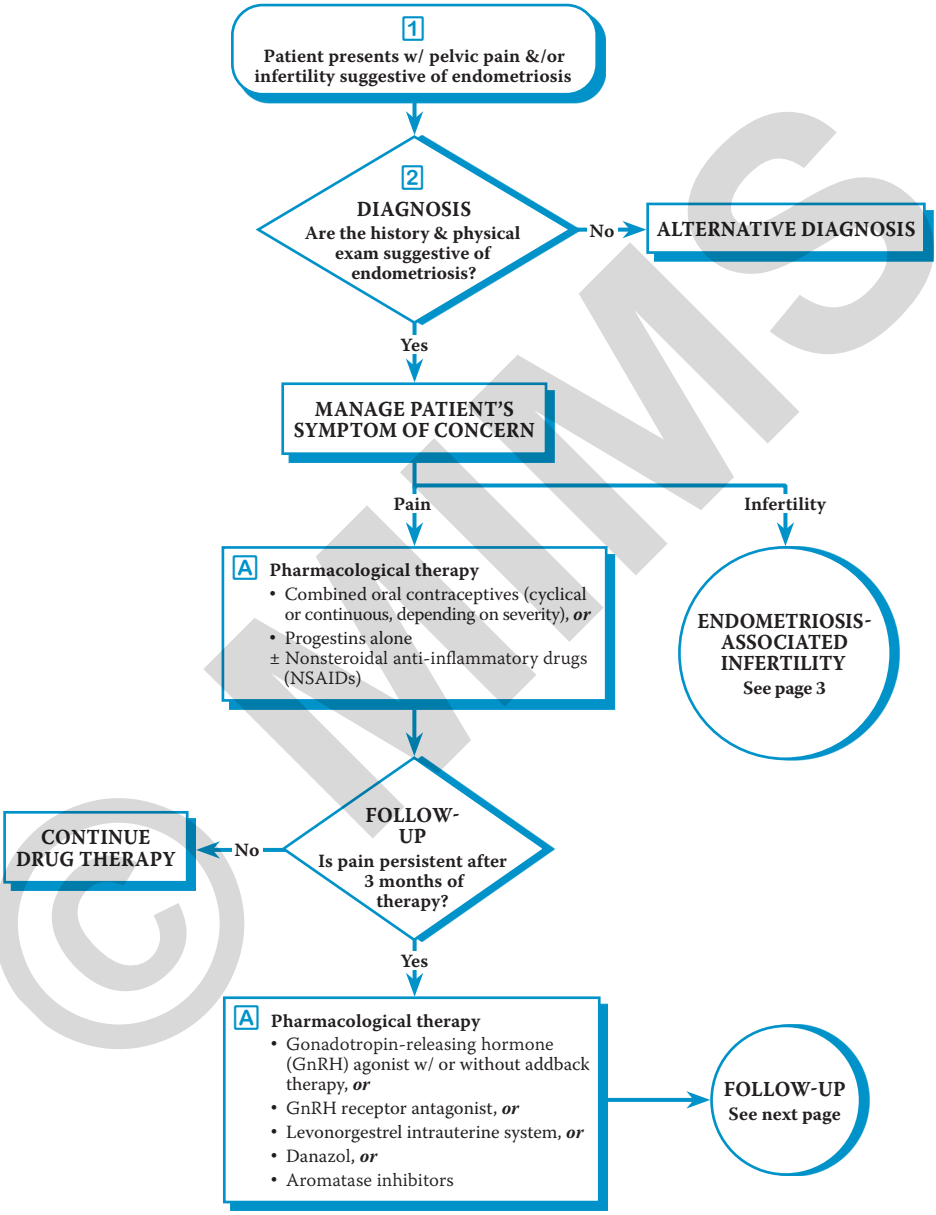
Endometriosis (1 of 11)



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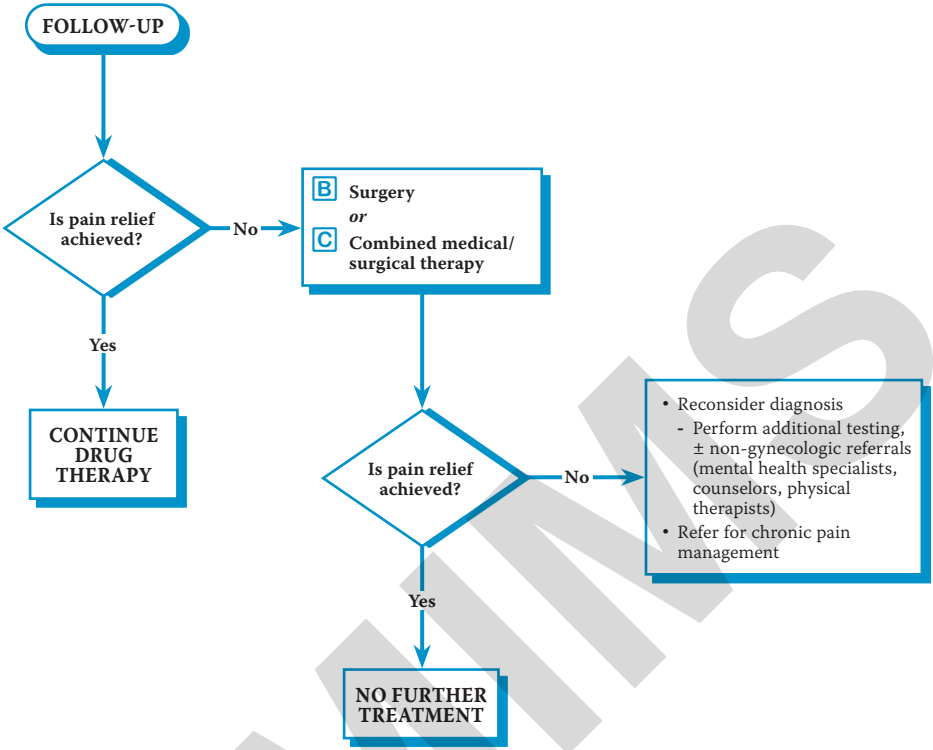

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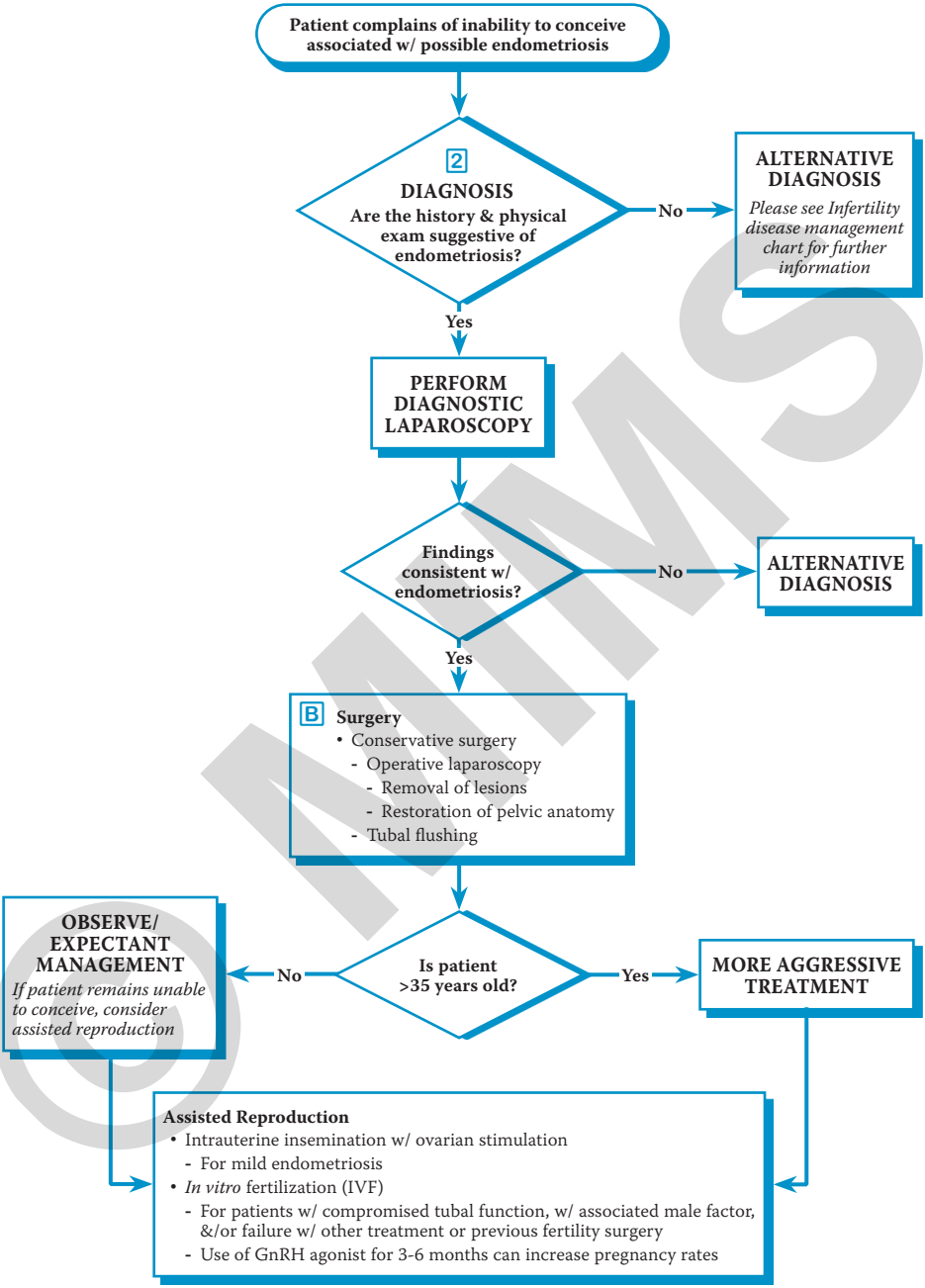

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1 ENDOMETRIOSIS

- An estrogen-dependent growth of endometrial-like tissue found outside the uterus inducing a chronic inflammatory response
  - Pelvic organs (especially ovaries) & peritoneum are frequently affected
- 5-10% of reproductive-aged women are affected
- Prevalence is higher in Asian women while a lower incidence is found among African women as compared to Caucasians
- Risk factors:
  - Genetics, particularly among the patient's 1st-degree relatives
  - Prolonged exposure to endogenous estrogen (early menarche or late menopause)
  - Short menstrual cycle
  - Low body mass index (BMI)
  - Obstruction of menstrual flow (eg müllerian anomalies)
  - High consumption of red meat & trans fat
- Pathogenesis of endometriosis remains unclear but theories include:
  - Retrograde menstruation (Sampson's theory)
  - Immune system problems
  - Metaplastic changes of the peritoneal coelomic mesothelial cells
  - Spread of ectopic menstrual tissue via the bloodstream or lymphatic system
  - Differentiation of cells from bone marrow into ectopic endometrial tissue
  - Increase in estrogen sensitivity w/ increase in progesterone resistance
- Types of endometriosis include adenomyosis (asymmetrical uterine enlargement), ovarian endometriomas or chocolate cysts, superficial peritoneal endometriosis, deep infiltrating endometriosis (lesions that penetrate >5 mm to the peritoneum), & disseminated endometriosis
- Main clinical features include:
  - Chronic pelvic pain (found in 70-82% of patients)
  - Dyspareunia (suggests deep posterior infiltration)
  - Infertility (21% prevalence rate)
- Other symptoms may include severe dysmenorrhea, pain on ovulation, noncyclical pelvic pain, cyclical bowel or bladder symptoms w/ or without abnormal bleeding or pain, dyschezia, dysuria, chronic fatigue, or abdominal or lower back discomfort
  - In adolescents, endometriosis is the most common cause of secondary dysmenorrhea
- Although it is vital to consider the patient's complaints affecting physical, mental & social well-being, it should be noted that patients w/ endometriosis may be completely asymptomatic (w/ 2-22% prevalence rate)
- Complications of endometriosis include pain, fertility problems, & risk of developing ovarian cancer

2 DIAGNOSIS

History

- Should include:
  - Age (reproductive year, most commonly at 25-29 years old)
  - In utero exposure to environmental toxins like Diethylstilbestrol which increases the incidence of endometriosis
  - Family history of endometriosis (7x higher risk than w/ no family history)

Physical Exam

- Ideally done during early menses because endometrial implants are likely to be largest & deep infiltrating, hence more easily detectable
- Perform abdominal inspection & palpation, a rectovaginal examination, & assess the uterus' mobility, position & size
- Diagnosis is more definite if deeply infiltrative nodules are found on the uterosacral ligaments or in pouch of Douglas, &/or lesions are directly seen in the vagina or cervix
- Note that there may be no abnormal findings on physical exam
- A cotton swab can be inserted into the vagina to document patency & exclude complete or partially obstructive anomalies such as a transverse vaginal septum, imperforate or microperforate hymen, or an obstructed hemivagina
- For patients who are not sexually active, a rectal-abdominal exam may be better tolerated than a vaginal-abdominal exam

Other Frequent Findings:

- Pain w/ uterine movement or pelvic tenderness
- Tender, enlarged adnexal masses
- Fixation of adnexa or uterus in a retroverted position
- Uterosacral ligament tenderness
- Rectovaginal septum induration

Laboratory Tests

- Urinalysis & urine culture to identify pain originating in the urinary tract (eg cystitis, stones)
- Pregnancy test & tests for sexually transmitted infections (STIs) like gonorrhea & chlamydia, when appropriate

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2 DIAGNOSIS (CONT'D)

Laparoscopy

- Gold standard for diagnosis, unless lesions are visible in the vagina
  - May also be used for therapeutic purposes
  - Should not be done during or within 3 months of hormonal treatment to avoid under-diagnosis
- Biopsy & histopathologic study of at least one lesion is ideal
  - 3 cardinal features (ie ectopic endometrial glands, ectopic endometrial stroma, & hemorrhage into adjacent tissue) should be present
  - In adolescents, features of endometriosis may be atypical (ie clear vesicles & red lesions)
- A negative laparoscopy does not exclude the diagnosis of endometriosis
- Depending on the severity of the disease found, it is best to remove the endometriotic lesion at the same time
- Differential diagnoses (eg endosalpingiosis, mesothelial hyperplasia, hemosiderin deposition, hemangiomas, adrenal rests, inflammatory changes, splenosis & reactions to oil-based radiographic dyes) can be excluded by biopsy

Laparoscopic Classifications (Based on location, extent & severity of lesions)

- Revised American Society for Reproductive Medicine (rASRM) Score [formerly the Revised American Fertility Society (rAFS) Score]
  - Noted aspects include bilaterality, depth of invasion, size, involvement of the ovary & cul-de sac, & density of adhesions
  - Scores are as follows: 1-5 for minimal disease (stage I), 6-15 for mild disease (stage II), 16-40 for moderate disease (stage III), >40 for severe disease (stage IV)
  - Does not take into account the retroperitoneal structures & deep infiltrating endometriosis
- Enzian Staging System
  - Presence of deep infiltrating endometriosis is taken into account
  - Supplements the rASRM score w/ a description of deep infiltrating endometriosis, retroperitoneal structures & other organ involvement

Imaging Studies

Transvaginal Sonography (TVS)

- Considered the 1st-line imaging tool to examine suspected endometriosis
- Should be performed to determine whether a pelvic mass or structural anomaly is present
- Useful in diagnosing or excluding rectal endometriosis
- May identify an ovarian endometrioma & help identify other structural causes of pelvic pain, such as ovarian cysts, torsion, tumors, genital tract anomalies & appendicitis
  - Distinguishes endometrioma from other ovarian cysts w/ 83% sensitivity & 89% specificity
  - Ovarian endometrioma may be diagnosed in premenopausal women w/ findings of ground glass echogenicity & 1-4 compartments & absence of papillary structures w/ blood flow

Magnetic Resonance Imaging (MRI)

- May be helpful in some cases to better define an abnormality suspected by sonography
  - Detects ovarian endometrial cysts w/ 90% sensitivity & 98% specificity
- Provides exact location of deep retroperitoneal lesion
- Useful in ruling out other pelvic organ involvement such as bowel or bladder
- May be used as part of pre-op workup, but should not be used as 1st-line

Computed Tomography (CT) Scan

- May show size & different characteristics & densities of adnexal masses
- Used to evaluate other pathology or organ involvement
- Chest CT is useful for thoracic endometriosis

Other Imaging Studies

- Cystoscopy, colonoscopy & rectal ultrasonography may be required if deep endometriosis is suspected

Miscellaneous Tests

Serum CA-125

- Women w/ endometriosis may have high serum CA-125 concentration
  - No value as diagnostic tool in endometriosis, though it may be used to assess the presence of an undiagnosed adnexal mass
  - Also elevated in ovarian epithelial neoplasia, myoma, adenomyosis, acute pelvic inflammatory disease (PID), ovarian cyst, pregnancy

Biopsy

- May be considered in suspected endometriosis lesions & endometriomas to help confirm the diagnosis & exclude possible malignancy
  - Recommended for the diagnosis of patients w/ mild to moderate endometriosis
  - In patients w/ endometriosis, prevalence of ovarian cancer is <1%

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A PHARMACOLOGICAL THERAPY

Principles of Therapy

- Short-term objectives in treating endometriosis are decreasing pain & enhancing fertility; long-term goal is to prevent progression or recurrence
  - Medical management of infertile patients w/ minimal & mild endometriosis should not be offered since it does not improve fertility
- No studies have shown benefit of one medical therapy over another when treating pain due to endometriosis
- 80-90% of patients will have some improvement in symptoms w/ medical therapy
  - W/ recurrence rate of 5-15% in the 1st year & 40-50% in the 5th year
- Due to the chronic nature of the condition, medical therapy should be safe & effective to use until pregnancy is desired or until menopause
- Patients w/ persistent symptoms after medical therapy should be referred for laparoscopy
- Severity of symptoms does not match w/ the degree of endometriosis

First-line Therapeutic Options

Combined Oral Contraceptives (COCs)[1]

- Combined estrogen & progestin OC is considered the 1st-line treatment for pelvic pain secondary to endometriosis
  - Decreases dysmenorrhea, non-menstrual pain, endometriosis-related dyspareunia
- Induce decidualization & subsequent atrophy of endometrial tissue by suppression of ovarian function
  - Low-estrogen combination pill w/ relatively high progestin is given to induce amenorrhea & "pseudopregnancy"
- A good choice for women w/ minimal or mild symptoms
- May be administered cyclically w/ 7 days placebo pills between cycles or may be taken continuously
  - Better pain relief may be achieved w/ continuous therapy since menses, withdrawal bleeding & associated pain are prevented
    - Withdrawal of pills every month that causes cyclic menstrual bleeding may be associated w/ some retrograde spill of blood that contains cytokines & other inflammatory chemicals
  - May decrease 80% of symptoms of patients during therapy
- Provide contraception & have a low rate of side effects (eg weight gain, breast tenderness)
- No OC combination has been shown to be more effective than another

Progestins

- Used for treating chronic pain in patients w/ endometriosis
- Inhibit endometriotic tissue growth by directly causing initial decidualization & eventual atrophy
  - Also inhibit pituitary gonadotropin secretion & ovarian hormone production
- First choice for the treatment of endometriosis due to its effective reduction in ASRM scores & pain, w/ lower cost & side effects as compared to GnRH analogues & Danazol
- >80% of patients have partial or complete relief
- Dienogest
  - A progestin w/ selective 19-nortestosterone & progesterone activity
  - Same effectivity as GnRH agonist therapy in relieving endometriosis-associated pelvic pain as shown in clinical trials & treatment of deep infiltrating endometriosis
    - May be an effective option in long-term treatment of endometriosis
- Depot Medroxyprogesterone acetate
  - May alleviate pelvic pain w/ low treatment cost
  - May be best indicated for patients w/ no issues regarding future conception & irregular uterine bleeding & has remaining endometriosis after hysterectomy w/ or without bilateral salpingo-oophorectomy
  - Not an option for women who desire pregnancy in the near future as it delays resumption of ovulation
  - Not recommended for long-term use as it may have negative effect on bone mineral density (BMD)
- Norethindrone acetate
  - Approved for continuous use in treating endometriosis
    - Relieves dysmenorrhea & chronic pelvic pain
  - May cause breakthrough bleeding in some patients but likely to have a positive effect on calcium metabolism maintaining a good BMD

[1]Various combinations of estrogen & progestogens are available. Please see the latest MIMS for specific formulations.

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A PHARMACOLOGICAL THERAPY (CONT'D)

Second-line Therapeutic Options

Gonadotropin-Releasing Hormone (GnRH) Agonists

- Recommended for patients who failed to respond to combined OCs or progestins or who have symptom recurrence after initial improvement
- Very effective in alleviating endometriosis-associated pelvic pain but not superior than other therapeutic options
- May induce hypoestrogenism that inactivates pelvic lesions & resolves pelvic pain
- Monotherapy w/ GnRH agonist may result in symptoms secondary to estrogen deficiency (eg hot flushes, insomnia, vaginal dryness, loss of BMD, breakthrough bleeding in the 1st month of therapy, irritability, fatigue, skin problems)
  - Hence, GnRH agonist may be given w/ addback therapy which can be started immediately
  - In estrogen & progestin addback therapy, the concentration of serum estrogen is low enough to cause endometriosis but high enough to prevent hypoestrogenic symptoms
  - Addition of addback therapy lessens or eliminates GnRH agonist-induced bone mineral loss & is also useful in relieving symptoms without affecting efficacy of GnRH agonist
  - Addback regimens (eg sex steroid hormones or other specific bone-sparing agents) are recommended in women who will undergo >6 months of GnRH agonist therapy
- Should be given w/ caution in young women & adolescents since they may not have reached their maximum bone density
- Daily calcium supplementation (1,000 mg) is advised in patients using GnRH agonists w/ addback therapy

GnRH Receptor Antagonist

- Eg Elagolix
- Indicated in patients w/ moderate to severe pain associated w/ endometriosis
- An oral, non-peptide, small molecule GnRH receptor antagonist that can dose-dependently suppress LH, FSH, estradiol & progesterone secretion
  - In comparison to GnRH agonists, its dose can be titrated to obtain a nearly full or partial hormonal suppression
- Causes a dose- & duration-dependent reduction in BMD
  - Assess patient's BMD if w/ risk factors for bone loss & limit treatment duration to decrease bone loss
- Advise patient to take adequate amounts of calcium & vitamin D

Levonorgestrel Intrauterine System (LNG-IUS)

- A 19-nortestosterone-derived progestin that has effective anti-estrogenic effects on the endometrium
  - Causes atrophic endometrium & amenorrhea in up to 60% of patients without affecting ovulation
- Provides continuous therapy for 5 years & has lesser systemic side effects
- May be a good option for rectovaginal endometriosis
  - Reduces dysmenorrhea, non-menstrual pelvic pain, deep dyspareunia & dyschezia
- May have 5% expulsion rate, 1.5% risk for pelvic infection & increased risk for ovarian endometrioma

Danazol

- Effective in resolving implants when treating mild or moderate stages of disease
- A synthetic isoxazole derivative of ethisterone which inhibits pituitary gonadotropin secretion, endometriotic implant growth & ovarian enzymes responsible for estrogen production
  - Has immunologic effects like decreasing serum immunoglobulins, auto-antibodies, & CA-125 levels, increasing serum C4, & inhibiting IL-1 & tumor necrosis factor (TNF) production
- Causes high androgen & low estrogen levels, amenorrhea, & prevents new seeding of implants from the uterus into the peritoneal cavity
- >80% of patients experience relief or improvement of pain symptoms within 2 months of treatment w/ beneficial effects lasting up to 6 months after stopping it
- Large endometriotic cysts & adhesions do not respond well to Danazol
- Use is limited by the occurrence of androgenic side effects (eg weight gain, acne, hirsutism, breast atrophy, rarely virilization) & adverse effect on blood lipid levels
  - Should be used if other medical therapies are unavailable & given in low doses or via vaginal route
  - Not to be used long term
  - A small study showed increased risk for ovarian cancer in endometriosis patients treated w/ Danazol

Aromatase Inhibitors

- Decrease local estradiol production thus lessening lesion growth
- Can reduce pain from rectovaginal endometriosis when combined w/ OCs, progestogens or GnRH analogues
- Should only be given to women refractory to medical or surgical treatment due to severe side effects (hot flushes, vaginal dryness, decreased BMD, arthralgia)
- Studies show lack of evidence on long-term effects

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A PHARMACOLOGICAL THERAPY (CONT'D)

Supportive Therapy

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- Central inhibition of prostaglandin synthesis, local anti-nociceptive effects, & anti-inflammatory effect
- Frequently given as initial treatment to women w/ pelvic pain where diagnosis of endometriosis is still uncertain
- May be given to patients to provide analgesia until primary medical management becomes effective

B SURGERY

- Recommended in some circumstances to confirm the diagnosis & provide treatment to achieve pain relief or improve fertility ie "see & treat"
- Surgery should only be done in women w/ endometriosis-related pain after medical treatment has failed
- May improve fertility
  - Patient benefits from the mechanical clearance of adhesions & obstructive lesions
  - *Please see Infertility disease management chart for further information*
- Indications:
  - Symptoms are severe, incapacitating or acute, eg acute adnexal torsion or rupture of ovarian cyst
  - Symptoms have failed to resolve or have worsened under medical management
  - W/ advanced disease or invasive disease that affected the bowel, ureters, bladder or pelvic nerves
  - Anatomic distortion of the pelvic organs, endometriotic cysts or obstruction of the bowel or urinary tract
  - Patient declines or has contraindication to medical treatment
  - Endometriosis-related infertility, pain or pelvic mass
  - Treatment for postmenopausal endometriosis
- May be performed by laparoscopy or laparotomy
  - Laparoscopy is preferred over laparotomy for treatment of endometriosis-related infertility
- After surgery, the median time for pain recurrence is 20 months
- May be classified as "conservative" or "definitive"

Conservative Surgery

- Preserves the uterus & as much ovarian tissue as possible
- Performed in women of reproductive age, those who wish to get pregnant, or those who wish to avoid menopausal induction at an early age
- Includes removal of macroscopic endometrial tissue, lysis of adhesions, & repair of normal anatomy
  - High recurrence rate (80-100%) is noted after 6 months of drainage of endometriomas
  - Excision of endometriomas provides better pain relief, decreased recurrence rate, a histopathological diagnosis, & improves chances of pregnancy
    - Women w/ >3-cm ovarian endometriomas & w/ pelvic pain should be advised to undergo excision of endometrioma
  - Surgical ablation or resection of endometriosis plus laparoscopic adhesiolysis should be offered to patients w/ minimal or mild endometriosis who will undergo laparoscopy to improve chances of pregnancy
  - Operative laparoscopy in patients w/ severe endometriosis increases spontaneous pregnancy rates

Laser Uterosacral Nerve Ablation (LUNA)

- Reduces pain in minimal-moderate endometriosis
- Disrupts the efferent nerve to reduce uterine pain
- Not performed as an additional procedure to conservative surgery for pain reduction as randomized controlled trials (RCTs) showed no additional benefit

Presacral Neurectomy

- Though rarely indicated, it may be helpful in decreasing midline pain (eg dysmenorrhea, dyspareunia) but not in other pelvic areas
- May be considered adjunct to surgical management of endometriosis-related pelvic pain

Tubal Flushing

- Studies have shown that flushing of fallopian tubes using oil-soluble media may increase chances of pregnancy

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B SURGERY (CONT'D)

Definitive Surgery

Cystectomy

- In women w/ ovarian endometrioma, cystectomy rather than drainage & coagulation or CO_2 laser vaporization should be performed

Hysterectomy

- Hysterectomy w/ or without removal of the fallopian tubes & ovaries
  - Case series studies have shown that 80-90% of women who failed w/ medical or surgical management experienced pain relief after hysterectomy w/ bilateral salpingo-oophorectomy; however, recurrence of pain was noted within 1-2 years in 10% of women
- May be an option for patients w/ intractable pain despite conservative treatment, severe disease, & if childbearing is no longer desired
- In young women who underwent total abdominal hysterectomy w/ bilateral salpingo-oophorectomy (TAHBSO), hormonal replacement therapy (HRT) is recommended
  - May give combined hormone therapy (estrogen & progestin) or Tibolone

C COMBINED MEDICAL/SURGICAL THERAPY

- Combination therapy wherein medical therapy is given before &/or after surgery
  - Hormonal suppression may be given prior to surgery in hopes of decreasing the size of endometriotic implants thereby reducing the extent of surgery required
  - In cases where complete removal of implants is not possible or advisable, post-op medical therapy may be used to treat residual disease & delay recurrence
    - An RCT showed reduction in recurrence w/ post-op use of COCs
    - LNG-IUS implanted after surgery showed major decrease in recurrence (10%) of moderate-severe dysmenorrhea after 1 year
  - Progestin, Danazol, or GnRH analogues may be used in conjunction w/ laparotomy or laparoscopic conservative or definitive surgical treatment
- It is not recommended to prescribe preoperative or adjunctive hormonal therapy after surgery for treatment of pain as it does not improve surgery's outcome for pain

Dosage Guidelines

ANTIGONADOTROPINS

Drug	Dosage	Remarks
Danazol	**Initial dose:** 200-800 mg/day PO divided 6-12 hrly should be started at menstrual onset ***Individualized dose depending on severity of endometriosis*** **Maintenance dose:** 800 mg/day PO divided 12 hrly **Duration:** 3-6 mth May extend to 9 mth	**Adverse Reactions** • Effects due to inhibition of pituitary-ovarian axis (menstrual disturbances, amenorrhea, sweating, hot flushes, libido changes, vag dryness & irritation, decreased breast size, nervousness); Androgenic effects [increased hair growth, acne, oily skin, mood changes, deepening of voice, wt gain, effects on serum lipids (ie decreased HDL & TG, increased LDL) & rarely liver damage]; Other effects (GI disturbances, headache, dizziness, fatigue, muscle spasm, tachycardia & hypertension) **Special Instructions** • Use w/ caution in conditions that may worsen fluid retention (eg CV, hepatic & renal disorders) & in patients w/ migraine, epilepsy, DM or polycythemia • Contraindicated in patients w/ severe hepatic, renal or cardiac dysfunction, porphyria, thromboembolic disease, w/ undiagnosed genital bleeding, & androgen-dependent tumors • Liver function should be monitored regularly during therapy
Gestrinone	2.5 mg PO on day 1 of menstrual cycle, 2.5 mg PO on day 4 of menstrual cycle, then 2.5 mg PO 2x/wk on succeeding wk May increase dose to 3x/wk ***Doses are preferably taken at consistent twice-wkly schedule*** **Duration**: 6 mth	

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Dosage Guidelines

ANTI-GONADOTROPIN-RELEASING HORMONE

Drug	Dosage	Remarks
Elagolix	150 mg PO 24 hrly for up to 24 mth **Women w/ dyspareunia:** 200 mg PO 12 hrly up to 6 mth	**Adverse Reactions** • Hypoestrogenism that manifests as hot flushes & night sweats, insomnia, headache, arthralgia, bone loss, amenorrhea; CNS & mental effects (anxiety, depression-related adverse reactions & mood changes); Other effects (nausea, hepatic transaminase elevations) **Special Instructions** • Take at approximately the same time each day, w/ or without food, using the lowest effective dose • A missed dose can be taken on the same day then continue regular dosing schedule • Use w/ caution in patients w/ bone loss • Contraindicated in pregnant patients & those w/ known osteoporosis, severe hepatic impairment & concomitant use of strong organic anion transporting polypeptide (OATP) 1B1 inhibitors • Use non-hormonal contraception during treatment & for 1 wk after discontinuing Elagolix • Counsel patient on signs & symptoms of liver injury & advise her to perform testing if pregnancy is suspected & to seek medical attention for suicidal ideation & mood disorders

GONADOTROPIN-RELEASING HORMONE ANALOGUES[1]

Drug	Dosage	Remarks
Buserelin	1 spray (150 mcg) into each nostril 8 hrly or 900 mcg/day **Duration:** 6 mth	**Adverse Reactions** • Hypoestrogenism that manifests as transient vag bleeding, hot flushes, vag dryness, decreased libido, breast tenderness, insomnia, depression, irritability & fatigue, decreased elasticity of the skin, headache, after several wk of treatment: increased bone pain, osteoporosis; GI effects (nausea, abdominal discomfort); Other effects (reduction in glucose tolerance, changes in serum lipids, hepatic effects & hypersensitivity reactions, skin rashes, hair loss, increased sweating) **Special Instructions** • Addback strategy w/ estrogen/progesterone or Tibolone can eliminate most of the side effects • OCs should be discontinued prior to therapy & other non-hormonal methods of birth control should be used - In later stages of treatment, pregnancy is unlikely as long as recommended doses are administered • Avoid in patients w/ metabolic bone disease, urinary tract obstruction or metastatic vertebral lesions • Monitor bone density during long-term treatment
Goserelin	3.6 mg depot inj SC into the anterior abdominal wall every 28 days **Duration:** 6 mth	
Leuprorelin/ Leuprolide	3.75 mg depot inj SC/IM once mthly **or** 11.25 mg depot inj IM as a single dose every 3 mth Start therapy during the 1st 5 days of the menstrual cycle **Duration:** 6 mth	
Nafarelin	1 spray (200 mcg) in 1 nostril each morning & another spray in other nostril each evening on days 2-4 of menstrual cycle May be increased to 2 sprays (400 mcg/nostril) if amenorrhea is not achieved after 2 mth **Duration:** 6 mth	
Triptorelin	3.75 mg depot inj IM once mthly **or** 11.25 mg depot inj IM as a single dose every 3 mth Start therapy during the 1st 5 days of the menstrual cycle **Duration:** 6 mth	

[1]Recommended to be given w/ addback therapy. Please see the latest MIMS for specific formulations.

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Dosage Guidelines

PROGESTOGENS[1]		
Drug	**Dosage**	**Remarks**
Dienogest	2 mg PO 24 hrly taken at the same time each day without interruption May be started on any day of the menstrual cycle	**Adverse Reactions** • GI effects (GI disturbances, change in wt/ appetite); Breast changes (enlargement, secretion, discomfort); Androgenic effects (acne, mental depression, changes in libido, hair loss, hirsutism, irregular menstrual bleeding); Dermatologic effects (allergic rash, pruritus, erythema multiforme, erythema nodosum, urticaria); Other effects (asthenia, malaise, headache, migraine, change in vag secretions, fluid retention, edema, fatigue, alterations in lipid profile) - Androgenic effects & lipid changes are more likely w/ Norethisterone **Special Instructions** • Use w/ caution in women w/ hypertension, cardiac or renal impairment, asthma, epilepsy, migraine, history of depression, or other conditions aggravated by fluid retention - High doses should be used w/ caution in patients at risk for thromboembolism • Avoid use in patients w/ unexplained vag bleeding, history or current high risk of arterial disease, severe hepatic impairment, breast or genital tract carcinoma unless progestogen is part of the management
Dydrogesterone	10 mg PO 8-12 hrly from day 5-25 of cycle or administer continuously **Duration:** 3 mth	
Lynestrenol	5 mg PO 24 hrly **Duration:** At least 6 mth	
Medroxy-progesterone	10 mg PO 8 hrly on consecutive days beginning on day 1 of cycle **Duration:** 3 mth ***or*** 50 mg IM wkly or 100 mg IM every 2 wk **Duration:** At least 6 mth	
Nomegestrol	5 mg PO 24 hrly from 16th-25th day of menstrual cycle	
Norethisterone (Norethindrone)	5 mg PO 24 hrly on days 5-25 of cycle **Duration:** 6 mth **or** 2.5 mg PO 24 hrly continuously starting on day 5 of cycle then increase the dose by 2.5 mg every 2-3 wk as required to avoid breakthrough bleeding **Duration:** 4-6 mth **or** 5 mg PO 12 hrly starting on day 5 of cycle May increase to 10 mg PO 12 hrly if spotting occurs Resume initial dose when spotting ceases **Duration:** 4-6 mth **Usual dose:** 5-25 mg/day PO continuously for 4-9 mth	

[1]Various combinations of estrogen & progestogens are available. Please see the latest MIMS for specific formulations.

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