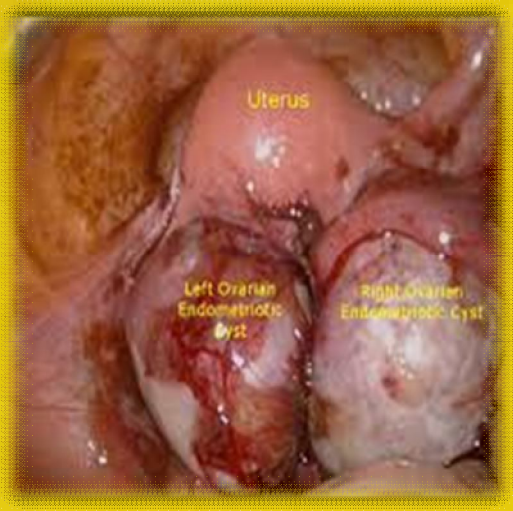
GOOD CLINICAL PRACTICE RECOMMENDATIONS ON ENDOMETRIOSIS



Theme: Enigmatic Disease - Educate Empower and Eradicate

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FOGSI

GOOD CLINICAL PRACTICE RECOMMENDATIONS ON ENDOMETRIOSIS

Under the agesis of FOGSI Endometriosis Committee 2014 – 2016

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Introduction

Endometriosis is an enigmatic disease. As per definition it is the presence of endometrial glands and stroma, outside the uterine cavity which induces chronic inflammatory reaction. General incidence is around 10 % of the women of reproductive age group. Among the infertile women 25 – 48 % suffers from endometriosis. 176 million women (1)or even more in the world suffer from endometriosis. The main symptoms are dysmenorrhoea, dyspareunia, dysuria, dyschezia, abnormal uterine bleeding and difficulty in conception.

The diagnosis of endometriosis is based upon history, symptoms and signs. Early diagnosis is not possible with imaging modalities. Laparoscopy is the gold standard in diagnosis and management of endometriosis.(2)Imaging modalities like USG and MRI help in diagnosis of moderate to severe endometriosis.

Visual recognition of endometriosis at laparoscopy alone is not confirmatory. Histopathology helps in confirmation of diagnosis in doubtful cases. If the surgeon performing laparoscopy is not familiar with the different appearances of the disease, it may even be missed or left untreated. [The eyes do not see what the mind does not know!]

Especially, deeply infiltrating lesions which are hidden beneath the peritoneal surface are very difficult to pick up even by laparoscopy.

Variable presentations of adolescent endometriosis are also missed during laparoscopy because of its atypical appearances. Laparoscopy helps in diagnosis and staging of endometriosis. Clinicians should follow the ASRM classification (3)and document the findings and appropriately stage the disease [minimal, mild, moderate, and severe]. However this classification has a limited role in deeply infiltrating endometriosis (4)There is a poor correlation between staging and endometriosis associated pelvic pain.(5) Due to wide variety of clinical practice in diagnosis and management of endometriosis. Clinicians experience difficulty in establishing the final diagnosis and proper management. This will lead to delay in diagnosis and sub-optimal health care.

Moreover, the social and economic burden of endometriosis is quite enormous. WERF [World Endometriosis Research Foundation] and Endocost study(6)showed several billion Euros towards the cost for treating these women.

Apart from the economic burden, work, study, social and sexual relationships are affected. The social stigmata of infertility is adding fuel to the fire. Clinicians should be aware of the chronic and recurrent nature of the disease and choose appropriate management according to the age and need of the patient keeping in mind the long term complications and sequalae.

Clinicians should also look at the psychological aspect of the patient and counselling is needed for the patient and the family. Clinicians should look at the requirement of the patient and individualize treatment accordingly.

So far, we have ESHRE (4), ASRM, SOGC (7) guidelines for the management of endometriosis. The need for developing recommendations for the Indian clinicians has become a necessity to treat our own population, where the incidence of endometriosis is increasing.

Being a chronic, progressive, recurrent, debilitating immune mediated disease, medical management or surgical management should be individualized. Medical management should be preferred over surgical management whenever feasible. Medical management shouldaim at alleviating the symptoms, reducing the size of the lesion and preventing recurrence. Surgical management should be selective at the right time at appropriate tertiary care centre, by experts in the field. Recurrent surgeries should be discouraged as it would be counterproductive and lead to more morbidity. Hence, this is an attempt by the group of experts to frame the GCPR for endometriosis under the agesis of FOGSI Endometriosis Committee 2014 – 2016.

Interpretation of Grading system of current GCPR (4) (8) (9)

GDG followed the grading system in accordance to the AACE protocol for standardised productionof clinical practice guidelines. After going through literature, available evidence and opinions internationally as well as from Indian perspective GDG formulated the recommendations. Recommendations were organised topic wise and assigned evidence levels for grades based on clinical importance &strength of the evidence as mentioned in the following table.

Grade	
A	Strongly recommended
B	Intermediate
C	Weak
D	Not evidence based
GPP	Expert/GDG consensus based

The evidence was further classified into four levels as mentioned in the Table below to facilitate the finding to be placed in the grades as mentioned above.

Evidence Level	
1	Meta-analysis of randomised controlled trials, randomized controlled trials
2	Meta-analysis of nonrandomised prospective or case-controlled trials, nonrandomised controlled trial, prospective cohort study, retrospective case-control study
3	Cross-sectional study, surveillance study (registries, surveys, epidemiologic

	study, retrospective chart review, mathematical modelling of database), consecutive case series, single case reports
4	No evidence (theory, opinion, consensus, review, or pre-clinical study)

As there are differences in racial, socioeconomic and cultural backgrounds of Indian and western populations, there is a need to formulate our own GCPR. The draft recommendations were framed by the committee and discussed during and expert panel meeting in April 2016. The expert panel discussed the draft recommendations on the basis of the clinical evidences from India and abroad and framed the final version. Where evidence is limited the panel relied on their vast experience and clinical judgement.

Diagnosis of endometriosis

Introduction

1.

Clinically defined as presence of Estrogen dependent endometrial-like tissue found outside uterus, resulting in sustained inflammatory reaction.(2) (10)

Deep infiltrating endometriosis (DIE) is considered a specific entity and has been arbitrarily defined as endometriotic lesions extending more than 5 mm underneath the peritoneum (11)

2.

a. GDG recommends that clinician should consider the diagnosis of endometriosis in the presence of gynecological symptoms such as Dysmenorrhea, Dyspareunia, Dysuria, Dyschezia, AUB, Difficulty in conception and non-cyclical pelvic pain. [Evidence level GPP].
b. Clinician should be aware of extra-genital endometriosis, when bleeding from unusual sites e.g: epistaxis, cyclical hemopneumothorax. haematochezia, haematuria, umbilical bleeding, and previous scars are seen. [Evidence level GPP].

3.

a. GDG recommends clinician should perform clinical examination in all women suspected of endometriosis, although vaginal examination may be inappropriate for adolescents and or women without previous sexual intercourse. In such cases, rectal examination can be helpful for the diagnosis of endometriosis. [Evidence level GPP]
b. Physical examination has poor sensitivity, specificity, and predictive value in the diagnosis of endometriosis.
c. Clinician should rule out non endometriotic causes in patients complaining of pelvic pain after thoroughly going through the findings of combination of history, physical examination, and imaging studies.

4.

a. In all women with suspected endometriosis clinical examination by the way of per abdominal, per speculum, per vaginal, per rectal and recto vaginal examination after counseling should be done. For adolescents an appropriate method of clinical examination should be done after counseling considering recommendation 3a above Patient [Evidence level GPP].

b. Clinician should consider the diagnosis of deep endometriosis in women with (painful) induration and/or nodules of the recto vaginal wall found during clinical

examination, or visible vaginal nodules in the posterior vaginal fornix. It is best seen during menstruation [Evidence level C]

c. Clinician should suspect presence of ovarian endometrioma in women if adnexal masses are detected during clinical examination [Evidence level C]

d. Absence of clinical evidence during examination does not rule out the disease. [Evidence level C]

5.

a. Imaging in endometriosis is not without drawbacks and limitations
b. Clinicians should recommend trans vaginal USG to diagnose or exclude ovarian endometrioma [Evidence level A]

c. Trans vaginal or endo rectal ultrasonographymay reveal ultra sonographic features varying from simple cysts to complex cysts with internal echoes to solid masses, usually devoid of internal vascularity but shows pericystic flow with high resistance [Evidence level GPP]

d. In women with symptoms and signs of endometriosis, trans vaginal sonography is useful for identifying rectal endometriosis. Probe tenderness may be elicited. [Evidence level A].

e. Clinicians should be aware that usefulness of 3D USG to detect recto vaginal endometriosis is not well established. [Evidence level D]

f. Bladder endometriosis may be seen by trans abdominal USG in clinically suspected cases. Hydronephrosis secondary to ureteric endometriosis may be detected by trans abdominal USG

6.

a. Clinicians should be aware that, peritoneal lesions will not be detected by MRI[Evidence level D]

b. MRI may detect small lesions more than 1cm and distinguish endometrioma Vsdermoids.

c. Clinician should be aware that MRI can accurately detect recto vaginal disease and obliteration of POD in more than 90% of the cases

7.

a. CT may reveal endometriomas appearing as cystic masses; however, appearances are nonspecific and imaging modalities should not be relied upon for diagnosis

8.

a. Laparoscopy is gold standard in diagnosis**.** (2) **(**Sensitivity: 97%, Specificity 95%).Tissue of biopsy may be of use and negative biopsy does not rule out endometriosis. [Evidence level A]

b. Types of lesions on laparoscopy are powder burn or black lesions, white opacified peritoneum, glandular excrescences, flame like red lesions, peritoneal pockets or windows, clear vesicles, yellow brown patches, unexplained adherence of ovary to peritoneum of ovarian fossa, encysted collection of thick chocolate colored or tarry fluids, adhesions to posterior lip of broad ligaments or other pelvic structures.[Evidence level A]

9.

a. Apart from research settings, biomarkers are not recommended for routine clinical use
b. CA-125 may be of value to rule out ovarian malignancies and presence of extensive peritoneal lesions. In some cases it may be of some value for treatment follow-up. [Evidence level A].

Adolescent Endometriosis

Introduction:

Adolescent girls (13 to 19 years) constitute around 3 to 5% of the patients suffering from endometriosis. Adolescent girls suffering from chronic pelvic pain, 70 – 80 % are reported to have endometriosis.(12). The presenting features differ from adult population. Most of them present with severe dysmenorrhoea and school absenteeism.(13). There are also difficulties in diagnosis as most of them present with atypical symptoms and are treated empirically. The diagnosis is often delayed in the adolescent girls for a period of more than 6 -8 years if high index of suspicion is not there.

1. Endometriosis has to be suspected in adolescents when they have severe dysmenorrhoea, interfering with daily activities and school absenteeism not responding to NSAIDS and OCPs when taken for pain relief. [Evidence level B]

2 Early onset progressive dysmenorrhoea in adolescents should be investigated for the possibility of Mullerian anomaly with outflow tract obstruction.[Evidence level GPP]

3 Diagnosis in adolescents are through history, physical examination, risk factors and family history combined with imaging technologies and biomarkers.[Evidence level D]

4 USG and MRI may be done. This may confirm diagnosis only in advanced lesions. Early lesions may not be picked out.[Evidence level D]

5 When the adolescents do not respond to NSAIDS and OCPs, diagnostic laparoscopy has to be done to confirm the diagnosis as well as to treat. [Evidence level GPP]

6Positive histology confirms the diagnosis, even though negative histology does not exclude it. [Evidence level GPP]

7 Expectant management for adolescent endometriosis when it is diagnosed incidentally, is debatable.[Evidence level GPP]

8 Continuous use of OCPs for adolescents is safe and effective for EAPP and can be used as first line of treatment.[Evidence level B]

9 Progestins are also used for endometriosis associated pelvic pain (EAPP) and have comparable results with that of GnRH analogues and Danazol. [Evidence level A], Newer progestins like dienogest may help to relieve pain in adolescent girls and can be used for a longer period.

10 GnRh agonists are used only for girls beyond 16 years.[Evidence level A]

11 When DMPA and GnRh are used, BMD reduction has to be monitored.[Evidence level B]

12 LNG IUS can be used in sexually active adolescents as second line of management (14).[Evidence level A]

13 Laparoscopy for endometriomas has to be balanced carefully, to avoid the loss of ovarian reserve Vs pain relief. [Evidence level GPP]

14 First surgery should be done by an experienced surgeon specialized in endometriosis, as adolescent endometriosis has atypical findings.[Evidence level GPP]

15 Long term follow up is a must to prevent recurrence. [Evidence level GPP].

16 Continuous OCPs can reduce the recurrence.[Evidence level C]

Endometriosis and Infertility

Endometriosis causes infertility due to immunological, ovulatory dysfunction, alteration in endometrial receptivity and tubal factors in severe cases. Endometriosis causes ovulatory infertility by altering folliculogenesis and ovulation due to inflammation associated with endometriosis. Endometriosis causes immunological infertility due to increased production of ROS by macrophages and poly morphonuclear cells associated with endometriosis which causes increased oxidative stress. Decreased expression of integrins and increased production of cytokines are noted. Endometriosis causes decreased sperm quality and function due to inflammatory toxic effects of the peritoneal fluid and activated macrophages upon the sperms.

Endometriosis affects endometrial receptivity by causing progesterone resistance, dysregulation of progesterone receptors and by increased E2 production secondary to elevated aromatase enzymes. Factors like age of patient, severity, duration of symptoms, stage of disease, previous treatment taken and associated male factor should be taken into consideration when treating endometriosis associated infertility.

1. Medical management in the form of ovulation suppression is ineffective in improving the pregnancy rates (15) (16) [Evidence level A].
2.
    a. Laparoscopic ablation or excision and adhesiolysis improves pregnancy rate in stage I and II endometriosis when compared to diagnostic laparoscopy alone. (17) (18)[Evidence level A].
    b. Operative laparoscopy is indicated in stage III and IV endometriosis compared to expectant management to increase spontaneous pregnancy rate (4) [Evidence level B].
    c. Excision of endometrioma i.e cystectomy is recommended to increase spontaneous pregnancy rates instead of drainage and coagulation (4) (19) [Evidence level A]
    d. The GDG recommends clinicians to counsel women with endometrioma regarding the reduction of ovarian reserve following surgery. In the event of previous surgery, the decisions for repeat surgery should be done carefully [Evidence level GPP]

3.
    a. GDG recommends clinicians should not prescribe adjunctive hormonal therapy before surgery to improve spontaneous pregnancy rates [Evidence level GPP]
    b. Clinicians should not prescribe adjunctive hormonal therapy after surgery to improve spontaneous pregnancy rates (20) [Evidence level A].

4.

a. In stage I and II endometriosis patients undergoing laparoscopy before ART, consider the complete surgical removal of endometriosis to improve live birth rate, although the benefit is not well established (18). [Evidence level C].
b. In stage I and II endometriosis, treatment with super ovulation and IUI improve fertility compared to expectant management. Clinicians should take into consideration, age, duration of infertility, ovarian reserve and male factor (16). [Evidence level A].
c. Previous ovarian surgery results in longer stimulation, higher FSH requirement, decreased oocyte number but no difference in fertilization, pregnancy outcome in subsequent ART cycles.
d. IVF or ICSI is indicated especially if tubal function is compromised, advanced reproductive age, male infertility and other treatment failures [Evidence level GPP]
e. Surgical management of endometrioma does not significantly increase IVF pregnancy rate and ovarian response to stimulation compared to no surgery (16) (21) (19). [Evidence level A].
f. COS using GnRh agonists or antagonists is effective in IVF patients with mild to moderate endometriosis and in those with endometrioma who did not undergo surgery [Evidence level A].
g. Ultra-long protocol of GnRh agonists for a period of 3 – 6 months before ART improves the clinical pregnancy rates [Evidence level A]
h. In women undergoing IVF, stage III and IV is associated with poor implantation and lower clinical pregnancy rate (22)[Evidence level A].
i. In women with endometrioma, clinicians may use antibiotic prophylaxis at the time of oocyte retrieval to reduce the risk of ovarian abscess. [Evidence level C].
j. In infertile women with endometrioma smaller than 3 cm cystectomy prior to ART does not improve pregnancy rates (23)[Evidence level A].
k. In women with endometrioma larger than 3 cm, cystectomy is indicated prior to ART when it is associated with pain or inaccessibility of follicles [Evidence level GPP].
l. Excision of endometrioma is strongly recommended in infertile women, when there is suspicion of malignancy or when there is rupture or torsion of the cyst [Evidence level A].
m. In severe endometriosis, IVF treatment after surgery does not increase the risk of recurrence [Evidence level B].
n. The effectiveness of surgical removal of deeply infiltrating lesions in women undergoing ART with regards to pregnancy outcome is debatable.[Evidence level C]
o. GDG does not recommend nutritional supplement, complementary or alternate medicine in the treatment of endometriosis associated infertility [Evidence level GPP].

Medical management of endometriosis

1. Indications for medical therapy

a). Empirical treatment, in suspected cases of endometriosis, to be started, based on the symptoms, after counselling the women thoroughly.

b) GDG recommends medical therapy for patients of endometriosis for

1. Prevention of recurrence following surgery and for long term follow up

2. If recurrence occurs

3. In patients who refuse surgery (Evidence level GPP)

2. Clinicians should counsel women with symptoms presumed to be due to endometriosis [CPP, dysmenorrhoea and dyspareunia] thoroughly. Empirical medical management includes NSAID's, OCP's and GnRH agonists. (Evidence level GPP)

a). NSAIDs

1. NSAID's or other analgesics to reduce endometriosis associated pain should be considered.(Evidence level GPP)

2. Mefenemic acid is the commonly used NSAIDs (Evidence level GPP)

b) Use of combined low dose hormonal contraceptives reduces EAPP.(24) [Evidence level-B]

1. Oral Pills [Evidence Level – B]

2). Use of vaginal contraceptive ring or a transdermal [oestrogen/progestin] patch for EAPP has been recommended (25) [Evidence level-C]

3). Continuous use of COC may be considered for EAPP. [Evidence level-C]

c) GnRh agonist

1). GnRH agonist is effective therapy for EAPP (26) (27).Commonly used GnRh agonist are Leuprolide and Goserelin[Evidence Level A]

2). Hormonal add-back therapy should be recommended when GnRH agonist is used for long-term to prevent bone loss and hypo-estrogenic symptoms (28)[Evidence level-A]

3.). Addition of add-back therapy does not reduce the effect of treatment for pain relief (28)[Evidence level-A]

4) GnRh agonists in young girls less than 16 years is not recommended due to adverse effects on BMD [Evidence level GPP]

5) Vitamin D and Calcium supplementation is recommended when patients are on GnRH agonist .(Evidence level GPP] (29)

6) Use of progesterone [likely MPA], oral or depot, norethisterone acetate, dienogest or danazol are indicated to reduce EAPP (30)[Evidence level-A]

a DMPA 150 mg or DMPA SC 104mg every 3 months are equally effective as GnRH agonists [Evidence level-A] (30)

b. Dienogest at the dose of 2mg/day is as effective as GnRH agonist but with much less side effects [Evidence level-A](31) (32) (33)

c. Subdermal implants [Etonogestrol] of depot Progesterone can be used if available (Evidence level GPP)

d. Anti-Progestins like Gestrinone are not commonly used (Evidence level GPP)

e. Levonorgesterol-releasing Intra-uterine system reduces EAPP as second line (14)[Evidence level-A-B]. It also helps in regressing associated adenomyosis (34)(Evidence level B)

4.Danazol

a). Oral danazol is effective in treatment of EAPP but serious androgenic side effects limits its use (Evidence level GPP)

b). Vaginal Danazol / IUCD loaded with danazol may be an option and it is recommended for DIE but it is currently not available in India (Evidence level GPP)

5.Aromatase inhibitor

1. a). Anastrazole [1mg] and Letrozole [2.5mg] can be given daily for 12 weeks with Progesterone add-back therapy (35) [Evidence Level B]

6.Anti-Angigenic Therapy

a). Cabergolin; [0.5 mg weekly twice for 3 months] reduced EAPP in early lesions and reduces the size of endometrioma, with comparable effect to LHRH agonist (36)

7.Lifestyle Modification

a.Dietary modifications and exercise have some influence on the severity of symptoms [Evidence level GPP]

b. Psychotherapy may be beneficial in EAPP [Evidence level GPP]

c. There is some evidence to show that Yoga and meditation help in alleviation of symptoms associated with EAPP [Evidence level GPP]

d.Alternate therapies like acupuncture and Chinese herbal medicine reduces EAPP (37) and left to the choice of the patient [Evidence Level-B]

f.High frequency TENS may be effective in treatment of EAPP[Evidence levelGPP]

e. Multidisciplinary approach is strongly recommended in EAPP [Evidencelevel GPP]

Surgical management of Endometriosis

Introduction:

Surgery is the mainstay for diagnosis and management of endometriosis. Surgery may be used primarily or whenever there is recurrence not responding to medical treatment or even in acute emergencies due to endometriosis.

The clinician should decide whether the surgery is indicated for pain relief, or for infertility or for both.

1.

a. The clinician should exclude pelvic aetiologies like primary dysmenorrhoea, interstitial cystitis, and IBS before planning for surgery.

b. In women with known or suspected endometriosis laparoscopic surgery is preferable over laparotomy for diagnosis and treatment of endometriosis associated pelvic pain (38) (17) and infertility.["See and treat"] [Evidence level A]

c. Clinicians should consider both ablation and excision of the lesion to reduce endometriosis associated pelvic pain and infertility. (Excision provides sample for HPE) [Evidence level C]

2. Clinicians should properly counsel regarding the choice of conservation Vs definitive surgery.

a. Clinicians should consider conservative surgeries in young and infertile women.

b.Clinicians should not prescribe pre-operative hormonal therapy to improve the outcome of surgery. (39)[Evidence level A].

c. When performing surgery in women with ovarian endometrioma (> 3 cm), clinicians should perform cystectomy instead of drainage and coagulation as it reduces the incidence of endometriosis associated pelvic pain and recurrence. (40)[Evidence level A].

d. Cyst aspiration and cauterization of the endometrioma is indicated in cases of recurrent endometriosis, when the ovarian reserve is poor, but the recurrence rate is high.(Evidence level GPP)

e. Post- operative medical suppressive therapy with COC's and LNG IUS is indicated immediately in women for whom surgery is done for endometriosis associated pelvic pain. [Evidence level A]. (14) (41)

f. If there is unilateral involvement, unilateral oophorectomy can be done in a woman who has completed the family. (Evidence level GPP)

g. Repeated surgeries should be avoided in young, infertile women as it reduces the ovarian reserve. [Evidence level GPP]
h. Clinicians should recommend repeat surgery only when the patient is not responding to medical management (pain) or in suspected malignancy. Repeat surgeries have more morbidities.(Evidence level GPP)

3. The GDG recommends definitive surgery [Hysterectomy with removal of the ovaries and all visible endometriotic lesions] in women who have completed their family and failed to respond to conservative treatment. [Evidence level GPP].

a. Women should be informed that hysterectomy will not necessarily cure the symptoms or the disease. [Evidence level GPP]

b. Clinician should inform the patient that recurrence rate is high if ovarian conservatism is done along with hysterectomy (42) [Evidence level A].

c. Clinicians should counsel regarding risks and benefits of oophorectomy.

4. Clinicians can consider performing surgical removal of deep endometriosis, as it reduces endometriosis associated pelvic pain and improves quality of life (43) [Evidence level B].

a. The GDG recommends that clinicians should refer women with suspected or diagnosed deep endometriosis to a centre of excellence that offers multi-disciplinary approach. [Evidence level GPP].

5.

a. Clinicians should not perform laparoscopic uterosacral nerve ablation [LUNA], as an additional procedure to conservative surgery to reduce endometriosis associated pelvic pain (4) (44).[Evidence level A].

b. Clinicians should be aware that Pre Sacral Neurectomy [PSN] is an effective additional procedure to conservative surgery to reduce mid-line pain, but requires high degree of skill and is potentially hazardous procedure with side effects like bladder and bowel disturbances (4).

6. HRT following definitive surgery increases the risk of recurrence. Tibolone may be a good alternative. [Evidence level GPP].

Pain management in Endometriosis

Introduction

Endometriosis associated pelvic pain affects the quality of life. It is very common, crippling and needs immediate treatment. Success of treatment of endometriosis associated pelvic pain lies in addressing the cause of the disease.

Peritoneal lesions cause chronic inflammation due to the production of pro-inflammatory prostaglandins, cytokines, histamine and kinins.DIE causes pain due to destruction of tissues and entrapment of nerves. Ruptured endometrioma causes pain due to peritoneal irritation. Adhesions cause mechanical pressure, devitalisation, anatomical distortion and ischaemia within the lesion. There is increasing evidence that nociceptional and neuronal involvement contribute largely to endometriosis associated pelvic pain.

The symptoms of Endometriosis associated pelvic pain are dysmenorrhoea, dyspareunia, dysuria, dyschezia, cyclical and acyclical pain. Endometriosis being an estrogen dependent disorder, most of the treatments are geared to address hormonal milieu alterations.

1. It is recommended that pain management should consist of empirical, medical, surgical, combination or alternative medical therapy as per suitability of patient. (Evidence level GPP)
2. Clinicians should be aware that endometriosis should be viewed as a chronic disease that requires life-long management plan with the goal of maximizing the medical treatment and avoiding repeated surgical procedure[ASRM recommendations]
3. Empirical treatment can be given to patients with suspected endometriosis associated pelvic pain. Clinicians should properly counsel these women and treat them with NSAID, COC and Progestogen [Evidence level GPP].
4. NSAID (Mefenamic acid) is given in endometriosis associated pelvic pain in women who are desirous of fertility [Evidence level GPP].
5. Both continuous and cyclical estrogen and progesterone are effective in relief of endometriosis associated pelvic pain (45)[Oral, vaginal ring and transdermal patch]. [Evidence level B]
6. Continuous oral progestin therapy is effective for treatment for endometriosis associated pelvic pain (46)[MPA, Norethisterone acetate, Cyproterone acetate, Dienogest and Danazol] [Evidence level A]
7. Depot MPA is effective for endometriosis associated pelvic pain [Evidence level A] comparable to GnRh agonist.
8. LNG IUS is effective for endometriosis associated pelvic pain and comparable to GnRh with less side effects [Evidence level A].
9. Oral Danazol is effective in treatment of endometriosis associated pelvic pain but serious side effects have limited their use.(Evidence level C)

10. Danazol, (ring, IUCD, intra cervical injections) are other options for treatment of endometriosis associated pelvic pain (47) (48) but currently not available in India[Evidence level B]
11. GnRh agonist is most effective in the treatment of endometriosis associated pelvic pain. However its side effects limits its prolonged use.[Evidence level A]
12. Add back therapy is recommended to prevent the side effects [Evidence level GPP].
13. The use of aromatase inhibitors in combination with progestins especially in rectovaginal endometriosis to reduce endometriosis associated pelvic pain is recommended (35) (49) (50). [Evidence level B]
14. GDG recommends that clinician take patient preference, side effects, efficacy, cost and availability into consideration when choosing hormonal treatment for endometriosis associated pelvic pain. [Evidence level GPP]
15. Failed medical management is an indication for surgery.[Evidence level GPP]

Surgical management of pain

1. Adjunct pre-surgical hormonal treatment does not improve the outcome of surgery for endometriosis associated pelvic pain (39). [Evidence level A]
2. Cystectomy for endometrioma reduces the symptoms and recurrence rather than drainage and ablation (40) [Evidence level A].
3. Laparoscopy is preferable over laparotomy [Evidence level D]
4. Complete excision of endometriotic lesions relieves pain in most patients (51) [Evidence level C]
5. In DIE, complete excision of the lesions relieves pain and promotes fertility (51) (52).A multidisciplinary approach is recommended.[Evidence level B]
6. In patients who have completed the family may be subjected for hysterectomy with or without BSO(Bilateral Salphingo oophorectomy) [Evidence level GPP]
7. It is recommended not to leave ovaries behind during surgery as it increases the recurrence 3 fold
8. LUNA is not effective in endometriosis associated pelvic pain (4) (44) [Evidence level A]
9. Pre sacral neurectomy is effective in relief of midline pain [Evidence level A]. (4) (44)
10. Post-surgical hormonal suppressive treatment reduces the incidence of endometriosis associated pelvic pain [Evidence level GPP]
11. For secondary prevention, post-operative medical hormonal therapy is used for more than 6 months.(Evidence level GPP)
12. Post-surgical hormonal therapy is indicated only in those women who are not desirous of pregnancy.(Evidence level GPP)

Non-medical management for treatment of endometriosis associated pelvic pain

Complementary therapies are used in 30 – 50 % of adults in western countries (37).YOGA and meditation can be adjuvant therapy in treatment of EAPP (53)

1. Combination diet may help to relieve the endometriosis associated pelvic pain [Evidence level C]
2. Chinese Herbal Medicine may relieve endometriosis associated pelvic pain similar to Danazol[Evidence level C]
3. Acupuncture may be useful in severe dysmenorrheal (54) [Evidence level C]
4. There is limited use of neuromodulators, anaesthesia, behavioural therapy, reflexology, homeopathy and psychological therapy in treatment of endometriosis associated pelvic pain. GDG does not recommend these modalities of treatment. However, GDG acknowledges that some women who seek complementary and alternative medicine may have benefit from this. [Evidence level GPP].

Recurrent endometriosis

Introduction

> Endometriosis is likely torecur after medical or surgical therapies.
> Endometriosis recurs because the basic pathophysiology cannot be corrected. Treatment only aims at symptom relief and removal of the disease as much as possible. Delaying pregnancy and persistence of the pathological mechanisms act synergistically. In cases of aggressive disease recurrence is more common with adverse prognosis

Post-operative recurrence rate is 21 % at the end of 2 years and 40 – 50 % at the end of 5 years even in expert hands.(55) (56)

Risk factors are

1. Younger age at the time of surgery(<25 years) (57)
2. Bilaterality (56)
3. Size of endometriotic lesion
4. Revised AFS score > 24 (58)
5. Pre-operative cyst rupture (59) (60)
6. Type and extent of surgery [Laparoscopy less risk Vs Laparotomy]

1.

a. Clinician should be aware that recurrence of endometriosis may be asymptomatic or may lead to pain and infertility (Evidence level GPP)

b. Asymptomatic patients are kept under follow up (Evidence level GPP)

c. Clinicians should recommend clinical examination in a known patient of endometriosis who has recent onset of recurrent pain and substantiate with imaging modalities. (Evidence Level GPP)

2. Clinician should understand that recurrence rates depend upon type of endometriosis, staging of endometriosis, method of surgery, post- operative intervention and the skill of the surgeon (56).(Evidence level B)

3. Clinician should recommend only cystectomy instead of drainage and electrocoagulation of the endometrioma wall (40)[Evidence level C]

4.Recurrence of the lesion is lower when cystectomy is done (40) [Evidence level A]

5. After primary surgery women desirous of pregnancy should be recommended for fertility treatment.(Evidence level GPP).
6. Clinician should recommend hormonal treatment or GnRh agonist, in women not desirous of pregnancy for prevention of recurrence (Evidence level C)
7. Clinicians are recommended not to use biomarkers to diagnose endometriosis or recurrence but there is some place for follow up (Evidence level)
8. Clinician should recommend combined treatment to prevent recurrence (Evidence level A,B)

    a. Long-term post-operative OCP's or progestins to reduce the risk of recurrence (41) [Evidence level A]
    b. Post -operative use of GnRh agonist for 6 cycles rather than 3 cycles prevent the recurrence of endometriosis (61)(Evidence level A)
    c. Oral progestins (MPA, Dienogest, Danazol) are effective in reducing pain and preventing the growth of lesion after surgery (55) (62) [Evidence level A]. Dienogest has added advantage of being anti-inflammatory, anti-angiogenic and anti-proliferative with less side effects (62).
    d. Prolonged therapy of endometriosis with LNG –IUS after conservative surgery controls symptoms, prevents recurrence and protects against bone loss. Maximum benefits is obtained if it is inserted soon after surgery (4) (63) [Evidence level A]
    e. Clinicians should take patient preference, side effects, efficacy, costs and availability when choosing the type of hormonal treatment (Evidence level A)
9. Recurrence of pain is managed with medical suppression (NSAID's, GnRh analogues) [Evidence level A], combined hormonal therapy [Evidence level B], aromatase inhibitors, progestins [Evidence level A]
10. Recurrence of lesion can be by surgical re-excision, nerve ablation surgeries (pre-sacral neurectomy) or radical surgery [Hysterectomy with BSO][Evidence level A]
11. LUNA is found to be of no benefit.[Evidence level A]
12. Hysterectomy with removal of ovaries and all visible endometriotic lesions can be done in women who have completed their family.
13. However, women should be informed that hysterectomy will not necessarily cure the symptoms or the disease.[Evidence level A]
14. Infertility treatment of women with recurrent endometriosis, ART is preferable over repeat surgery. [Evidence level A]
15. Surgery is indicated only when endometrioma is > 3 cm or associated with pain or suspicious of malignancy[Evidence level A]

Follow up:

1. These patients should be followed up with USG for development of hydronephrosis due to entrapment of ureters by the surrounding fibrosed tissues(Evidence level GPP)
2. Sudden increase in the size of endometrioma, appearance of new symptoms should alert the clinician towards the onset of malignancy.(Evidence level GPP)

Endometriosis and Malignancy

Introduction

Although endometriosis is not a frank malignancy, it mimics malignancy. It can metastasize to local and distant sites and like malignancy it can attach, invade and damage other tissues. Unlike malignancy it does not result in catabolic state and is rarely fatal.
Incidence of clear cell carcinoma and endometroid carcinoma are higher among ovarian malignancies associated with endometriosis (64).
Ovarian cancer is known to develop in 0.3-1.6 % of women with endometriosis. (65)
Endometriosis is observed in 4-29% of patients with ovarian cancer.
There is 4 fold increase of ovarian cancer in patients with endometriosis (66).
Adenomyosis is associated with 4-5 fold increased risk of ovarian and endometrial cancer (67).
A 13 fold increased risk of colorectal cancer in women with adenomyosis with coexistent endometriosis is observed (67) .

Women with high risk factors should be followed closely

Endometriosis is not associated with an altered risk of uterine cancer

Relationship between endometriosis and breast cancer is uncertain (67).[Evidence level B]

Incidence of non Hodgkins lymphoma was increased in women with endometriosis[Evidence level B]

Endometriosis is associated with a lower risk of cervical cancer[Evidence level B]

1.

a. Serum CA 125 is non-specific especially in pre-menopausal women
b. No definite cut off level should be considered in isolation
c. Serial follow up of levels of CA125 is a useful method for detection of change into malignancy.

2. Role of Imaging:

There is no definitive role for imaging

a.In all modalities, there is significant overlap in finding of Endometriosis Vs Malignancies

b. Positron Emission Tomography scan also has not been shown to be helpful in prediction of ovarian carcinoma beforehand (68).

c. Screening for prevention of carcinoma associated with endometriosis is not advised (Evidence level GPP)

3. Surgical management of suspected malignancy

a.Management of endometriosis associated ovarian cancer Vs non endometriosis associated ovarian cancer is the same and there is no difference in the outcome (69).

b. When in doubt, laparotomy is always preferred. (Frozen section can be done) (69)

c.Ideally cyst should not rupture and should be removed intact(69)

d. In high risk cases, laparoscopy is recommended only when cyst can fit into the endo-bag (69).

4.

a. There is no advantage of risk reducing salpingectomy with or without oophorectomy (70)(Evidence level GPP)

5.

a. Patients diagnosed with adenomyosis may harbor an increased risk of developing endometrial cancer in later life. Closer monitoring is advised for this patient population (71)[Evidence level B]

b.High index of suspicion is required and good pathological evaluation of specimen is needed.

c. Management has to be individualized to have the best outcomes.

Asymptomatic Endometriosis

1. By definition, asymptomatic endometriosis means incidental finding of peritoneal, ovarian or deep endometriosis without pelvic pain or infertility.
2.
    a. Treatment of endometriosis patients are usually based on overall symptoms
    b. In asymptomatic patients diagnosis and treatment becomes more challenging
    c. Accuracy of diagnosis is mainly by non-invasive modalities
3.
    a. The nature of the treatment of asymptomatic endometriosis depends upon the patient
    b. Asymptomatic endometriosis found during laparoscopy or tubal ligation may not warrant any treatment or monitoring. Treatment in the form of excision is not required. Since the natural course of the disease is not clear (72).[Evidence level GPP]
    c. In cases of incidental finding of endometriosis, it may be removed for tissue diagnosis. GDG recommends that clinicians should fully inform and counsel women about any incidental finding of endometriosis. In asymptomatic recurrence of proven endometriosis observation is recommended
    d. Asymptomatic endometriosis diagnosed in infertile women during laparoscopy will necessitate early intervention and referral for advanced fertility treatment.
4.
    a. We should view asymptomatic endometriosis as a marker for potential problem.
    b. It does not require treatment but requires monitoring.
5. The management of asymptomatic endometriosis depends on the accuracy of diagnosis, size of the mass, age of the patient, desire to preserve fertility and her psychological make-up.[Evidence level GPP]
6.
    a. For expectant management, repeated imaging every 3 – 6 months is appropriate when the morphology of the lesion on USG suggests benign disease.
    b. During the course of observation of asymptomatic endometriosis suspicion of malignancy warrants further investigation and referral to oncologist [Evidence level B]
7.

    a. Medical management will not result in complete resolution [Evidence level GPP].
    b. Surgical management should be considered if there is a sudden enlargement in the cyst, when there are symptoms such as pain and infertility and when malignancy cannot be ruled out, or if the patient cannot come for follow-up regularly.
8. The management of asymptomatic endometriosis depends upon the relevance of the finding in that particular patient, with her particular problem, at that particular time and the need for therapeutic intervention.

Adenomyosis

1. Adenomyosis is defined as a disorder characterized by the presence of heterotopic endometrial glands and stroma in the myometrium with hyperplasia of the adjacent smooth muscle (73).[Evidence level GPP]

2. Adenomyosis is considered relatively common but its exact incidence has not been accurately determined and ranges from 5 % to 70 % in symptomatic women (73) (74) (75) (76) (77) (78) (79).[Evidence level D]

3. There is increased incidence of adenomyosis in multiparous women, women getting married at later age, and in women who had spontaneous abortions undergoing multiple D&Cs. Generally seen in 3rd and 4th decade and rarely seen in adolescent girls. (79) (80) (81) (82) (83) . [Evidence level C]

4. The exact etiology and pathophysiology of uterine adenomyosis is still unknown. [Evidence level GPP].

5.

    1. TVS, 3D, color Doppler and MRI are currently used to make a diagnosis of adenomyosis (73) [Evidence level C].

    2. MRI is more reliable than TVS and is essential to plan for uterine sparing surgeries (73) [Evidence level A].

6. Women with adenomyosis present with heavy uterine bleeding and severe dysmenorrhoea (73).[Evidence level C].

7. Women with Adenomyosis have difficulty in conception. It is still unclear how it causes infertility (84)[Evidence level GPP]

8. Management of adenomyosis is either medical or surgical

    1. Surgical management may be conservative or radical (73)[Evidence level C]

2. Medical management includes COC's, GnRh agonists, Progestins. (85) (MPA, Dienogest, Danazol, LNG-IUS), SPRM's and SERM'(86) (87) (88) (89) [Evidence level C].
3. Medical management avoids surgery but not very effective in relieving pain [Evidence level B].

9.
    1. NSAID's have no effect on the disease and its progression
    2. It can be given for pain relief who want to conceive[Evidence level GPP]

10. GnRh provides symptomatic relief, reduces uterine volume and allows spontaneous conception after cessation of therapy (84).[Evidence level C]

11.
    1. Pre-operative GnRh may reduce the size, vascularity and blood loss during surgery.
    2. This facilitates laparoscopy rather than laparotomy.
    3. Sometimes during surgery there may be difficulty in delineating the margins and complete excision may be difficult.[Evidence level C]

12.
    1. Dienogest may be useful in long- term treatment of symptomatic adenomyosis (62) [Evidence level B].
    2. Oral MPA or injectable DMPA 150mg once in 3 months may be cost effective in treatment of adenomyosis. [Evidence level A]
    3. LNG-IUS reduces uterine volume and relieves symptoms within a period of 3 – 6 months (90) (91).[Evidence level C].
    4. LNG-IUS also improves quality of life when compare to hysterectomy (90) (91).
    5. LNG-IUS relieves chronic pelvic pain associated with adenomyosis (90) (91).
    6. Locally delivered Danazol may be used as an alternate treatment for symptomatic adenomyosis. Danazol loaded IUCD's, rings and intra-cervical injections are the newer methods of delivering Danazol locally (86).

13. Continuous combined oral contraceptive pills show overall safety, good efficacy and appreciable tolerability at low cost [Evidence level B].

14. SERMs and SPRMs have a limited role in clinical practice.[Evidence level B]

15. Aromatse inhibitors may be as effective as GnRh agonists in improving the symptoms and reducing the volume of adenomyosis (35) [Evidence level B]

16. Uterine artery embolization may improve the symptoms of Adenomyosis but recurrence may be high (92) [Evidence level A].

There is some evidence that HIFU and Magnetic Resonance guided ultrasound are effective ablative technique for symptomatic adenomyosis (93) (94) (95) (96) [Evidence level C].

17. Surgical management

a. Consists of uterine sparing and radical surgery (73).
b. Hysterectomy is the definitive surgical treatment. It is the treatment of choice in failed medical management (73).
c. Conservative uterine surgery is indicated in symptomatic women who desire fertility (97)
d. Focal adenomyosis can be managed by laparoscopic or open adenomyomectomy (98).
e. Diffuse adenomyosis can be tackled by various methods of cyto-reductive surgeries (99) (100).
f. Hysteroscopic adenomyomectomy is done wherever possible as an alternative to laparoscopy (101)[Evidence level C]
g. High level of expertise is needed in doing conservative adenomyotic surgeries to preserve future fertility.

18. Combination treatment

Conservative surgery followed by GnRh agonist / LNG-IUS may be a long –term treatment option (102)[Evidence level C]

Scar Endometriosis

Introduction

Scar endometriosis is a rare disease with non-specific symptoms like pain and swelling at the scar site especially during menstruation. Diagnosis is often very difficult or delayed or misdiagnosed which leads to emotional and physical distress to the patients. The incidence may vary between 0.03 to 0.1 % (103).

The cause for Scar endometriosis is often iatrogenic transplantation of endometrial implants [stem cells]to the wound edge during abdominal or pelvic surgeries. The onset may vary from 3 months to 12 years (104). [Evidence level A]

Recommendations

1. Clinicians should be aware that cyclical changes of size and intensity of pain noted during menstruation over the implant, points towards scar endometriosis [Evidence level A]

2. 20 – 70 % can present with cyclical symptoms of tenderness on palpation. Hypertrophic and hyper pigmented scars due to haemosiderin deposits are seen.[Evidence level B].

3. Clinicians should have a high index of suspicion of scar endometriosis in these patients and a thorough history and clinical examination are mandatory.

4. Clinicians should be aware that scar endometriosis occurs following C-section, hysterotomy, hysterectomy, tubal ligation, episiotomy, laparoscopy ports and amniocentesis tract. They should also be aware that ,it commonly involves only the skin and the subcutaneous plane and very rarely involves muscle ,fascia and the pelvic organs (103) (105). [Evidence level A].

5. Clinicians are recommended to use Ultrasonogram and Color doppler as a mode of investigation. In rare situations, MRI might help and CT is of limited use. Confirmation of the diagnosis is by trucut biopsy (106) (107) (108).

6. Clinicians are recommended to consider the following differential diagnosis like stitch granuloma, lipoma, desmoid tumour, abscess, cyst, keloid, primary or secondary malignant nodules and inguinal or incisional hernias.

7. Clinicians should be aware that the first line of management of scar endometriosis is wide excision of the mass. Smaller lesions may respond to medical management with drugs like progestins, OCP's danazol, GnRh agonists and dienogest (62) .They can only reduce the symptoms but not the size of the lesion.

8. Clinicians should suspect malignancy in the event of recurrence, though the incidence is less than 1% of the scar endometriosis (109) (110).

9. Clinicians should be aware of the preventive measures to be taken during LSCS like excluding the decidua while closing the uterus, using different mops and needles for different layers.

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