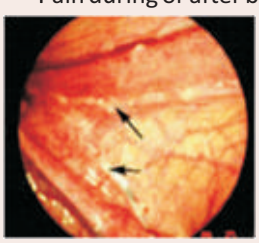


Fig 2 :Nonpigmented endometriosis

The frequency and intensity of these symptoms varies and there is no direct relationship between symptoms and severity of endometriosis.

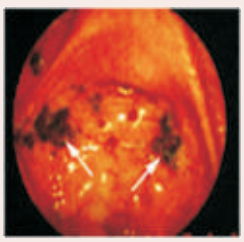


Fig 3: Typical lesions in the cul-de-sac

Some women have advanced endometriosis and few, if any, symptoms; others have severe symptoms with minimal disease. The intensity of symptoms is most likely related to the local inflammatory reaction and production of substances, such as prostaglandins and cytokines, by the endometriotic cells and cells of of the immune system.

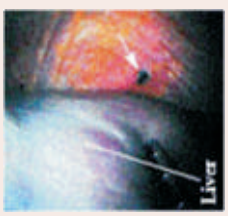


Fig 4: Endometriosis of the diaphragm

Endometriotic lesions, although benign, may spread like cancer from the reproductive system to other organs and sometimes even to distant locations away from the pelvis. We have seen women with endometriosis of the bladder, bowel, liver, lungs, arms, thighs, and even brain. If endometriosis spreads outside of the pelvis, it can cause generalized symptoms and/or symptoms of pain or bleeding in other organs. In general, any symptom or change in the body that undergoes cyclic changes coincidental with

the menstrual cycle, should be suspect of being endometriotic in origin.

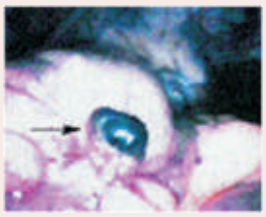


Fig 5: Bowel endometriosis

Treatment: The choice of treatment in endometriosis depends on several factors such as:

- Woman's age
- Severity of symptoms
- Fertility status
- Stage of the disease
- Prior treatments (if any) and treatment response and side effects (if any)

These factors as well as patient-specific indications and contraindications, advantages and disadvantages, and risks and benefits of different treatment options need to be thoroughly discussed and considered prior to treatment selection.

Medical Treatment:

Medical treatment can supress endometriotic lesions and decrease the size of endometriomas. Pain improvement is observed in over 80% of patients but the effect is gradual over a period of six months of typical treatment. Because all medications used in the treatment of endometriosis change the hormonal status of the patient, there may be a variety of side effects. GnRH agonists are the most commonly used hormones. They include Depot Lupron, Zoladex and Synarel. They lower estradiol levels to less than 20/pg/mL, causing menopausal symptoms and changes. After endometriosis is suppressed, the GnRH agonist may be used for a longer period of time with estrogen added back to control the symptoms and changes of menopause. Danocrine is an anabolic steroid that lowers the estradiol level only 10-60 pg/mL, suppressing the menstral cycle and endometriosis without severe menopausal symptoms. Increase in appetite and weight gain are the major side effects. Birth control pills, especially those with strongly progestational properties when given as a long-cycle regimen, may control pelvic pain symptoms but generally have only a limited effect on endometriosis. Their side effects, however, are tolerable by most patients. Progestogens alone can control pelvic pain symptoms in some women. Their effect on endometriosis and their side effects are similar to those of birth control pills.

New Treatment Methods:

Several new hormonal preparations are being tested for effectiveness in controlling endometriosis and pelvic pains. Newer studies on endometriosis treatment have studied the effects of Abarellx, which is a GnRH antagonist. Abarellx is more effective than GnRH agonists and seems to have fewer and less bothersome side effects.

Newer approaches to the management of endometriosis and pelvic pains are based on a local intravaginal-rather than systemic-administration of the hormones such as intravaginal Danocrine. A similar clinical effect as with oral administration but without systemic side effects are expected. In the future, we anticipate that a new class of medications, the immunomodulators-will become available to treat endometriosis and pelvic pains more effectively.

Surgical Treatment-Advanced Laparoscopic Surgery

Advanced laparoscopic surgery for chronic pelvic pains and suspected endometriosis should be performed by a surgeon with the necessary skills and expertise in the resection of such lesions and in an operating room equipped for such a surgery. Endometriotic implants should be resected, vaporized or fulgerated and care should be taken to perform as complete as possible resection of deep infiltrating endometriotic nodules which

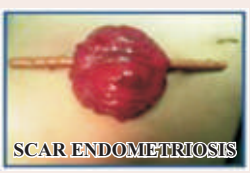
are usually the cause of pelvic pains. To reduce pain transmission, nerve interruption procedures such as uterosacral (US) nerve abalation or presacral neurectomy should be considered. Adhesions (scar tissues) should be completely resected and measures preventing their reformation should be applied. Endometriotic cysts should be resected with their capsule using ovarian tissue-sparing technique-rather than be drained. The surgeon should also be prepared to resect endometriotic lesions that may involve other organs such as the bowel or bladder. Appendectomy should also be performed if there are adhesions or if endometriosis involves the appendix

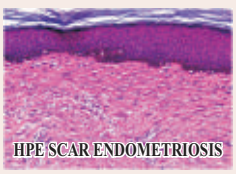
Newer Research In endometriosis Management:

Based on new research in the pathogensis of endometriosis, it has become clear that pelvic inflammation,increased macrophage activation,pelvic angiogenesis and invasion of extracellular matrix associated with endometriosis are potential targets for current therapy. Few of the promising areas seem to be the selective blockade of TNF alfa ,Pentoxifylline, interferon alfa, interleukin 12, loxoribine and levamisole.

CASE STUDIES:

CASE 1:

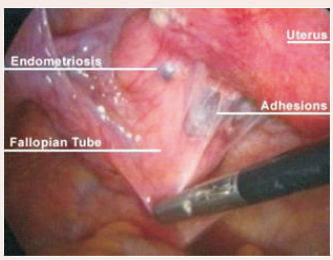




A 33-year-old woman was seen in the surgery clinic with the complaint of swelling and pain at the upper part of cesarean scar for the last 5 years which was initially present at the time of menstrual cycle but later became continuous in nature. She had one prior cesarean delivery 14 years ago. Examination revealed a 4 x 4 cm tender subcutaneous mass in the upper part of the midline vertical scar. The overlying skin was normal. Patient underwent excision of the mass under local anesthesia with a diagnosis of stitch granuloma. HPE revealed it to be a case of scar endometriosis and subsequently patient was referred to the gynaecology unit. As the excision was partial patient continued to be symptomatic. Treatment with Danazol 200 mg TDS for four months was unsuccessful. Wide excision of the mass was undertaken and the defect in the rectus sheath was closed by prosthetic mesh. Postoperative period was uneventful

CASE 2 :

A 28-year-old nulliparous female presented with colicky periumbilical pain for 2 years. There was no history of vomiting, haematemesis or malena. The patient had painful, irregular menstrual periods every 20-25 days lasting for 34 days. Abdominal examination was normal.



A laparoscopic examination showed dense adhesions between the adnexa, the uterus and the cul-de-sac with multiple chocolate brown endometrial deposits in the lower half of the abdomen. Several loops of small bowel were seen to be adherent. In view of adhesions seen at laparascopy, a small bowel series (barium meal follow through) was performed. This showed a fixed loop of ileum in the infraumbilical region. In addition, several loops of ileum were seen to be adherent in the pelvis. There was no evidence of small bowel obstruction. The patient was started on danazol.

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Cancer in Endometriosis

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"It is a riddle wrapped in a mystery inside an enigma."
Winston Churchill

Introduction:

Endometriosis is an important benign gynaecological disease that is pathologically defined by the ectopic presence of endometrial glands and stroma within the pelvic peritoneum and other extra-uterine sites and is linked to pelvic pain and infertility. It is estimated to affect 2%- 10% of women in the reproductive age group (1, 2, 3). Women with endometriosis have a well-documented increased risk for infertility, but endometriosis as a cause of infertility has been a focus of controversy. Infertility and nulliparity per se are known risk factors for cancer, above all in the ovaries(4,5,6). Endometriosis is considered a polygenically inherited disease with a complex, multifactorial etiology.

Epidemiological evidence:

Studies by Ness et al have indicated endometriosis as a risk factor for ovarian cancer in about 0.7-5% of patients(7,8). This has also been seen in other similar studies(9,10). Some authors also suggest that there is an also increased risks of colon cancer, ovarian cancer, thyroid cancer non-Hodgkin's lymphoma and malignant melanoma in women with endometriosis when compared with the general population(11). Larger epidemiological studies have been possible in the recent times due to national data records and they also show similar incidences(1,5,6). In these cohort studies(1,3,4,6,11), there is no valid way to account for the stage of endometriosis, because staging of the disease is never entered in the registry. Despite this, one might still assume that most registries are of the indoor patients; these would mainly be moderate-to-severe cases of endometriosis and few cases where the endometriosis diagnosis may have been an unexpected finding in a patient admitted for other reasons. Given these limitations, it is not possible to generalize and extrapolate the cancer risk to the whole endometriosis population. It is now necessary to study if there is a difference in cancer risk between severe endometriosis and mild endometriosis. Another limitation of epidemiology is that cases where it is not possible to show that the endometriosis started 1 year or more before the cancer diagnosis will need to be excluded, resulting in an underestimation of the true risk of cancer for women with endometriosis.

Endometriosis and Ovarian Cancer :

The relationship between endometriosis and ovarian cancer is an intriguing and still poorly investigated issue. Specifically, histological

findings indicate a definitive association between endometriosis and endometrioid/clear cell carcinoma of the ovary. It has been suggested that endometriosis may be associated with a definitive risk of ovarian malignancy(7). Melin's(1) study shows that the increased risk of ovarian cancer exists in all cases of endometriosis, even after controlling for parity. This is a very important finding since parity was postulated to have a protective role against the risk of developing epithelial ovarian cancer(12). It is suggested that one full-term pregnancy has more protection against ovarian cancer than an incomplete pregnancy(13).

Whether there is any correlation between ovulation and the risk of ovarian cancer is still being extensively debated. Repetitive ovulation trauma to the ovarian surface epithelium and exposure to high levels of estrogen, has been claimed as a risk factor(14). Ovulation stimulating drugs for infertility treatment as well as hormonal treatment for endometriosis have been suggested to increase the risk of epithelial ovarian cancer, but there is no conclusive evidence yet(6,7,8,15,16).

Large population-based cohort studies have reported a slightly higher incidence of clear cell /endometriod ovarian cancer in women with endometriosis with standardized incidence ratio varying between 1.3 and 1.95,(6,11). However, the precise link and incidence is still lacking. More importantly, current evidence is insufficient to deduce a causative relationship between endometriosis and ovarian cancer.

Currently, scientific research is focusing on the potential development of cancer from pre-existing endometriosis. However, the scenario may be broadened, as endometriosis and cancer have similar risk factors and/or antecedent mechanisms for malignant change. These studies addressing the malignant potential of endometriosis are very troublesome evidence but urgently needed. One of the main problems of these epidemiological studies, is that, we still do not know the exact incidence of endometriosis in general population(17,18). In addition to these, are the problems of cellular heterogeneicity and sample collection. These have not been able to identify the specific causative loci common to endometriosis and cancer, which is the only way to eventually confirm the existence of a mechanism of tumourigenesis conforming to a progression model. As a result we are still years of research away from knowing the entity of the risk for endometriosis to undergo malignant transformation, to understand the molecular bases and even less to have a cellular marker for predicting the malignant change.

Endometriosis and other cancers

Lambe et al (19) showed that nulliparous women with endometriosis had a higher risk of developing gliomas compared with parous women. The author's interpretation of that study was that the reduced androgen level during pregnancy might contribute to the risk, or that the malignant brain tumour itself reduced fertility. An association between endometriosis and dysplastic naevi as well as an increased family history of malignant melanoma among endometriosis patients was suggested by Hornstein et al(20) and also confirmed by Brinton(5,11). There is also an increased risk of breast cancer in women with endometriosis as suggested by Melin et al(1). Brinton et al(6) also showed an increased incidence of colon cancer, thyroid cancer as well as non-Hodgkin's lymphoma in women with endometriosis when compared with the general population6

Aromatase Expression In Mullerian-Derived Tissues

Until recently, estrogen action was classically viewed to occur only through an "endocrine" mechanism. Studies on aromatase expression in breast cancer have demonstrated that paracrine mechanisms play an importance role in estrogen action in this tissue (21,22). Estrogen produced by aromatase activity in breast adipose fibroblasts was demonstrated to promote the growth of adjacent malignant breast epithelial cells. Mullerian tissues are known targets of estrogen action. Disease free endometrium and myometrium lack aromatase expression. On the other hand, neoplastic counterparts of these tissues display high levels of aromatase expression and activity(23). Whether this is the possible mechanism of malignant transformation or not remains to be studied.

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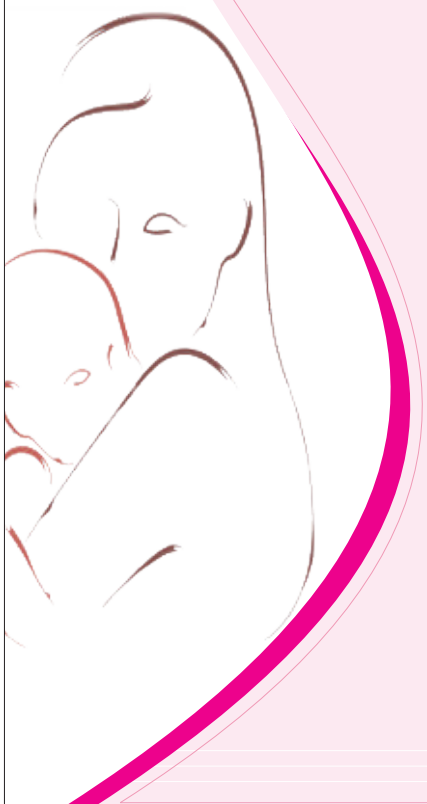

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